Common Drug Review
Clinical Review Report

August 2015

Drug	aclidinium bromide (Tudorza Genuair) (oral inhalation powder)
Indication	Long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema.
Listing request	Listing in a manner similar to tiotropium bromide
Manufacturer	Almirall Canada Ltd.

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

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ABBREVIATIONS

AE	adverse event
ACL	aclidinium bromide
AUC	area under the curve
BDI	Baseline Dyspnea Index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EQ-5D	EuroQol 5-Dimensions Questionnaire
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool — Patient-Reported Outcomes
EXACT-RS	Exacerbations of Chronic Pulmonary Disease Tool — Respiratory Symptoms
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GOLD	Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease
HR	hazard ratio
HRQoL	health-related quality of life
ICS	inhaled corticosteroids
ITT	intention-to-treat
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
LOCF	last observation carried forward
LSM	least squares mean
MCID	minimal clinically important difference
OR	odds ratio
PP	per protocol
RCT	randomized controlled trial
RR	rate ratio (also relative risk in Appendices)
SABA	short-acting beta-2 agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
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 between individuals but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema). Bronchodilator therapy with short- or long-acting inhaled beta-2 agonists (SABAs, LABAs) or muscarinic antagonists (SAMAs, LAMAs) is a mainstay of COPD therapy. Aclidinium bromide (ACL) (Tudorza Genuair) is an inhaled LAMA indicated for long-term maintenance bronchodilator treatment in patients with COPD, including chronic bronchitis and emphysema. In Canada, ACL is available in a pre-loaded, multi-dose dry powder inhaler that is used to deliver the recommended dose (400 mcg twice daily by oral inhalation). The objective of the review was to evaluate the beneficial and harmful effects of ACL in adult patients with moderate to severe COPD.

Results and Interpretation

Included Studies

Six prospective, double-blind, randomized controlled trials (RCTs) were included in the review, of which three were placebo-controlled trials (M/34273/34 [N = 828], LAS-MD-33 [N = 561], and LAS-MD-38 Part A [N = 544])[1-3] and three were active comparator trials (M/34273/23 [N = 30], M/34273/29 [N = 79], and M/34273/39 [N = 414]).[4-6] The placebo-controlled trials ranged from 12 to 24 weeks' duration and also included an ACL 200 mcg twice-daily group; however, as this is not an approved dose, results from this treatment group are not reported in this review. Two of the active comparator trials (M/34273/23 and M/34273/29) were crossover trials with treatment periods of 15 and 7 days, respectively, whereas Study M/34273/39 was a parallel group trial of 6 weeks' duration. All of the trials included patients who were at least 40 years of age, had moderate to severe COPD, and had smoked at least 10 pack-years. The primary outcome in the placebo-controlled trials was the change from baseline in the pre-dose (trough) forced expiratory volume in one second (FEV_1) at 12 weeks, whereas in the active comparator trials, the primary outcome was the change from baseline in the normalized FEV_1 area under the curve $(AUC)_{0\text{-}12/12h}$ (Studies M/34273/23 and M/34273/29) or FEV_1 $AUC_{0\text{-}24/24h}$ (Study M/34273/39). Key limitations include baseline patient characteristics that affect the generalizability of the findings to Canadian COPD patients (e.g., age, smoking status, pre-study COPD medication use, proportion of patients with bronchial reversibility, and the exclusion of patients with unstable cardiac conditions), the short duration of the trials, and the lack of prospective design or power to assess COPD exacerbation rates. The baseline imbalance in the proportion of patients with severe COPD between the ACL 400 mcg and placebo groups in Study LAS-MD-38 Part A compromises interpretation of the results from this trial and possibly biases results toward the null hypothesis.

Efficacy

Key outcomes identified in the review protocol included pulmonary function tests, COPD exacerbations, all-cause mortality, quality of life, exercise tolerance, symptoms, dyspnea, and patient satisfaction. In all six trials, ACL 400 mcg twice daily resulted in statistically significantly greater bronchodilation compared with placebo as assessed by spirometry measurements (e.g., FEV_1, forced vital capacity (FVC), and inspiratory capacity). The least squares mean (LSM) differences between groups in the change from baseline in the trough FEV_1 at 12 weeks in the placebo-controlled trials ranged from 0.072 L to 0.124 L. The suggested minimal clinically important difference (MCID) in the literature for trough FEV_1 is a change of 0.100 L to 0.140 L.[7,8] The difference between the ACL 400 mcg twice daily and placebo groups at week 12 was at the lower range of the MCID in Study M/34273/34 (0.105 L) and was not reached in

Study LAS-MD-38 Part A (0.072 L). In the active comparator trials, the LSM differences between ACL 400 mcg twice daily and placebo ranged from 0.141 L (week 6 in Study M/34273/39) to 0.186 L (day 15 in Study M/34273/23), both exceeding the MCID. The differences observed with ACL 400 mcg twice daily were comparable to those with tiotropium 18 mcg once daily, which ranged from 0.102 L (week 6 in Study M/34273/39) to 0.150 L (day 15 in Study M/34273/23) and for formoterol 12 mcg twice daily (0.148 L at day 7 in Study M/34273/29). The only statistically significant difference between active treatments for trough FEV_1 was on day 1, when a difference was observed between ACL 400 mcg twice daily and tiotropium 18 mcg once daily. The only statistically significant differences between active treatments for other spirometry measures (e.g., FEV_1 AUC_{0-24} or AUC_{12-24} in favour of ACL) were found when a 24-hour period was assessed, underscoring the importance of the second evening dose of ACL.

None of the included trials were designed or powered to prospectively assess treatment differences in COPD exacerbations, an important measure for treatment decisions in COPD and a key health care cost driver. Rates of "any" exacerbation in the placebo-controlled trials ranged from 6.3% to 14.1% in the ACL 400 mcg groups and from 10.4% to 20.5% in the placebo groups. The odds ratio (OR) for COPD exacerbations was not statistically different between groups in any of the trials. Hospitalizations due to COPD exacerbations were also very few (one to 10 patients per group) and the trial durations too short to assess any meaningful treatment differences in these outcomes. Deaths occurred infrequently, and only in the placebo-controlled trials, with no apparent differences between treatments.

Statistically significant improvements in symptom-related outcomes with ACL 400 mcg twice daily, as measured by the St. George's Respiratory Questionnaire (SGRQ), Transition Dyspnea Index (TDI), patient reports of morning and night-time COPD symptoms and sleep disturbance, as well as rescue medication use, support the efficacy of ACL in patients with moderate to severe COPD. However, the results do not provide robust evidence of clinically meaningful symptomatic benefit. Changes from baseline in SGRQ total score or from the Baseline Dyspnea Index (BDI) score in the TDI focal score were assessed as powered secondary outcomes only in Study M/34273/34 and as additional efficacy variables in Studies LAS-MD-33 and LAS-MD-38 Part A. At week 12, although statistically significant differences were observed between ACL 400 mcg twice daily and placebo for LSM differences in the change from baseline in the SGRQ total score in Studies M/34273/34 (–4.1; 95% confidence interval [CI], –5.06 to –2.13; $P < 0.0001$) and LAS-MD-33 (–2.5; 95% CI, –4.7 to –0.4; $P = 0.0186$), the MCID (reduction of 4 units or more) was achieved only in Study M/34273/34. At week 12 in Study LAS-MD-38 Part A, the MCID was achieved in both the ACL 400 mcg twice daily (–5.4) and the placebo groups (–4.3), and the difference between groups was not statistically significant. Inconsistency between trials is also demonstrated by the OR (ACL 400 mcg versus placebo) for the proportion of patients achieving the MCID for the SGRQ (i.e., OR was statistically significant at all-time points in Study M/34273/34, only at week 4 in Study LAS-MD-33, and at no time point in Study LAS-MD-38 Part A). Changes from the BDI in TDI focal scores ranged from 1.3 to 1.74 across the ACL 400 mcg twice-daily groups and from 0.3 to 0.86 for the placebo groups. The LSM differences between treatments in each trial were statistically significant; however, the magnitude of the differences ranged from 0.88 to 1.0, which is of uncertain clinical significance, as the reported MCID for the TDI focal score is an improvement of one unit or more.[9] The OR of achieving the MCID was statistically significant in all studies at the time points measured.

There was substantial heterogeneity in the manner in which COPD symptoms were measured and analyzed across the included trials. In general, statistically significant improvements in various COPD symptoms were observed with ACL 400 mcg twice daily over placebo; however, the uncertainty with regard to how symptom scores were derived over the treatment periods, and the small magnitude of the change in scores from baseline, results in uncertainty of the clinical relevance of these findings. In

general, the use of rescue medication was statistically significantly reduced in the ACL 400 mcg twice daily compared with placebo groups; however, the results are inconsistent among trials, and the clinical significance of the LSM difference between-treatment groups (amounting to less than one puff of salbutamol 100 mcg) is questionable.

In keeping with these findings, Health Canada concluded that the pivotal (placebo-controlled) studies have provided substantial evidence for the efficacy of ACL 400 mcg twice daily as a bronchodilator in patients with moderate to severe COPD; however, they have not provided robust evidence for the drug's efficacy in providing symptom relief, which was reflected in the final indication.[10]

In the active comparator trials, the manufacturer captured information on patient satisfaction and perception of different inhaler attributes by administering patient questionnaires. It is not clear how the questionnaires were administered and whether potential biases could have influenced the results. In addition, there are no data available to confirm that patients used the inhaler devices correctly or incorrectly. It follows that patients may have preferred one inhaler over another or found one easier to use, even if they were using the inhaler incorrectly. More patients in Studies M/34273/23 and M/34273/29 found the Genuair inhaler easier to use, and more patients definitively preferred the Genuair inhaler over the HandiHaler (30.00% versus 6.67%) or the Aerolizer (62.8% versus 6.4%) devices, although between 40.0% and 14.1% of patients, respectively, did not have any preference. In Study M/34273/39, a statistically significant higher proportion of patients preferred the Genuair inhaler over the HandiHaler (80.1% versus 10.7%) and statistically more patients (88.8%) were also willing to continue using the Genuair device over six weeks of treatment than the HandiHaler device (45.4%). These findings are supported by the results of other manufacturer-sponsored studies summarized in Appendix 8: SUMMARY OF DRY POWDER INHALERS.

The manufacturer also submitted a systematic review and network meta-analysis (summarized and critically appraised in Appendix 7: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS) that assessed the comparative efficacy of ACL, tiotropium, and glycopyrronium. Based on the outcomes of mean change from baseline in FEV_1, SGRQ total score, TDI focal score, COPD exacerbations, and drug discontinuations, it was concluded that the efficacy of ACL was not superior to that of either tiotropium or glycopyrronium. In addition, a published systematic review and network meta-analysis of similar design also came to the same conclusion — that maintenance treatment with ACL 400 mcg twice daily is expected to produce similar improvements in lung function, health-related quality of life, and dyspnea compared with tiotropium and glycopyrronium.[11]

Harms

Overall, ACL was well tolerated in patients with moderate to severe COPD. In the placebo-controlled trials, treatment-emergent adverse events (AEs) occurred with similar frequency in the ACL 400 mcg twice daily (44.7% to 53.5%) and placebo groups (49.5% to 57.1%). The most frequently reported AEs in the ACL 400 mcg twice-daily groups were COPD exacerbations (7.4% to 14.1%), headache (1.6% to 12.3%), and nasopharyngitis (1.6% to 11.2%) compared with 11.5% to 20.5% (COPD exacerbations), 2.2% to 8.1% (headache), and 1.1% to 8.4% (nasopharyngitis) in the placebo groups. The frequency of serious AEs (SAEs) and withdrawal due to AEs (WDAEs) were low and similar between-treatment groups. The pattern and type of AEs, SAEs, and WDAEs experienced in the active comparator trials were comparable, and there did not appear to be any differences in these safety outcomes among ACL, tiotropium, or formoterol. Notable harms included anticholinergic AEs and cardiovascular AEs; the overall frequency of each was low and similar between-treatment groups in the trials. In the active comparator trial

M/34273/39, the frequency of pharyngitis (1.3% versus 0.6%), dry mouth (1.3% versus 0.6%), and constipation (1.3% versus 0%), was higher in the tiotropium 18 mcg once-daily group compared with the ACL 400 mcg twice-daily group. Due to the identified differences in baseline patient characteristics, the safety populations in the included trials may not be representative of the target treatment population in Canada.

Pharmacoeconomic Summary

Tudorza Genuair (aclidinium bromide [ACL]) is a LAMA indicated for long-term maintenance bronchodilator treatment in patients with COPD, including chronic bronchitis and emphysema. ACL is available as a 400 mcg powder in an inhaler containing 60 actuations. The manufacturer has submitted a confidential price of $[redacted] per inhaler or $[redacted] per day at the recommended dose of 400 mcg twice daily.

The manufacturer submitted a cost-minimization analysis in which ACL was compared with tiotropium or glycopyrronium. Indirect costs were assumed to be the same for the three drugs, except for the cost of secondary pharmacotherapy. Secondary pharmacotherapy was related to drug tolerability and was defined as the alternative COPD treatment that patients would use were they to discontinue the primary COPD treatment due to AEs. The manufacturer assumed that the tolerability of ACL was better than that of both tiotropium and glycopyrronium. The results of the manufacturer's base case suggested that use of ACL would result in annual cost savings to public drug plans of $[redacted] ([redacted]%) per patient compared with tiotropium, or an annual incremental cost of $[redacted] ([redacted]%) per patient compared with glycopyrronium.

The manufacturer's analysis had several limitations, the most significant of which was the assumption that ACL had better tolerability than both tiotropium and glycopyrronium. This assumption was not supported by the manufacturer's indirect comparison of these treatments, which did not demonstrate any significant differences in tolerability or efficacy among ACL, tiotropium, and glycopyrronium. Recalculations by CADTH of the cost of treatments, assuming no difference in tolerability among treatment, did not substantially alter the results: there was a cost saving of $[redacted] ([redacted]%) for ACL compared with tiotropium, but a cost increase of $[redacted] ([redacted]%) per patient compared with glycopyrronium.

Conclusions

Six prospective, double-blind RCTs, including three placebo-controlled trials (N = 1,933) and three active comparator trials (N = 593), that compared ACL to placebo, tiotropium, or formoterol in patients with moderate to severe COPD were included in the review. Compared with placebo, treatment with ACL 400 mcg twice daily was associated with statistically significant improvements in trough FEV_1 ranging from 0.072 L to 0.124 L at 12 weeks in the placebo-controlled trials, and 0.141 L (week 6) to 0.186 L (day 15) in the active comparator trials. The MCID reported for this outcome in the literature is 0.100 to 0.140 L. The magnitude of the treatment effect was comparable to that of tiotropium 18 mcg once daily and formoterol 12 mcg twice daily. None of the trials was designed or powered to assess treatment differences in COPD exacerbations. Statistically significant improvements in symptom-related outcomes with ACL 400 mcg twice daily compared with placebo, as measured by the SGRQ, TDI, patient reports of morning and night-time COPD symptoms, and use of rescue medication were reported. However, the results do not provide robust evidence of clinically meaningful symptomatic benefit as a result of inconsistencies between trials and uncertain clinical relevance of the magnitude of the treatment effect when compared with the MCIDs for these outcomes. Overall, ACL 400 mcg twice daily was well tolerated, and treatment-emergent AEs, SAEs, and WDAEs occurred with similar frequency as

in placebo and other active treatment groups. The most frequently reported AEs were COPD exacerbations, headache, and nasopharyngitis. Rates of anticholinergic and cardiovascular AEs were low and similar between-treatment groups.

Key limitations of the evidence from the trials include baseline patient characteristics that affect the generalizability of the findings to Canadian COPD patients (e.g., age, smoking status, pre-study COPD medication use, proportion of patients with bronchial reversibility, and the exclusion of patients with unstable cardiac conditions) as well as the short duration of the trials. The baseline imbalance in the proportions of patients with severe COPD between-treatment groups in Study LAS-MD-38 Part A compromises interpretation of the results from this trial.

TABLE 1: SUMMARY OF RESULTS

	Placebo-Controlled Trials					
	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400	PL	ACL 400	PL	ACL 400	PL
Trough FEV_1: Baseline						
Mean (SD)	1.508 (0.525)	1.500 (0.489)	1.376 (0.570)	1.332 (0.493)	1.249 (0.519)	1.459 (0.519)
Trough FEV_1: Change from baseline at week 12						
LSM (SE)	0.058 (0.015)	–0.047 (0.015)	0.099 (0.015)	–0.025 (0.015)	0.064 (0.016)	–0.008 (0.015)
LSM diff vs. PL (95% CI)	0.105 (0.065 to 0.144)[a]		0.124 (0.08 to 0.16)[a]		0.072 (0.03 to 0.12)[a]	
COPD exacerbation rate						
Any exacerbation, n (%)	38 (14.1)	56 (20.5)	12 (6.3)	22 (11.9)	19 (10.7)	19 (10.4)
OR (95% CI)	0.64 (0.41 to 1.00)		0.51 (0.24 to 1.07)		0.95 (0.48 to 1.88)	
SGRQ total score: Baseline						
Mean (SD)	47.4 (18.4)	44.9 (16.7)	48.3 (17.8)	45.1 (16.3)	50.4 (16.9)	49.2 (17.4)
SGRQ total score: Week 12						
LSM (SE)	–6.45 (0.72)	–2.36 (0.72)	–4.6 (0.8)	–2.0 (0.8)	–5.4 (1.0)	–4.3 (1.0)
LSM diff vs. PL (95% CI)	–4.10 (–6.06 to –2.13)[a]		–2.5 (–4.7 to –0.4)[a]		–1.1 (–3.8 to 1.6)	
Patients with ≥ 4-point ↓, n (%)	153 (56.9)	107 (39.5)	84 (44.4)	65 (35.9)	77 (44.8)	69 (38.8)
OR diff vs. PL (95% CI)	1.96 (1.375 to 2.802)[a]		1.37 (0.90 to 2.09)		1.28 (0.83 to 1.97)	
TDI focal score: Baseline						
Mean (SD)	6.7 (2.1)	6.7 (2.0)	6.2 (2.1)	6.5 (2.2)	6.0 (1.9)	6.2 (2.2)
TDI focal score: Week 12						
LSM (SE)	1.74 (0.19)	0.86 (0.20)	1.5 (0.2)	0.5 (0.2)	1.3 (0.2)	0.3 (0.2)
LSM diff vs. PL (95% CI)	0.88 (0.35 to 1.41)[a]		1.0 (0.4 to 1.6)[a]		1.0 (0.3 to 1.7)[a]	
Patients with ≥ 1-point ↑, n (%)	156 (59.5)	109 (42.4)	82 (47.7)	53 (32.9)	72 (50.7)	156 (59.5)
OR diff vs. PL (95% CI)	2.06 (1.444 to 2.935)[a]		1.77 (1.12 to 2.79)[a]		1.84 (1.13 to 3.00)[a]	
Discontinued, n (%)	17 (6.3)	41 (14.9)	24 (12.6)	37 (19.9)	39 (16.9)	31 (17.0)
Deaths, n (%)	1 (0.37)	1 (0.37)	1 (0.53)	0 (0)	1 (0.56)	1 (0.55)
AEs, n (%)	**144 (53.5)**	**156 (57.1)**	**85 (44.7)**	**97 (52.2)**	**90 (50.8)**	**90 (49.5)**
SAEs, n (%)	**15 (5.6)**	**18 (5.5)**	**6 (3.2)**	**4 (2.2)**	**8 (4.5)**	**12 (6.6)**
WDAEs, n (%)	**8 (3.0)**	**11 (4.0)**	**8 (4.2)**	**14 (7.5)**	**13 (7.3)**	**8 (4.4)**

	Active Comparator Trials								
	M/34273/34			LAS-MD-33			LAS-MD-38 Part A		
	ACL 400	TIO 18	PL	ACL 400	FOR 12	PL	ACL 400	TIO 18	PL
Trough FEV_1: Baseline									
Mean (SD)	1.463 (0.500)	1.493 (0.469)	1.444 (0.444)	1.422 (0.471)	1.383 (0.458)	1.441 (0.455)	1.462 (0.481)	1.543 (0.536)	1.422 (0.521)
Trough FEV_1: Change from baseline at end of study period									
End point:	**Day 15**			**Day 7**			**Week 6**		
LSM (SE)	0.143 (0.079)	0.107 (0.079)	–0.043 (0.078)	0.130 (0.023)	0.123 (0.023)	–0.025 (0.023)	0.029 (0.018)	–0.009 (0.018)	–0.112 (0.024)
LSM diff ACL vs. PL (95% CI)	0.186 (0.124 to 0.248)[a]			0.154 (0.112 to 0.197)[a]			0.141 (0.083 to 0.199)[a]		
LSM diff TIO vs. PL (95% CI)	0.150 (0.086 to 0.213)[a]			NA			0.102 (0.043 to 0.161)[a]		
LSM diff ACL vs. TIO (95% CI)	0.036 (–0.027 to 0.099)			NA			0.038 (–0.010 to 0.087)		
LSM diff FOR vs. PL (95% CI)	NA			0.148 (0.105 to 0.190)[a]			NA		
LSM diff ACL vs. FOR (95% CI)	NA			0.007 (–0.036 to 0.050)			NA		
Discontinued, n (%)	3 (10.0)			11 (13.9)			5 (2.9)	4 (2.5)	5 (5.9)
Deaths, n (%)	0 (0)			0 (0)			0 (0)	0 (0)	0 (0)
AEs, n (%)	7 (24.1)	3 (10.7)	8 (26.7)	14 (18.9)	11 (14.9)	16 (21.1)	47 (27.5)	47 (29.7)	22 (25.9)
SAEs, n (%)	0 (0)	0 (0)	1 (3.3)	1 (1.4)	0 (0)	2 (2.6)	3 (1.8)	4 (2.5)	0 (0)
WDAEs, n (%)	0 (0)	0 (0)	3 (10.0)	2 (2.7)	1 (1.4)	3 (4.0)	3 (1.8)	2 (1.3)	3 (3.5)

ACL = aclidinium bromide, AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FOR = formoterol; LSM diff = least squares mean difference; OR = odds ratio; PL = placebo; SAE = serious adverse event; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index; TIO = tiotropium; vs. = versus; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A,[14] M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]
[a] Indicates $P < 0.05$.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

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.[18,19] Pathological changes in the lung vary between individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema).[20] There is significant overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD.[19] COPD is largely caused by smoking and is associated with multiple comorbid conditions (e.g., diabetes, ischemic heart disease, muscle wasting, bone loss, anemia, cancer, anxiety, and depression).[10,19]

COPD is a major public health problem and a leading cause of morbidity and mortality worldwide, constituting an economic and social burden that is both substantial and increasing.[21] According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population 35 years of age or older.[22] Among COPD patients in Canada aged 35 to 79 years, 7% had stage II (moderate) or higher COPD.[23] Diagnosing and determining the severity of COPD typically requires the use of spirometry. The two indicators necessary for establishing a diagnosis of COPD are forced expiratory volume in one second (FEV_1), the amount of air that one can expel in one second, and FVC, the amount of air that one can expel upon full inspiration with no limit to duration of expiration. A post-bronchodilator FEV_1/FVC ratio less than 0.7 indicates airway obstruction. The Canadian Thoracic Society classification of COPD severity is summarized in Table 2.

TABLE 2: CANADIAN THORACIC SOCIETY CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY BY SYMPTOMS, DISABILITIES, AND IMPAIRMENT OF LUNG FUNCTION

COPD Stage	Spirometry (post-bronchodilator)	Symptoms
I: Mild	$FEV_1 \geq 80\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD when hurrying on the level or walking up a slight hill
II: Moderate	$50\% \leq FEV_1 < 80\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD causing the patient to stop after walking approximately 100 m (or after a few minutes on the level)
III: Severe	$30\% \leq FEV_1 < 50\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD resulting in the patient being too breathless to leave the house, breathless when dressing or undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure
IV: Very severe	$FEV_1 < 30\%$, predicted, $FEV_1/FVC < 0.7$	NA

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second of expiration; FVC = forced vital capacity; NA = not available.
Source: O'Donnell et al., 2007.[18]

COPD is associated with an increased risk of mortality and was ranked as the fourth leading cause of death in Canada in 2004.[18] By 2020, COPD is projected to become the third leading cause of death worldwide.[21] COPD is associated with high rates of admissions and readmissions to hospital (i.e., of all COPD patients hospitalized in 2006-2007, 18% of COPD patients were readmitted once and 14% were admitted twice).[24] Hospital admissions for COPD exacerbations averaged a 10 day length of stay at a cost

of $10,000 per stay. The total cost of COPD hospitalizations in Canada is estimated at $1.5 billion a year.[25]

1.2 Standards of Therapy

The goals of COPD management are to prevent disease progression, reduce frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[18] Management decisions are guided by disease severity (i.e., symptoms/disability and spirometry) and the frequency of acute exacerbations.

Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and the only intervention shown to slow the rate of lung function decline.[19] Regular exercise with cardiorespiratory conditioning can improve functional status and sensation of dyspnea in COPD patients, more than use of medications alone.

Bronchodilators form the mainstay of pharmacotherapy for COPD.[19] These include short-acting beta-2 agonists (SABAs) such as salbutamol and muscarinic antagonists (SAMAs) such as ipratropium. Long-acting beta-2 agonists (LABAs) such as salmeterol, formoterol, and indacaterol, or muscarinic antagonists (LAMAs) drugs such as tiotropium and glycopyrronium, as well as combinations of fixed-dose LABAs and inhaled corticosteroids (LABA + ICS) such as fluticasone/salmeterol (Advair) or budesonide/formoterol (Symbicort) are the most commonly used treatments for COPD in Canada. Antimuscarinic and beta-2 agonist drugs are often used in combination for maximal improvement in dyspnea and function. ICS may not be useful for mild disease; however, they may have a role in the management of moderate to severe COPD or of persistent symptoms.[26-28] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, in whom ICS use may be beneficial.[29-31] Phosphodiesterase inhibitors (theophylline, and more recently, roflumilast) are adjunctive therapies for COPD management that may be more effective in those with demonstrable neutrophilic airway inflammation. Inhaled medications are most commonly delivered as pressurized metered dose inhalers and dry powder inhalers.

Pulmonary rehabilitation is recommended for moderate to very severe COPD, while oxygen therapy is used in patients with very severe COPD and persistent hypoxemia.

Acute exacerbations of COPD are managed with optimized bronchodilator therapy, oral or parenteral corticosteroids, and antibiotics.[19]

1.3 Drug

Aclidinium bromide (ACL) is a LAMA administered through a pre-loaded, multi-dose dry powder inhaler for the maintenance treatment of COPD. Preclinical studies have shown that ACL is a competitive muscarinic receptor antagonist. It has a similar potency at all five human muscarinic receptors (M1 to M5) but kinetically shows a preference for the M3 receptor, which is known to mediate both contraction of smooth muscle in the respiratory tract and mucous secretion.[32] Non-clinical in vitro and in vivo studies demonstrated rapid, dose-dependent, and long-lasting inhibition by ACL of acetylcholine-induced bronchoconstriction due to its high affinity (Ki, 0.12 nmol/L) and long residence time (half-life of 29 hours) on human M3 receptors. Inhaled ACL is rapidly absorbed, with a plasma concentration reached by 15 minutes in COPD patients and an absolute bioavailability of less than 5%.[10] Following absorption, ACL is rapidly hydrolyzed to two major inactive metabolites.[32] The recommended dose is one inhalation of 400 mcg ACL twice daily, once in the morning and once in the evening.[32] No dosage adjustments are required for elderly patients or patients with renal or hepatic impairment.[32]

Indication under review
Tudorza Genuair (aclidinium bromide) is indicated as a long-term maintenance bronchodilator treatment in patients with COPD, including chronic bronchitis and emphysema. Tudorza Genuair is not indicated for the relief of an acute deterioration of COPD.
Listing criteria requested by sponsor
Listing in a manner similar to tiotropium bromide.

TABLE 3: KEY CHARACTERISTICS OF ACLIDINIUM BROMIDE, TIOTROPIUM BROMIDE, AND GLYCOPYRRONIUM BROMIDE

	Aclidinium bromide	Tiotropium bromide	Glycopyrronium bromide
Mechanism of action	LAMA with similar potency for all (M1 to M5) receptor subtypes but kinetically has a preference for M3.	LAMA with high affinity for M3 receptor subtype.	LAMA with high affinity for M1, M2, and M3 receptor subtypes.
Indication[a]	Long-term maintenance bronchodilator treatment in patients with COPD, including bronchitis and emphysema.	Long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.	Long-term, once-daily maintenance bronchodilator treatment in adult patients with COPD, including chronic bronchitis and emphysema.
Route of administration	One inhalation of 400 mcg twice daily using the Genuair device.	Oral inhalation of contents of a hard capsule (18 mcg) using the HandiHaler device.	Oral inhalation of contents of a hard capsule (50 mcg) using the Breezhaler device.
Recommended dose	400 mcg twice daily, once in the morning and once in the evening	18 mcg once-daily inhalation.	50 mcg once-daily inhalation
Serious side effects / safety issues	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention.	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction. Use in patients with moderate to severe renal impairment only if expected benefit outweighs potential risk.	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention. Use only in patients with severe renal impairment if expected benefit outweighs potential risk.
Other (delivery)	Multi-dose dry powder inhaler	Single dose dry powder inhaler	Single dose dry powder inhaler

COPD = chronic obstructive pulmonary disease; LAMA = long-acting muscarinic antagonist.
[a] Health Canada indication.
Source: Product monographs: Tudorza,[32] Spiriva,[33] Seebri.[34]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ACL 400 mcg inhalation powder twice daily for long-term maintenance bronchodilator treatment in patients with COPD, with or without chronic bronchitis and emphysema.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Adult patients (≥ 18 years of age) with COPD, with or without chronic bronchitis and emphysema **Subgroups:** Age, sex, BMI, COPD severity, smoking status, bronchodilator reversibility, concomitant COPD medication use
Intervention	Aclidinium bromide 400 mcg by inhalation twice daily
Comparators	The following comparators used alone or in combination (as appropriate): • Tiotropium bromide • Glycopyrronium bromide • Ipratropium bromide • SABA (e.g., salbutamol) • LABA (e.g., salmeterol, formoterol, indacaterol) • ICS (in combination only, e.g., LABA + ICS) • PDE4 inhibitors (e.g., roflumilast) • Theophylline • Placebo
Outcomes	**Key efficacy outcomes:** • Pulmonary function tests (e.g., spirometry measures: FEV_1 [trough and peak], FVC, IC) • Exacerbations and time to first exacerbation • All-cause mortality • Health care resource utilization (e.g., hospitalization, emergency room visits) • QoL with a validated measure (e.g., SGRQ) • Exercise tolerance • Symptoms (i.e., day and night) **Other efficacy outcomes:** • Dyspnea (e.g., TDI) • Rescue medication use • Patient adherence/satisfaction • Days of missed work/school **Harms outcomes:** AEs, SAEs, WDAEs, AEs of special interest (e.g., CV, RTIs, anticholinergic AEs)
Study design	Published and unpublished double-blind RCTs

AE = adverse event; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IC = inspiratory capacity; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonist; PDE4 = phosphodiesterase 4; QoL = quality of life; RCT = randomized controlled trial; SABA = short-acting beta-2 agonist; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; RTI = respiratory tract infection; TDI = Transition Dyspnea Index; WDAE = withdrawal due to adverse events.

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

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2: LITERATURE SEARCH STRATEGY the detailed search strategies.

The initial search was completed on October 15, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on March 19, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), including websites of regulatory agencies, health technology assessment agencies, and clinical guideline repositories. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 2: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy.

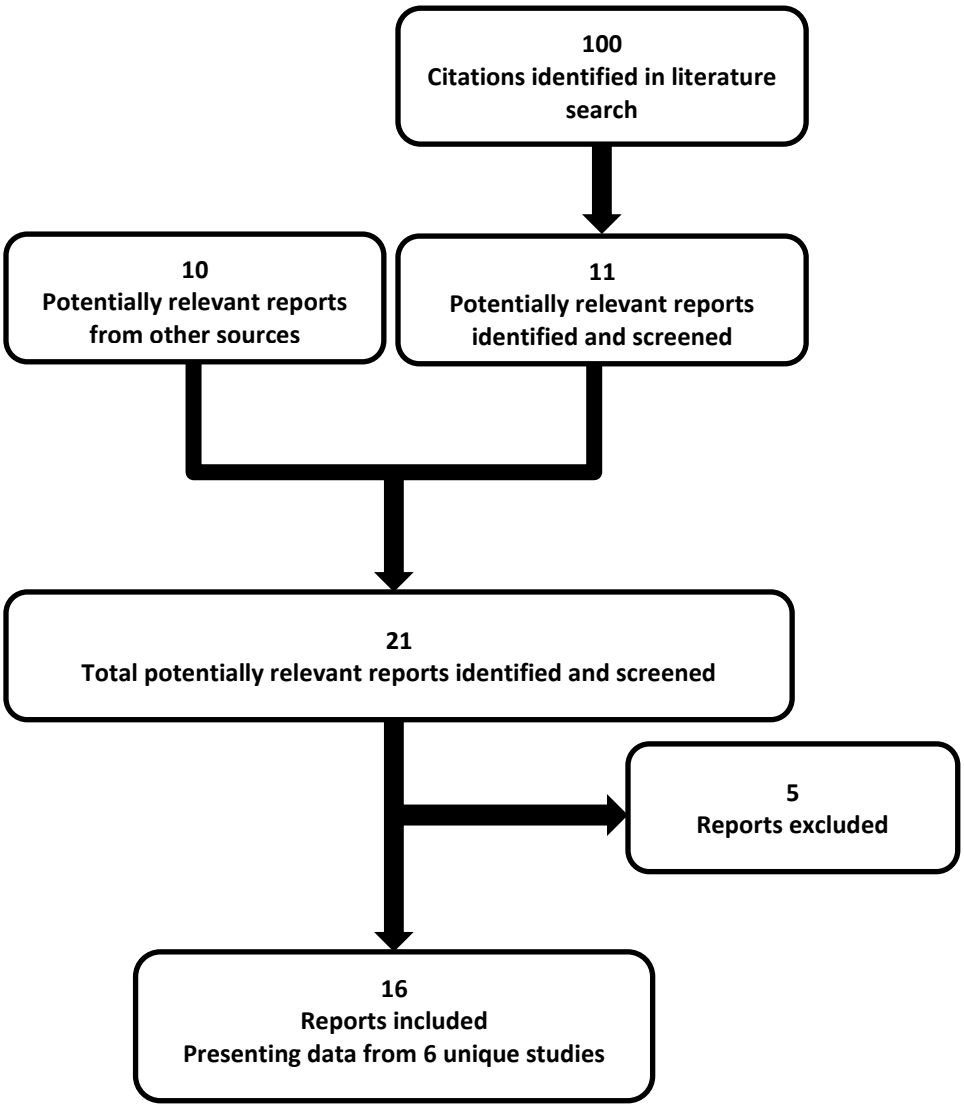
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5 and Table 6; excluded studies (with reasons) are presented in Appendix 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of six studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 (Placebo-Controlled Trials) and Table 6 (Active Comparator Trials) and are described in detail in Section 3.2. A list of excluded studies is presented in Appendix 3: EXCLUDED STUDIES.

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



QUORUM = Quality of Reporting of Meta-Analyses.

3.2 Included Studies

3.2.1 Description of studies

A total of six prospective RCTs met the selection criteria for inclusion in the systematic review, of which three were placebo-controlled trials (M/34273/34 [N = 828], LAS-MD-33 [N = 561], and LAS-MD-38 Part A [N = 544])[1-3] and three were active comparator trials (M/34273/23 [N = 30], M/34273/29 [N = 79], and M/34273/39 [N = 414]).[4-6]

All three placebo-controlled trials were of similar design, as illustrated in Figure 2 to Figure 4. All were phase 3, multi-centre, randomized, double-blind, parallel group, three-group trials with identical objectives — to assess the efficacy and safety/tolerability of ACL 200 mcg and 400 mcg twice daily compared with placebo in patients with moderate to severe COPD (Table 5). As the 200 mcg twice daily dose of ACL was not approved by Health Canada, only the results for the 400 mcg twice daily dose groups will be reported. In all three trials, patients meeting screening criteria entered a two-week run-in period during which prohibited medications (Section 3.2.3 Interventions) were withdrawn, if ethically justified, before the patient entered the study. Patients who still met inclusion criteria were randomized (1:1:1) to one of three treatment groups according to a computer-generated randomization scheme and interactive voice response system (IVRS). It did not appear that patients were stratified for any baseline characteristics. Patients were treated for either 12 weeks (LAS-MD-33 and LAS-MD-38 Part A) or 24 weeks (M/34273/34) and followed up 2 weeks later by phone call or visit. Patients enrolled in Study LAS-MD-38 Part A could enter into an open-label, 40-week treatment continuation phase (LAS-MD-38 Part B), which is summarized in Appendix 6: SUMMARY OF LONG-TERM AND EXTENSION STUDIES.

At visits 1 (screening) and 2 (randomization) in the placebo-controlled trials, all eligible patients were trained on the use of the Genuair inhaler with the use of a placebo dry powder. For training purposes, a patient educational video demonstrating proper use was provided to all sites. In addition, patients were provided with printed instructions. The investigator was required to ensure that the patient understood the instructions and knew how to correctly use the Genuair inhaler at visits 1 and 2. At each visit, the investigator confirmed the patient was using the inhaler properly and provided reinstruction when appropriate. After the patient had completed the inhalation, the investigator assessed whether the patient had properly inhaled the treatment by checking the control window of the inhaler. Last, patients unable to properly use a dry powder or metered dose inhaler, or to perform spirometry measurements, were excluded.

TABLE 5: DETAILS OF INCLUDED STUDIES: PLACEBO-CONTROLLED TRIALS

		M/34273/34	LAS-MD-33	LAS-MD-38 Part A
DESIGNS & POPULATIONS	**Study design**	Phase 3, DB RCT, PG, MC × 24 weeks	Phase 3, DB RCT, PG, MC × 12 weeks	Phase 3, DB RCT, PG, MC × 12 weeks
	Locations	Europe, Russia, Ukraine, Peru, and South Africa	Canada and US	Canada and US
	Randomized (N)	828	561	544
	Inclusion criteria	≥ 40 years of age, current or former smokers (i.e., smoking history ≥ 10 pack-years), moderate to severe COPD by GOLD criteria		
	Exclusion criteria	Key criteria: other significant respiratory conditions (including asthma), RTI, COPD exacerbation ≤ 6 weeks or ≤ 3 months if hospitalized, unstable cardiac conditions, contraindication to anticholinergic drug		
DRUGS	**Intervention**	ACL 200 mcg ACL 400 mcg twice daily by oral inhalation (Genuair)		
	Comparator(s)	Placebo twice daily by oral inhalation (Genuair)		
DURATION	**Phase**			
	Run-in	2 weeks	2 weeks	2 weeks
	Double-blind	24 weeks	12 weeks	12 weeks
	Follow-up	2 weeks	2 weeks	2 weeks
OUTCOMES	**Primary end point**	Change from BL in trough FEV_1 at week 12 (US) or week 24 (EU) regulatory filing	Change from BL in trough FEV_1 at week 12	Change from BL in trough FEV_1 at week 12
	Other end points	FEV_1, FVC, IC at various time points, SGRQ, EQ-5D, TDI, COPD symptoms (EXACT-RS) and exacerbations, rescue med use	Peak FEV_1 at various time points, SGRQ, TDI, COPD night-time symptoms, exacerbations, daily sleep diary, night-time symptom questionnaire, rescue medication use	FEV_1 at various time points, FVC, IC, SGRQ, EQ-5D, TDI
NOTES	**Publications**	Jones et al., 2012[1]	Kerwin et al., 2012[2]	Rennard et al., 2013[3]

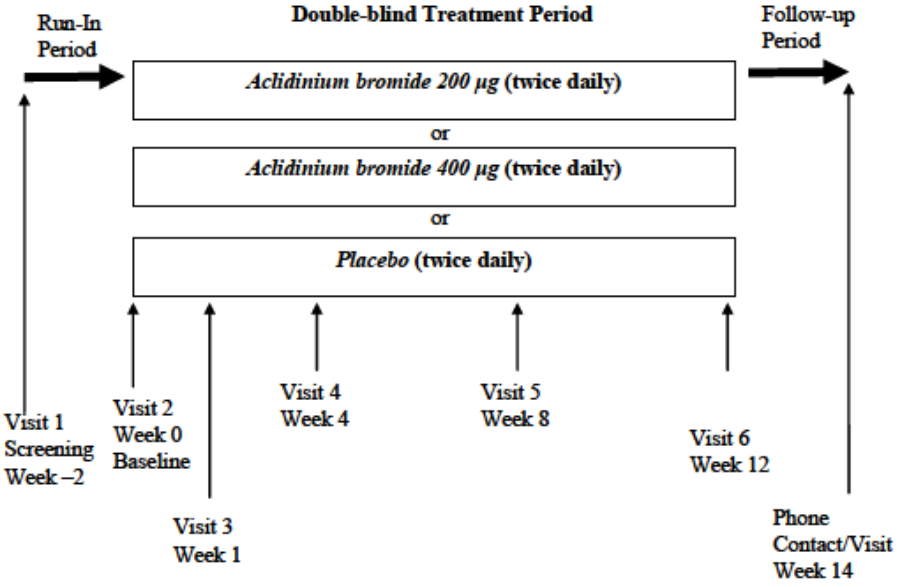
ACL = aclidinium bromide; BDI = Baseline Dyspnea Index; BL = baseline; COPD = chronic obstructive pulmonary disease; DB = double-blind; EU = European Union; EQ-5D = EuroQol 5-Dimensions Questionnaire; EXACT-RS = Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Strategy for the Diagnosis, Management and Prevention of COPD; IC = inspiratory capacity; MC = multi-centre; PG = parallel group; RCT = randomized controlled trial; RTI = respiratory tract infection; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.
Note: 4 additional reports were included.[10,35-37]
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

FIGURE 2: STUDY DESIGN FOR STUDY M/34273/34

	Run-in	Double-blind treatment							Follow-up (FU)
		Randomisation ↓							
Visit no.	1	2	3	4	5	6	7	8	9
Week	-2	0	1	4	8	12	18	24	26
Study day	-14	**1**	7 +/-3	29 +/-3	57 +/-3	85 +/-3	127 +/-3	169 +/-3	+14 +/-3
Study IMP		**Group A: Aclidinium bromide 200 µg BID for 24 weeks**							
		Group B: Aclidinium bromide 400 µg BID for 24 weeks							
		Group C: Placebo (BID for 24 weeks)							

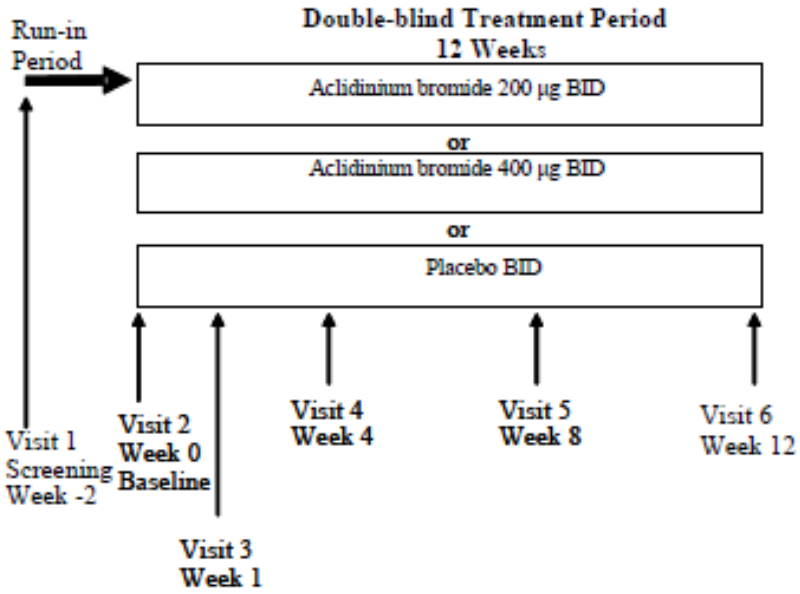
BID = twice daily; IMP = investigational medicinal product.
Source: Clinical Study Report for M/34273/34.[12]

FIGURE 3: STUDY DESIGN FOR STUDY LAS-MD-33



Source: Clinical Study Report for LAS-MD-33.[13]

FIGURE 4: STUDY DESIGN FOR STUDY LAS-MD-38 PART A



BID = twice daily.
Source: LAS-MD-38 Part A.[14]

Two of the three active comparator trials (M/34273/23 and M/34273/29)[4,5] were phase 2, randomized, double-blind, crossover trials that utilized a double-dummy technique, as described in Section 3.2.3 and illustrated in Figure 5 and Figure 6. The objective of Study M/34273/23 was to compare the efficacy and safety of ACL 400 mcg twice daily with placebo twice daily or tiotropium 18 mcg once daily. Study M/34273/29 was a dose-finding study designed to compare the efficacy and safety of ACL 100 mcg, 200 mcg, or 400 mcg twice daily with placebo twice daily or formoterol 12 mcg twice daily. Study M/34273/23 included a run-in period of five to nine days, followed by three treatment periods of 15 days each (Figure 5). The run-in period was used to assess the stability of the patient's COPD and helped to establish the patients' baseline characteristics. Study M/34273/29 included a two-week run-in period to assess disease stability, followed by five treatment periods of seven days each (Figure 6). Prohibited medications (as per Section 3.2.3 Interventions) were gradually withdrawn during the run-in period before the patient entered the study, if considered appropriate by the investigator. The washout phases between periods ranged from 9 to 15 days in both studies, and follow-up was 4 to 6 days (in M/34273/23) and two weeks (in M/34273/29). The clinical expert consulted for this review advised that a washout phase of five to nine days can be considered to be adequate; however, if an ICS were being investigated, a longer washout phase would be required. Patients were randomized in equal numbers to one of the three treatment groups (400 mcg ACL, placebo, 18 mcg tiotropium in M/34273/23) or to one of the five treatment groups (ACL 100 mcg, ACL 200 mcg, ACL 400 mcg, placebo, formoterol 12 mcg in M/34273/29). Patients did not appear to be stratified for any baseline characteristics (Table 6).

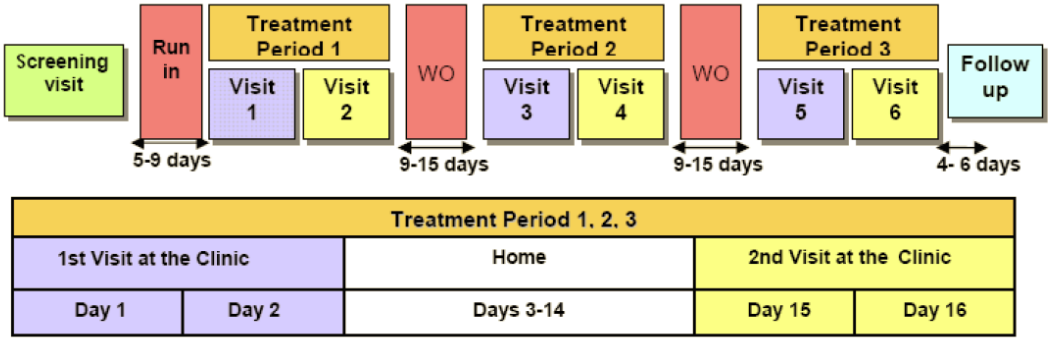
Similar to the placebo-controlled trials, in the active comparator trials the investigator ensured that patients were using the different inhaler devices properly through appropriate training at visit 1 (screening) and day 1 of each treatment period, before dosing with the study drug. Patients unable to properly use a dry powder inhaler or a metered dose inhaler or to perform spirometry measurements were excluded.

TABLE 6: DETAILS OF INCLUDED STUDIES: ACTIVE COMPARATOR TRIALS

		M/34273/23	M/34273/29	M/34273/39
DESIGNS & POPULATIONS	**Study design**	Phase 2, DB, DD, 3-way CXO RCT × 3 periods of 15 days	Phase 2, DB, DD, 5-way CXO MC RCT × 5 periods of 7 days	Phase 3, DB, DD, PG, MC RCT × 6 weeks
	Locations	Germany	Germany and Belgium	Czech Republic, Germany, Hungary, and Poland
	Randomized (N)	30	79	414
	Inclusion criteria	≧ 40 years of age, current or former smokers (i.e., smoking history ≥ 10 pack-years), moderate to severe COPD by GOLD criteria, post-salbutamol FEV_1 predicted < 80% and ≥ 30% and FEV_1/FVC < 70%		
	Exclusion criteria	Key criteria: other significant respiratory conditions (including asthma), RTI, COPD exacerbation ≤ 6 weeks or ≤ 3 months if hospitalized, unstable CV conditions, contraindication to anticholinergic drug		
DRUGS	**Intervention**	ACL 400 mcg twice daily by oral inhalation (Genuair™)	ACL 100 mcg ACL 200 mcg ACL 400 mcg twice daily by oral inhalation (Genuair™)	ACL 400 mcg twice daily by oral inhalation (Genuair™)
	Comparator(s)	TIO 18 mcg once daily by oral inhalation (HandiHaler) Placebo twice daily by oral inhalation (Genuair or HandiHaler)	FOR 12 mcg twice daily by oral inhalation (Aerolizer) Placebo twice daily by oral inhalation (Genuair or Aerolizer)	TIO 18 mcg once daily by oral inhalation (HandiHaler) Placebo twice daily by oral inhalation (Genuair)
DURATION	**Phase**			
	Run-in	5 to 9 days	2 weeks	2 to 3 weeks
	Double-blind	3 × 15 days	5 × 7 days	6 weeks
	Follow-up	4 to 6 days	2 weeks	None
OUTCOMES	**Primary end point**	Change from BL in normalized FEV_1 $AUC_{0\text{-}12/12h}$ at day 15	Change from BL in normalized FEV_1 $AUC_{0\text{-}12/12h}$ at day 7	Change from BL in normalized FEV_1 $AUC_{0\text{-}24/24h}$ at week 6
	Other end points	Change from BL in normalized FEV_1 $AUC_{0\text{-}12h}$ at various time points, $AUC_{12\text{-}24h}$, peak and trough FEV_1 and FVC, symptoms (patient diary) and rescue medication use	Change from BL in normalized FEV_1 $AUC_{12\text{-}24\ h}$ and $AUC_{0\text{-}24h}$ at various time points, peak and trough FEV_1 and FVC, symptoms (patient diary) and rescue medication use	Changes from BL in normalized FEV_1 $AUC_{0\text{-}12}$ and $AUC_{12\text{-}24h}$, trough and peak FEV_1 and FVC, symptoms (EXACT-RS)
NOTES	**Publications**	Fuhr et al., 2012[4]	Singh et al., 2012[5]	Beier et al., 2013[6]

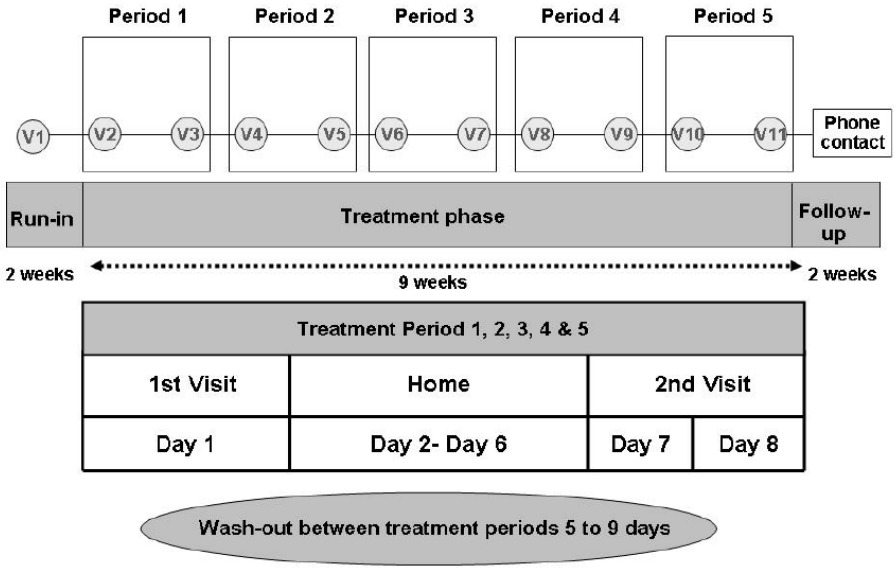
ACL = aclidinium bromide; AUC = area under the curve; BL = baseline; COPD = chronic obstructive pulmonary disease; CXO = crossover; DB = double-blind; DD = double-dummy; EXACT-RS = Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in one second; FOR = formoterol; FVC = forced vital capacity; GOLD = Global Strategy for the Diagnosis, Management and Prevention of COPD; MC = multi-centre; PG = parallel group; RCT = randomized controlled trial; TIO = tiotropium.
Note: Only results for the ACL 400 mcg twice daily treatment group are reported in the clinical review.
Source: Clinical Study Reports for M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

FIGURE 5: STUDY DESIGN FOR STUDY M/34273/23



WO = washout.
Source: Clinical Study Report for M/34273/23.[15]

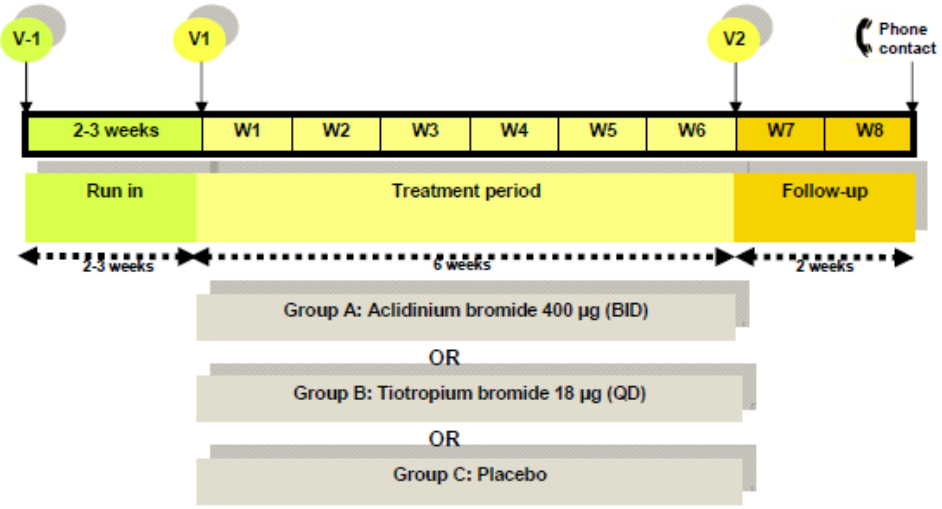
FIGURE 6: STUDY DESIGN FOR STUDY M/34273/29



V = study visit.
Source: Clinical Study Report for M/34273/29.[16]

The third active comparator trial, Study M/34273/39, was a phase 3, randomized, double-blind, parallel group study that compared the efficacy and safety of ACL 400 mcg twice daily with tiotropium 18 mcg once daily or placebo twice daily utilizing a double-dummy technique, as described in Section 3.2.3. Patients were randomized to one of the three groups (ACL 400 mcg, tiotropium 18 mcg, or placebo) in a ratio of two patients to each treatment group for each patient receiving placebo, as illustrated in Figure 7.

FIGURE 7: STUDY DESIGN FOR STUDY M/34273/39



BID = twice daily; V = study visit; W = week.
Source: Clinical Study Report for M/34273/39.[17]

3.2.2 Populations

a) Inclusion and exclusion criteria

Inclusion criteria were similar across all six included trials (Table 5 and Table 6). All trials included adult male and female patients who were at least 40 years of age and who were current or former cigarette smokers (i.e., smoking history ≥ 10 pack-years). Patients were required to have a diagnosis of moderate to severe COPD according to the Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) criteria (i.e., post-bronchodilator FEV_1 predicted < 80% and ≥ 30% and FEV_1/FVC < 70%).[21] Key exclusion criteria are listed in Table 5 and Table 6, and, as noted, patients with unstable or clinically significant cardiovascular conditions were excluded from the trials. This included patients who had had myocardial infarction during the previous six months or who had unstable or newly diagnosed arrhythmia within three months before screening. Across all trials, patients unable to properly use a multi-dose dry powder inhaler or a pressurized metered dose inhaler, or to perform spirometry measurements, were excluded.

b) Baseline characteristics

In keeping with the similar inclusion criteria, the patient populations across the trials were comparable (Table 7). The mean age of patients ranged between 61 to 65 years of age, with the exception of Study M/34273/23, which enrolled slightly younger patients (i.e., mean age 58.4 years). In general, the majority of patients were less than 70 years of age (75.7% to 83.5%), and between 32.2% and 39.6% of patients were aged less than 60 years across treatment groups. The exception to this was for Study LAS-MD-33, which included a lower proportion of patients less than 60 years (23.2% to 24.7%) and a higher percentage of patients aged 70 years or more (29.6% to 31.1%) compared with the other trials. More than 50% of patients across all trials were male and approximately 95% or more were Caucasian, reflecting the demographic characteristics of the geographic locations of the trials. A high percentage (42.1% to 63.3%) of patients were current smokers; although the proportions of smokers/ex-smokers, smoking duration, and consumption (mean pack-years) appeared to be similar among treatment groups in individual trials. The majority of patients (> 92%) were classified as having moderate or severe COPD, as per the inclusion criteria. In Study LAS-MD-38 Part A, there was a baseline imbalance in COPD severity between-treatment groups, with patients with more severe COPD enrolled in the ACL 400 mcg group

than in the placebo group.[3] The proportion of patients with moderate COPD was 44.6% versus 62.1%, and the proportion of patients with severe COPD was 54.2% versus 36.8%, in the ACL 400 mcg and placebo groups, respectively. This imbalance was also observed in the post-bronchodilator FEV_1 values observed at screening (i.e., 1.45 L ± [standard deviation] 0.52 L in the ACL 400 mcg group compared with 1.64 L ± 0.52 L in the placebo group).[3] The mean duration of COPD ranged from 6.4 to 10.4 years across the trials; however, durations were similar between-treatment groups in individual trials. The rate of self-reported COPD exacerbations in the prior year was low, ranging from 0.3 to 1.7 exacerbations in the trials where it was reported, likely reflective of the inclusion of only stable patients following the run-in phase. The mean values for post-bronchodilator FEV_1 predicted ranged from 50.17% to 56.56% and FEV_1/FVC ratios ranged from 45.1% to 52.75%. Post-bronchodilator reversibility (calculated as 100 × (FEV_1 post-bronchodilator) – (FEV_1 pre-bronchodilator) / (FEV_1 pre-bronchodilator) ranged from 10.6% to 15.7%.

Approximately 77% to 100% of patients had used COPD medications before study entry (Table 8). There was considerable variation in the proportion of patients who had used ICS (8.4% to 46.7%) or LABA + ICS therapy (14.3% to 37.5%) among trials; however, in general the use of the different categories of medications was similar across treatment groups in individual trials. The low use of LABA plus ICS therapy in this patient population may be attributed to the geographic location of the trials (primarily Eastern Europe) and to lack of access to combination therapy, in contrast to what would be expected in Canada. Please see Section 3.5 Critical Appraisal for further discussion. Approximately one-quarter to one-third of patients (25.6% to 33.3%) had previously used LAMA therapy. There were very few patients who had used systemic corticosteroids or who required oxygen therapy. Please see Section 3.2.3 for further details of prohibited medications and concomitant use of medications.

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS (SAFETY POPULATION)

Characteristic	M/34273/34		LAS-MD-33		LAS-MD-38 Part A		M/34273/23	M/34273/29	M/34273/39		
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)	TOTAL (N = 30)[a]	TOTAL (N = 79)[a]	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Age (years)											
Mean (SD)	**62.9 (8.4)**	**62.0 (8.0)**	**64.9 (9.5)**	**65.1 (9.2)**	**63.2 (9.0)**	**61.7 (9.3)**	58.4 (7.9)	61.1 (8.5)	**61.8 (8.2)**	**62.8 (7.9)**	**62.2 (8.2)**
Min, Max	**41, 82**	**41, 84**	**40, 89**	**40, 89**	**41, 82**	**41, 84**	43, 73	41, 81	**41, 80**	**45, 83**	**42, 86**
< 60 years ≥ 60 to < 70 years ≥ 70 years	**96 (35.7)** **108 (40.2)** **65 (24.2)**	**102 (37.4)** **121 (44.3)** **50 (18.3)**	**44 (23.2)** **87 (45.8)** **59 (31.1)**	**46 (24.7)** **85 (45.7)** **55 (29.6)**	**57 (32.2)** **77 (43.5)** **43 (24.3)**	**72 (39.6)** **72 (39.6)** **38 (20.9)**	NR	NR	**65 (38.0)** **73 (42.7)** **33 (19.3)**	**56 (35.4)** **68 (43.0)** **34 (21.5)**	**28 (32.9)** **43 (50.6)** **14 (16.5)**
Male, n (%)	**182 (67.7)**	**189 (69.2)**	**100 (52.6)**	**96 (51.6)**	**89 (50.3)**	**100 (54.9)**	19 (63.3)	59 (74.7)	**114 (66.7)**	**116 (73.4)**	**48 (56.5)**
Caucasian/white, n (%)	**257 (95.5)**	**260 (95.2)**	**181 (95.3)**	**175 (94.1)**	**160 (90.4)**	**168 (92.3)**	30 (100.0)	79 (100.0)	**171 (100)**	**158 (100)**	**84 (98.8)**
BMI (kg/m^2), mean (SD)	**27.0 (4.8)**	**26.6 (5.2)**	**27.6 (5.0)**	**27.5 (5.2)**	**27.5 (5.7)**	**27.2 (5.9)**	26.1 (4.4)	27.1 (5.1)	**27.5 (4.9)**	**27.6 (4.8)**	**26.7 (4.9)**
Smoking status, n (%)											
Current smoker	**148 (55.0)**	**144 (52.8)**	**80 (42.1)**	**87 (46.8)**	**89 (50.3)**	**102 (56.0)**	19 (63.3)	45 (57.0)	**93 (54.4)**	**84 (53.2)**	**47 (53.3)**
Ex-smoker	**121 (45.0)**	**129 (47.3)**	**110 (57.9)**	**99 (53.2)**	**88 (49.7)**	**80 (44.0)**	11 (36.7)	34 (43.0)	**78 (45.6)**	**74 (46.8)**	**38 (44.7)**
Smoking duration[b] (years), mean (SD)	**39.8 (9.9)**	**38.3 (10.1)**	**NR**	**NR**	**NR**	**NR**	39.4 (9.0)	40.5 (8.4)	**38.3 (10.0)**	**40.2 (9.9)**	**38.7 (8.6)**
Consumption[b] (pack-years), mean (SD)	**41.7 (21.1)**	**38.9 (18.3)**	**57.2 (28.5)**	**52.7 (28.1)**	**54.2 (27.7)**	**52.6 (28.4)**	41.1 (15.9)	50.7 (26.8)	**41.5 (22.4)**	**45.0 (21.8)**	**39.6 (15.4)**
COPD severity (GOLD Stage), n (%)											
Stage I (mild)	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**2 (1.1)**	0 (0)	0 (0)	**0 (0)**	**0 (0)**	**0 (0)**
Stage II (moderate)	**184 (68.7)**	**178 (65.9)**	**118 (62.1)**	**111 (59.7)**	**79 (44.6)**	**113 (62.1)**	19 (63.3)	46 (59.0)	**108 (63.2)**	**104 (66.2)**	**58 (68.2)**

Characteristic	M/34273/34		LAS-MD-33		LAS-MD-38 Part A		M/34273/23	M/34273/29	M/34273/39		
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)	TOTAL (N = 30)[a]	TOTAL (N = 79)[a]	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Stage III (severe)	**84 (31.3)**	**92 (34.1)**	**68 (35.8)**	**73 (39.2)**	**96 (54.2)**	**67 (36.8)**	10 (33.3)	32 (41.0)	**63 (36.8)**	**53 (33.8)**	**27 (31.8)**
Stage IV (very severe)	**0 (0)**	**0 (0)**	**1 (0.5)**	**1 (0.5)**	**0 (0)**	**0 (0)**	1 (3.3)	0 (0)	**0 (0)**	**0 (0)**	**0 (0)**
COPD duration (years), mean (SD)	**7.2 (6.7)**	**6.4 (5.4)**	**8.9 (6.4)**	**8.5 (6.5)**	**8.5 (6.2)**	**7.7 (6.0)**	9.2 (6.9)	10.4 (7.9)	**8.8 (5.9)**	**8.2 (6.0)**	**9.6 (6.7)**
Self-report COPD exacerbations in prior year, mean (SD)	**0.4 (0.9)**	**0.5 (0.7)**	**1.4 (1.5)**	**1.4 (1.0)**	**1.6 (1.6)**	**1.7 (1.1)**	NR	NR	**0.5 (0.7)**	**0.3 (0.6)**	**0.3 (0.5)**
Screening lung function: Post-bronchodilator, mean (SD)											
FEV_1 (L)	**1.63 (0.50)**	**1.62 (0.46)**	**1.53 (0.54)**	**1.56 (0.56)**	**1.45 (0.52)**	**1.64 (0.52)**	1.71 (0.48)	1.64 (0.46)	**1.61 (0.50)**	**1.67 (0.54)**	**1.57 (0.52)**
FEV_1 % pred. (L)	**56.20 (12.2)**	**56.56 (12.8)**	**54.10 (12.9)**	**54.64 (13.5)**	**50.17 (13.1)**	**55.18 (13.2)**	55.8 (13.7)	53.7 (11.8)	**55.8 (13.3)**	**56.0 (13.2)**	**55.5 (11.8)**
FEV_1/FVC ratio (%)	**49.74 (10.2)**	**49.34 (10.7)**	**51.5 (10.2)**	**52.75 (10.5)**	**49.18 (10.3)**	**53.3 (11.2)**	46.2 (10.3)	45.1 (9.7)	**47.6 (11.5)**	**48.6 (11.1)**	**48.4 (10.9)**
Bronchial reversibility (%)	**11.3 (12.9)**	**12.3 (15.7)**	**15.5 (12.0)**	**17.1 (15.5)**	**17.0 (12.6)**	**15.7 (13.9)**	18.2 (11.9)	13.7 (11.9)	**14.6 (14.2)**	**11.2 (12.4)**	**11.0 (10.6)**
Reversible, n (%)	**81 (30.2)**	**81 (30.0)**	**77 (40.5)**	**80 (43.0)**	**67 (37.9)**	**76 (41.8)**	16 (53.3)	33 (42.3)	**72 (42.1)**	**53 (33.8)**	**23 (27.1)**
SGRQ total score, mean (SD)	**47.6 (17.7)**	**45.1 (15.8)**	**48.3 (17.8)**	**45.2 (16.2)**	**50.4 (16.9)**	**49.2 (17.4)**	NR	NR	**NR**	**NR**	**NR**
BDI focal score, mean (SD)	**6.7 (2.1)**	**6.7 (2.0)**	**6.2 (2.1)**	**6.5 (2.2)**	**6.0 (1.9)**	**6.2 (2.2)**	NR	NR	**NR**	**NR**	**NR**

ACL = aclidinium bromide; BDI = Baseline Dyspnea Index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Strategy for the Diagnosis, Management and Prevention of COPD; NR = not reported; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium bromide.

[a] Crossover studies; therefore, the total number of patients were included in each treatment group.

[b] Includes both current and ex-smokers.

Note: For studies M/34273/34, LAS-MD-33 and LAS-MD-38 Part A the ACL 200 mcg treatment group is not included in the above table.

Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A,[14] M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

TABLE 8: NUMBER (%) OF PATIENTS USING PRE-STUDY COPD MEDICATION BY THERAPEUTIC CATEGORY (SAFETY POPULATION)

Prior COPD medication	M/34273/34 (N = 819)	LAS-MD-33 (N = 561)	LAS-MD-38 Part A (N = 544)	M/34273/23 (N = 30)[a]	M/34273/29 (N = 79)[a]	M/34273/39 (N = 414)
Any category	736 (89.9)	455 (81.3)	419 (77.3)	30 (100)	63 (79.8)	359 (86.7)
SABA	413 (50.4)	359 (64.1)	284 (52.4)	30 (100)	46 (58.2)	257 (62.1)
ICS	312 (38.1)	47 (8.4)	63 (11.6)	14 (46.7)	8 (10.1)	87 (21.0)
LABA	248 (30.3)	27 (4.8)	25 (4.6)	1 (3.3)	14 (17.7)	148 (35.7)
LAMA	221 (27.0)	169 (30.2)	143 (26.4)	10 (33.3)	24 (30.4)	106 (25.6)
Xanthines	171 (20.9)	8 (1.4)	18 (3.3)	—	4 (5.1)	78 (18.8)
SAMA	131 (16.0)	28 (5.0)	13 (2.4)	1 (3.3)	3 (3.8)	78 (18.8)
LABA + ICS	117 (14.3)	210 (37.5)	166 (30.6)	7 (23.3)	24 (30.4)	109 (26.3)
SABA + SAMA	88 (10.7)	2 (0.4)	65 (12.0)	—	4 (5.1)	22 (5.3)
Systemic corticosteroids	21 (2.6)	—	—	—	—	7 (1.7)
Influenza vaccine	4 (0.5)	—	—	—	—	1 (0.2)
Oxygen	7 (0.9)	33 (5.9)	—	—	—	2 (0.5)
Leukotriene	3 (0.4)	—	18 (3.3)	—	—	1 (0.2)
SABA + ICS	1 (0.1)	—	—	—	—	—
Oral PDE4	—	—	—	—	—	1 (0.2)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid(s); LABA = long-acting beta-2 agonists; LAMA = long-acting muscarinic antagonists; PDE4 = phosphodiesterase-4; SABA = short-acting beta-2 agonists; SAMA = short-acting muscarinic antagonists.

[a] Crossover studies; therefore, the total number of patients were included in each treatment group.

Note: For studies M/34273/34, LAS-MD-33 and LAS-MD-38 Part A the ACL 200 mcg treatment group is included in the above table.

Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A,[14] M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

3.2.3 Interventions

In all six included trials, ACL 400 mcg was administered by oral inhalation (one puff) using the Genuair multi-dose dry powder inhaler twice daily, once in the morning (at approximately 8:00 a.m. to 10:00 a.m.) and once in the evening (at approximately 8:00 p.m. to 10:00 p.m.). In the placebo-controlled trials, a matched placebo-to-ACL was administered by oral inhalation using the Genuair inhaler twice daily in the same manner as active treatment.

All three active comparator trials utilized double-dummy techniques. In Study M/34273/23, depending upon the treatment period, each morning the patient would inhale from two devices (i.e., either ACL 400 mcg through the Genuair inhaler + placebo-to-tiotropium, tiotropium 18 mcg through the HandiHaler + placebo to ACL, or placebo to ACL + placebo-to-tiotropium). In the evening, the patient would inhale from only one device (i.e., either ACL 400 mcg through the Genuair inhaler or placebo-to-ACL) as tiotropium is dosed only once daily. In Study M/34273/29, during each treatment period, patients would receive either ACL 100 mcg, 200 mcg or 400 mcg through the Genuair inhaler + placebo-to-formoterol; formoterol 12 mcg through the Aerolizer inhaler + placebo-to-ACL; or placebo-to-ACL + placebo-to-formoterol, twice daily, in both the morning and evening. In Study M/34273/39, patients were supplied with two Genuair inhalers (pre-loaded with either ACL 400 mcg or matched placebo) and

one tiotropium HandiHaler (with tiotropium or matched placebo). Patients were instructed to use both inhalers each morning and the Genuair inhaler only each evening.

Training on the correct use of the inhalers was provided at screening, before randomization. If needed, patients were re-instructed at each visit. Permitted concomitant medications included albuterol/salbutamol (100 mcg per puff as rescue medication), ICS, oral or parenteral corticosteroids (≤ 10 mg/day of prednisone or 20 mg every other day or equivalent), theophylline, oxygen therapy, and H_1 receptor antagonist antihistamines if treatment was stable for 4 weeks or more before screening. Rescue medication and other permitted COPD medications were discontinued at least six hours before study visits and continued after the study visit.

Prohibited medications included anticholinergic drugs (e.g., tiotropium, ipratropium, oxitropium), beta-2 agonists (e.g., inhaled fenoterol and terbutaline; oral salbutamol, terbutaline, and metaproterenol; inhaled formoterol and salmeterol), combinations of inhaled drugs, continuous oral or parenteral corticosteroids, methylxanthines, and others (e.g., cromolyn sodium, nedocromil, leukotriene receptor antagonists, and non-selective beta-1 blockers). In some cases, patients taking these medications could still participate in the trials if treatment was interrupted (i.e., withdrawn gradually before the patient entered the study, presumably with the option to continue after study completion) at least 72 hours (LAMAs) and 12 hours (SAMAs) before screening. In addition, patients on SABAs (except for salbutamol as a rescue) and oral beta-2 agonists or LABAs were required to interrupt treatment at least 6 hours and 48 hours, respectively, before screening to be able to participate in the trials. Patients on combinations of LABA + ICS were required to interrupt treatment 48 hours before screening, although patients were permitted to use the same ICS as monotherapy. Fixed inhaled combinations of a SABA and an anticholinergic drug (e.g., Combivent) were prohibited, but patients could participate if treatment was interrupted at least 12 hours before screening. In addition, although methylxanthines, cromolyn sodium, nedocromil, leukotriene receptor antagonists, and non-selective beta-1 blockers were prohibited, patients could still participate if adequate time (i.e., ranging from 72 hours to six weeks) had passed from interruption of therapy to screening.

In the case of a COPD exacerbation, the investigators could initiate treatment as they deemed appropriate. The use of a prohibited medication did not constitute a reason for study discontinuation provided it was a short course of treatment (< 10 days duration). Antibiotics or oxygen therapy were permitted at the discretion of the investigator, but only as a short course.

3.2.4 Outcomes

a) Pulmonary function tests

In the placebo-controlled trials, the primary efficacy outcome was the change from baseline in the morning pre-dose (trough) FEV_1 at 12 weeks (M/34273/34 for the US filing, LAS-MD-33, and LAS-MD-38 Part A) and 24 weeks (M/34273/34 for the EU filing). The MCID is reported to be a change of 0.100 L to 0.140 L (Appendix 5: VALIDITY OF OUTCOME MEASURES). According to the Health Canada Reviewer's Report,[10] in Canada the primary end point was considered to be at 12 weeks for Study M/34273/34.

The primary efficacy outcome in the active comparator trials was the normalized area under the curve (AUC) for FEV_1 over 12 or 24 hours measured on the last day of the study period: $AUC_{0\text{-}12/12h}$ on day 7 (M/34273/23) or day 15 (M/34273/29) or $AUC_{0\text{-}24/24h}$ at week 6 (M/34273/39). The AUC was calculated using the trapezoidal method from serial measurements of FEV_1. The time interval represents the time period for which data were collected divided by the number of hours over which the data are averaged.

For all included trials, the baseline for all spirometric variables (FEV_1, FVC, and IC) was defined as the average of two values measured before the first dose of study drug on day 1 (i.e., day 1 of each treatment period for the active comparator trials). Trough FEV_1 was the average of two pre-dose FEV_1 measurements conducted just before the morning dose of study drug. Standardized spirometric measurements (FEV_1 and FVC) were also performed at 0.5, 1, 2, and 3 hours following the morning dose at each post-randomization visit. In addition, IC measurements were obtained 3 hours post-dose at pre-specified study visits. Spirometry measurements were performed by a centralized spirometry company (CareFusion), and all study centres had identical spirometry equipment, detailed study manuals, and trained study personnel. Only technically adequate spirometry measurements were accepted (i.e., those meeting acceptability and reproducibility criteria conducted under standardized conditions).

b) COPD exacerbations

COPD exacerbations were reported as an additional efficacy outcome in the placebo-controlled trials. COPD exacerbations were defined as an increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, or sputum purulence) during at least two consecutive days, with severity categorized as follows:

Mild: Increase of COPD symptoms during at least two consecutive days, self-managed by the patient at home by increasing usual COPD medication (SABA or ICS).

Moderate: Increase of COPD symptoms during at least two consecutive days that does not lead to hospitalization, but is treated with antibiotics or systemic corticosteroids or both, or an increase in dose of systemic corticosteroids.

Severe: Increase in COPD symptoms during at least two consecutive days, which leads to hospitalization (overnight stay at hospital or emergency room).

COPD exacerbations were evaluated by the investigator at each visit on the basis of the information entered by the patient into an electronic diary. If the patient had been off oral steroids and antibiotics for ≥ 14 days since a prior exacerbation, an exacerbation was defined as new. Episodes of COPD exacerbation were not recorded as AEs, but rather were reported in a health care resource utilization electronic case report form (eCRF); however, COPD exacerbations that met the criteria of "severe" were reported as SAEs.

c) Health care resource utilization

All three placebo-controlled trials evaluated health care resource utilization. In Studies M/34273/34 and LAS-MD-33, health care resource utilization was captured on an eCRF. In Study LAS-MD-38 Part A, patients were administered a COPD Resource Utilization Questionnaire developed by the manufacturer. Hospitalization was defined as an overnight stay at the hospital or emergency room.

d) St. George's Respiratory Questionnaire

Disease-specific health status was evaluated by means of the SGRQ, which is a standardized, self-administered instrument for measuring impaired health and perceived well-being in respiratory disease. Details on the SGRQ are provided in Appendix 5: VALIDITY OF OUTCOME MEASURES. The SGRQ contains 50 items divided into three dimensions: symptoms (measuring distress due to respiratory symptoms), activity (measuring the effect of disturbances on mobility and physical activity), and impacts (measuring the psychosocial impact of the disease). Total SGRQ scores range from 0 to 100, with higher values indicating lower health-related quality of life. A score of zero indicates no impairment of quality of life. The MCID has been reported to be an improvement of at least four units in the SGRQ total score. Negative changes in scores indicate improvement in health-related quality of life.

e) EuroQol 5-Dimensions Questionnaire

The EQ-5D is a self-administered, three-level (i.e., no problems, some/moderate problems, extreme problems), five-dimensional (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) generic measure of health-related quality of life. It is a generic instrument applicable to a wide range of health conditions and was used to complement the disease-specific SGRQ in Studies M/34273/34 and LAS-MD-38 Part A. Information from the EQ-5D was used to calculate a self-rated health index, which was converted to a weighted healthy state index by applying preference weights elicited from general population samples. The EQ visual analogue scale was a vertical graduated (0 to 100) 20 cm scale used to record patient self-rated health status, with 100 representing the best imaginable health state and 0 the worst. Although listed as an outcome, the EQ-5D was not performed in Study LAS-MD-33 because the protocol amendment adding the EQ-5D was approved after patients had been randomized; thus, a baseline EQ-5D could not be obtained.

f) Respiratory symptoms

In Studies M/34273/34 and M/34273/39, respiratory symptoms were based on the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) – Respiratory Symptoms (E-RS) algorithm, derived from the EXACT – Patient-Reported Outcomes (EXACT-PRO) instrument (Appendix 5: VALIDITY OF OUTCOME MEASURES). The total score for the E-RS ranges from 0 to 40, with higher scores indicating more severe symptoms. Daily symptoms were assessed by patients at the same time each morning and evening using the EXACT-PRO tool, and responses were recorded in an electronic diary. Night-time and morning symptoms of COPD were assessed by patients each morning by completing a six-item questionnaire asking about presence of breathlessness, cough, expectoration, chest tightness, or congestion and wheezing at night, and responses were entered into an electronic diary. The questionnaire assessed how these symptoms were disturbing sleep and limiting the patients' morning activities. Symptoms were recorded as follows: Sleep disturbed: 0 = No, it was not disturbed by these symptoms; 1 = Slightly disturbed by these symptoms; 2 = Moderately disturbed by these symptoms, but I was still able to get some sleep; 3 = Severely disturbed by these symptoms; 4 = Extremely disturbed by these symptoms, these symptoms kept me awake most of the night; Lung condition: 1 = Very poor; 2 = Poor; 3 = Fair; 4 = Good; 5 = Very good. Morning-time disturbance: 0 = These symptoms did not limit what wanted to do this morning; 1 = Slightly limited what I wanted to do this morning; 2 = Moderately limited what I wanted to do this morning; 3 = Severely limited what I wanted to do this morning; 4 = Extremely limited in what I wanted to do, I was unable to do what I wanted to do this morning.

In Study LAS-MD-33, symptoms were self-recorded by patients using a non–disease-specific Daily Sleep Diary[38] and a Night-time Symptoms (Modified Welte) Questionnaire.[39] Night-time symptoms were recorded as follows: Frequency: 0 = never, 1 = 1 to 2 times, 2 = 3 to 4 times, 3 = 5 to 6 times, 4 = 7 or more times; Quantity of sputum production: 0 = none, 1 = amount of 1 teaspoon, 2 = amount of 1 tablespoon, and 3 = more than 1 tablespoon; Activity: 0 = none; 1 = symptoms present, but caused little or no discomfort; 2 = mild symptoms that were unpleasant, but caused little or no discomfort; 3 = moderate symptoms that caused discomfort, but did not affect normal daily activities; 4 = severe symptoms that interfered with normal daily activities; Sleep: 0 = none; 1 = symptoms causing early awakening or awakening once during the night; 2 = symptoms causing early awakening or awakening two or more times during the night; 3 = symptoms causing awakening for most times during the night; 4 = symptoms that were so severe that I could not sleep at all. The daily average rating of severity of breathlessness for the first hour on getting up in the morning during week 12 was scored as: 0 = none; 1 = symptoms present, but caused little or no discomfort; 2 = mild symptoms that were unpleasant, but caused little or no discomfort; 3 = moderate symptoms that caused discomfort, but did not affect normal activities; and 4 = severe symptoms that interfered with normal activities. The daily average

rating of usual activities that were restricted by breathlessness in the morning during week 12 was scored as follows: 0 = none; 1 = symptoms present, but caused little or no restriction of morning activities; 2 = mild symptoms that were unpleasant, but caused little restriction of morning activities; 3 = moderate symptoms that caused discomfort and moderately restricted morning activities; and 4 = severe symptoms that interfered greatly with morning activities. It appears that the values for COPD symptom and sleep scores were calculated using weekly averages derived from the sum of daily averages based on the information entered into the electronic diaries by patients.[2]

In Studies M/34273/23 and M/34273/29, COPD symptoms were recorded by patients on patient diary cards, with symptom scores ranging from 0 for none, to 1 to 4 for increasing severity of breathlessness/dyspnea, cough, sputum, and night-time symptoms.[4]

It does not appear that MCIDs have been established for the various tools used to measure respiratory symptoms reported above.

g) Transition Dyspnea Index

The evaluation of dyspnea (i.e., BDI at baseline and TDI during treatment) was performed by an independent interviewer who was experienced in taking the history of respiratory disease and unaware of other patient parameters (e.g., SGRQ, FEV_1, AEs, etc.), to avoid bias. The objective was to measure the severity of breathlessness in symptomatic patients. The BDI and TDI each have three domains: functional impairment, magnitude of task, and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired) and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score, the worse the severity of dyspnea. The TDI domains are rated from –3 (major deterioration) to 3 (major improvement), and the rates are summed for the transition focal score ranging from –9 to 9; negative scores indicate deterioration. Thus, the BDI measured the severity of dyspnea at the beginning of the study, and the TDI evaluated changes from the BDI at different time points. The BDI was determined at visit 2 (randomization) and the TDI focal score at weeks 4, 12, and 24 (M/34273/34). The MCID for the TDI focal score has been reported to be an improvement of at least 1 unit from the BDI.

h) Rescue medication use

Patients recorded in electronic diaries use of rescue medication, as the number of puffs of 100 mcg albuterol/salbutamol used during the day and night. The use of rescue medication was assessed over the study period as the mean change from baseline (i.e., use of rescue medication during the run-in period).

i) Patient adherence and satisfaction

At each visit, investigators assessed adequate treatment compliance by reviewing the returned inhalers used by the patients. Assessment consisted of checking whether the dose indicator for the unlocked inhalers was adequate considering the number of daily doses expected to be taken since the previous visit. In addition, the total number of inhalations from each inhaler administered between visits, including the inhalation performed at the clinic, was recorded by the patients in electronic diaries. In case of inadequate compliance, the patient was re-instructed accordingly by the investigator.

Treatment compliance, both according to the electronic diary and the dose indicator, was assessed by the investigator at each visit. Compliance with the double-blind study treatment regimen for a specified period was defined as the total number of treatment applications (puffs) actually taken by a patient during that period, as recorded in the electronic diary, divided by the number of puffs expected to be

taken during the same period, multiplied by 100. A patient was considered compliant if the treatment compliance rate was at least 75%.

In Studies M/34273/23 and M/34273/29, convenience of the use of the inhaler devices was assessed at the end of the study using an 11-item or 7-item questionnaire, respectively. It was not explicitly stated in the studies whether these were manufacturer-developed or validated questionnaires. In Study M/34273/39, overall inhaler preference and willingness to continue each inhaler were assessed after six weeks by asking patients a series of questions based on specific inhaler attributes.

j) Safety assessments

Safety outcomes reported in all six studies included all-cause mortality, AEs, SAEs, WDAEs, and AEs of special interest (i.e., anticholinergic AEs and cardiac disorder AEs).

Outcomes included in the study protocol, for which there were no outcome data available, include exercise tolerance and days of missed school/work.

3.2.5 Statistical analysis

All three placebo-controlled studies were designed as superiority trials, and efficacy analyses were performed on the intention-to-treat (ITT) population (as defined by the manufacturer) using the last observation carried forward (LOCF) method for imputation of missing values. For spirometry data, linear interpolation and time-matched LOCF were applied. For Study M/34273/34, a sample size of 244 per treatment group was estimated to provide at least 90% power to detect a difference of 0.090 L in trough FEV_1 between the ACL groups and placebo at week 24 with a two-sided 5% level of significance, assuming a standard deviation (SD) of 0.240 L and adjusting for multiple treatment comparisons. For Study LAS-MD-33, a sample size of 165 patients per treatment group would give > 90% power to detect a 0.100 L difference in trough FEV_1, adjusting for multiple comparisons and assuming an SD of 0.0240 L. For Study LAS-MD-38 Part A, a sample size of 165 patients per treatment group also would give > 90% power to detect 0.100 L (trough) and 0.150 L (peak) treatment differences in FEV_1, adjusting for multiple comparisons at the overall significance level of 5% and assuming SDs of 0.240 L and 0.300 L, respectively.

The primary efficacy variable was analyzed by means of an analysis of covariance (ANCOVA) model with treatment and sex as factors and baseline FEV_1 and age as covariates. For each treatment comparison, the results of the ANCOVA were summarized using LSM for each treatment group with standard error (SE), the LSM difference between groups with 95% confidence interval (CI), and two-sided *P* values. Sensitivity analyses were performed using a mixed-effects model for repeated measures based on observed cases and per-protocol (PP) analyses based on LOCF. Changes from baseline in other lung function, SGRQ, and TDI scores were evaluated using ANCOVA, with treatment group and sex as factors, and age and baseline value as covariates. The proportions of patients with clinically significant improvements in SGRQ and TDI scores were analyzed using logistic regression with treatment group, sex, age, and baseline value as covariates. Use of rescue medication was analyzed using normal scores ANCOVA, with treatment group and sex as factors, and age and corresponding normal score baseline as covariates.

The number of COPD exacerbations per patient was analyzed by Poisson regression with correction for over-dispersion with treatment group, sex, and baseline COPD severity as factors, and age as a covariate. The proportion of patients with one or more COPD exacerbation was analyzed by logistic regression, including treatment group and baseline COPD severity as covariates. The time to first

moderate or severe COPD exacerbation was analyzed by means of Kaplan-Meier estimators and the Cox Proportional Hazards model for estimating hazard ratios (HRs) with treatment group and sex as factors, and age and baseline COPD severity as covariates. The placebo-controlled trials were not powered to compare treatment differences in COPD exacerbation rates.

COPD symptoms, sleep disturbances, and rescue medication use were analyzed using an ANCOVA model with treatment group as a factor, and the baseline value as covariate. Change from baseline in rescue medication use was analyzed using a normal scores ANCOVA model with treatment and sex as factors, and age and corresponding normal score baseline as covariate.

Examination of pre-specified subgroups appears to have been conducted only in Study M/34273/34, where descriptive statistics and analyses based on an ANCOVA model for change from baseline in trough FEV_1 at week 24 by sex, age, BMI, COPD severity, smoking status, reversibility, and use of ICS were performed.

According to the publication for Study LAS-MD-38 Part A,[3] an exploratory post-hoc analysis was performed to investigate whether treatment effects in trough FEV_1 would be modified by applying a matching-based adjustment for the imbalanced baseline variables. The post-hoc analysis grouped patients into an increasing number of homogeneous subgroups based on various baseline lung function parameters. While the results apparently supported the conclusion that the improvement in trough FEV_1 with ACL over placebo was greater than expected in the pre-specified analysis, only the ACL 400 mcg group exceeded the MCID (i.e., a change from baseline versus placebo of 0.102 L). These data should be interpreted with caution, as this statistical analysis was not specified a priori.

Adjustment for multiplicity of outcome testing was performed using the Hochberg method. The change from baseline in peak FEV_1 (primary analysis) was examined first applying the Hochberg procedure at the 5% level of significance. The process for moving in the sequential procedure was the following: testing continued with the next outcome if at least one null hypothesis of the two treatment comparisons was rejected; otherwise, the sequential testing procedures were stopped for inferential purposes. If both doses (treatment comparisons) were significant (i.e., null hypothesis rejected) then Hochberg's procedure was used to correct for multiple outcome comparisons for the treatments; otherwise, no correction was applied and the discarded dose could not be inferentially tested any further in any of the remaining secondary outcomes in the sequence.

All active comparator trials were designed as superiority trials. Study M/34273/23 was an exploratory phase 2a study; therefore, a sample size of 24 patients was considered sufficient to meet the study objectives. Taking into account a 10% dropout rate, a total of 30 patients were randomized. In Study M/34273/29, a sample size of 60 patients (12 per treatment sequence) provided at least 90% power to detect a difference of 0.120 L in change from baseline in FEV_1 normalized AUC_{0-12} after seven days between ACL and placebo, assuming an SD of 0.200 L. This sample size also provided 76% power to detect a difference of 0.070 L in change from baseline in FEV_1 normalized AUC_{0-12} after seven days between active treatments. A total of 65 patients were planned to account for a dropout rate of 10%. In Study M/34273/39, a target population of 405 patients was planned to provide a sample size of 385, taking into account a 5% dropout rate. This provided > 90% power to detect a 0.130 L difference between ACL and placebo for the primary and secondary outcomes and > 80% power to detect a 0.070 L difference between ACL and tiotropium for secondary outcomes.

In Studies M/34273/23 and M/34273/29, all efficacy outcomes were analyzed using an ANCOVA model for crossover designs with sequence, treatment, and period as fixed effects, patients within sequence as random effects, and baseline value as a covariate. Study M/34273/39 used an ANCOVA model with treatment and sex as factors, and age and baseline values as covariates. The primary and secondary outcome analyses were conducted in a stepwise manner to control for multiplicity. All statistical comparisons were two-sided hypothesis tests with the significance level set at 5%.

In all trials, safety outcomes (e.g., AEs, SAEs) were summarized by means of descriptive statistics.

a) Analysis populations

In general, five analysis populations were defined by the manufacturer for the included studies:

- Screened population: defined as all patients who attended visit 1 (screening), signed a written informed consent, and received a screening number.
- Randomized population: defined as all patients in the screened population who were randomized to a treatment group in the study.
- Safety population: defined as all randomized patients who took at least one dose of study drug.
- ITT population: defined as all randomized patients who took at least one dose of study drug and had a baseline and at least one post-baseline FEV_1 assessment.
- PP population: defined as a subset of ITT population, including patients who:
  - met all inclusion/exclusion criteria liable to affect the efficacy assessment;
  - attained a sufficient compliance to the treatment received; and
  - did not present serious deviations from the protocol that may have affected efficacy.

The ITT population, as defined by the manufacturer, is not a true ITT population, but rather a modified ITT population. Nonetheless, the ITT and safety populations were identical in all treatment groups across all six included trials, with the exception of the placebo group in Study LAS-MD-33, in which the populations differed by one patient who did not have one post-baseline FEV_1 measurement (Table 9).

3.3 Patient Disposition

Patient disposition for all six included trials is summarized in Table 9. Overall, the proportion of patients who permanently discontinued the trials was moderate, ranging from 2.5% to 19.9% across individual treatment groups. The primary reasons for discontinuation were AEs (1.5% to 10.0%) and personal request (0.6% to 6.2%). Discontinuation rates appeared to be similar between-treatment groups in individual trials, with numerically higher rates of discontinuation due to AEs in the placebo group compared with the ACL 400 mcg group in Studies M/34273/34 and M/34273/39. In Study M/34273/39, the rates of discontinuation due to AEs were almost identical between ACL 400 mcg twice daily (1.8%) and tiotropium 18 mcg once daily (1.9%). The low rates of discontinuation are not surprising given the relatively short durations of the included trials.

3.4 Exposure to Study Treatments

Median exposure to study drug was identical between-treatment groups in all included studies (Table 10). In Study M/34273/34, patients were exposed to study treatment for an average of 163 days (ACL 400 mcg) and 152 days (placebo). In comparison, mean exposure for Studies LAS-MD-33 and LAS-MD-38 Part A was approximately half as long (i.e., 78 days for ACL 400 mcg and 75 to 78 days for placebo), in keeping with the 24 and 12 week duration of the studies, respectively. In keeping with the study design, mean exposure to study treatment in the active comparator trials was commensurate with the length of each crossover study period.

TABLE 9: PATIENT DISPOSITION IN INCLUDED STUDIES

Study	M/34273/34		LAS-MD-33		LAS-MD-38 Part A		M/34273/23	M/34273/29	M/34273/39		
	ACL 400	Placebo	ACL 400	Placebo	ACL 400	Placebo	TOTAL	TOTAL	ACL 400	TIO 18	Placebo
Screened, N[a]	1,061		1,062		1,236		41	99	485		
Randomized, N	272	276	190	186	178	182	30	79	171	158	85
Completed, N (%)	252 (92.6)	232 (84.1)	166 (87.4)	149 (80.1)	148 (83.1)	151 (83.0)	27 (90.0)	68 (86.1)	166 (97.1)	154 (97.5)	80 (94.1)
Discontinued, N (%)	17 (6.3)	41 (14.9)	24 (12.6)	37 (19.9)	39 (16.9)	31 (17.0)	3 (10.0)	11 (13.9)	5 (2.9)	4 (2.5)	5 (5.9)
Primary reason for treatment discontinuation											
AEs	4 (1.5)	6 (2.2)	7 (3.8)	7 (3.7)	8 (4.5)	4 (2.2)	3 (10.0)	7 (8.9)	3 (1.8)	3 (1.9)	4 (4.7)
Protocol violation	1 (0.4)	1 (0.4)	3 (1.6)	2 (1.1)	3 (1.7)	3 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lost to follow-up	0 (0)	1 (0.4)	0 (0)	0 (0)	2 (1.1)	3 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient personal request	7 (2.6)	17 (6.2)	7 (3.7)	9 (4.8)	0 (0)	0 (0)	0 (0)	3 (3.8)	2 (1.2)	1 (0.6)	0 (0)
COPD exacerbation	4 (1.5)	5 (1.8)	1 (0.5)	7 (3.8)	6 (3.4)	4 (2.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lack of efficacy	0 (0)	8 (2.9)	1 (0.5)	10 (5.4)	2 (1.1)	6 (3.3)	0 (0)	1 (1.3)	0 (0)	0 (0)	1 (1.2)
Other	1 (0.4)	3 (1.1)	3 (1.6)	2 (1.1)	3 (1.7)	3 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Analysis populations											
Safety, N (%)	269 (98.9)	273 (98.9)	190 (100)	186 (100)	177 (99.4)	182 (100)	30 (100)	79 (100)	171 (100)	158 (100)	85 (100)
ITT, N (%)	269 (98.9)	273 (98.9)	190 (100)	185 (99.5)	177 (99.4)	182 (100)	30 (100)	79 (100)	171 (100)	158 (100)	85 (100)
PP, N (%)	250 (91.9)	248 (89.9)	184 (96.8)	175 (94.1)	164 (92.1)	167 (91.8)	27 (90.0)	73 (92.4)	162 (94.7)	149 (94.3)	80 (94.1)

ACL = aclidinium bromide; AE = adverse event; COPD = chronic obstructive pulmonary disease; ITT = intention-to-treat; PP = per protocol; TIO = tiotropium bromide.
[a] Includes patients in the aclidinium bromide 200 mcg group.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A,[14] M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

TABLE 10: EXTENT OF EXPOSURE TO STUDY MEDICATION (SAFETY POPULATION)

Length of exposure	M/34273/34		LAS-MD-33		LAS-MD-38 Part A		M/34273/23		
Days	**ACL 400 (N = 269)**	**Placebo (N = 273)**	**ACL 400 (N = 190)**	**Placebo (N = 186)**	**ACL 400 (N = 177)**	**Placebo (N = 182)**	**ACL 400 (N = 29)**	**Placebo (N = 30)**	**TIO 18 (N = 28)**
Mean (SD)	163.1 (28.3)	151.8 (45.4)	78.1 (22.3)	75.4 (24.9)	77.7 (21.9)	77.7 (21.4)	15.0 (0.0)	14.9 (1.0)	15.1 (0.4)
Median	169.0	169.0	85.0	85.0	85.0	85.0	15.0	15.0	15.0
Range, min, max	7.0, 224.0	1.0, 200.0	1, 99	1, 111	1, 113	1, 99	15.0, 15.0	10.0, 17.0	15.0, 17.0

Length of exposure	M/34273/29			M/34273/39		
Days	**ACL 400 (N = 74)**	**FOR 12 (N = 74)**	**Placebo (N = 76)**	**ACL 400**	**TIO 18**	**Placebo**
Mean (SD)	7.0 (0.5)	7.0 (0.2)	7.0 (0.7)	42.2 (3.9)	42.1 (4.8)	41.6 (6.0)
Median	NR	NR	NR	43.0	43.0	43.0
Range, min, max	3.0, 8.0	6.0, 8.0	2.0, 9.0	12.0, 60.0	2.0, 51.0	4.0, 50.0

ACL = aclidinium bromide; FOR = formoterol; SD = standard deviation; TIO = tiotropium bromide.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A,[14] M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

3.5 Critical Appraisal

3.5.1 Internal validity

- In all included trials, the methods used for randomization (i.e., IVRS and computer-generated randomization schedules) and methods of allocation concealment appeared to be appropriate. The use of a double-dummy technique in the active comparator trials, although complex and difficult to accomplish, also appeared to be appropriately conducted. It does not appear that any treatment-emergent AEs compromised the double-blind conditions of the trials.
- Adequate sample sizes appear to have been recruited in all studies based on a priori power calculations. Of note, the sample size in Study M/34273/34 was based on an anticipated difference of 0.090 L in trough FEV_1 between the ACL groups and placebo at week 24. This difference is below the MCID (0.100 to 0.140 L); however, the sample size appeared to provide sufficient power to detect treatment differences in the primary and secondary end points. In comparison, sample size calculations for the other placebo-controlled trials were based on differences in line with the suggested MCID for change from baseline in trough FEV_1 (0.100 L).
- Across all trials, efficacy analyses were conducted on the ITT population (as defined by the manufacturer), which included all treated patients who received at least one dose of study drug and had a baseline and at least one post-baseline FEV_1 measurement. This is not a true ITT population, but rather a modified ITT population. Nonetheless, given that the ITT population (as defined by the manufacturer) and the safety population (defined as all randomized patients who took at least one dose of study drug) are almost identical across all the trials, this is likely not a significant concern.
- Multiplicity adjustments were made for the primary and select secondary outcomes when multiple statistical tests were conducted.
- It is unclear how the change from baseline in COPD symptom scores, in the trials that reported this outcome, was measured and analyzed. First, it is not clear how baseline symptom scores were derived (e.g., if this was done, and how it was done, during the run-in period). Furthermore, it is also not clear how daily symptom scores were averaged into weekly symptom scores, and how, in turn, weekly scores were used to provide a measure of change from baseline to study end. It appears that categorical data were treated as continuous data (i.e., as a change from baseline over the duration of the study); however, the intervals or distance between categories based on the instruments or questionnaires used were not equal (e.g., a score of 1 = 1 to 2 whereas a score of 4 = 7 or more). These data are categorical and therefore should not be analyzed with averages, as it cannot be assumed that the distance between the categories is equal.
- Rates of patient discontinuation across trials were moderate; however, the trials were of relatively short duration for a chronic medication.
- The statistically significant baseline imbalance in the severity of COPD in enrolled patients in Study LAS-MD-38 Part A brings the validity of the results of this trial into question. According to the Health Canada Reviewer's Report, the manufacturer stated that there was a failure in randomization in this trial, which resulted in more patients with severe COPD being randomized to the 400 mcg twice-daily group, thus making it difficult to interpret the results.[10] This trial had the smallest treatment effect for ACL 400 mcg twice daily when compared with the other trials, and it is difficult to determine whether this was due to chance or to the true treatment effect of ACL. Although a post-hoc adjusted analysis appears to have been conducted by the manufacturer,[3] these data were not available; hence, caution in the interpretation of such data are warranted.
- According to the clinical expert, the decision to prescribe Tudorza Genuair will, in large part, be made on the basis of the ease of use of the Genuair inhaler, when compared with other treatment alternatives (e.g., the HandiHaler or Breezhaler). As a result, a more controlled and rigorous assessment of patient satisfaction and preference for type of inhaler in the active comparator trials

would have resulted in more confidence in the results derived from comparison of these outcomes. Although patients appear to have received instruction on the proper use of the inhaler devices in the trials, and the inability to use the inhaler devices was an exclusion criterion, there appear to be no data available on the proportions of patients who used the various devices correctly or incorrectly. This has implications for the evaluation of patient satisfaction and inhaler preference; while patients may have found a particular inhaler device easier to use or preferable to another, the patients may not have been using the devices correctly.

- Active comparators assessed in the trials were relevant, especially the direct head-to-head comparison with another LAMA (tiotropium) and LABA (formoterol); however, the sample sizes in Studies M/34273/23 (N = 30) and M/34273/29 (N = 79) were small and the trial durations were short.
- It is not clear whether the length of the washout periods (five to nine days) between-treatment phases in the crossover trials (M/34273/23 and M/34273/29) was adequate, as it does not appear that any assessment of carryover effect was conducted. The clinical expert was of the opinion that the length of washout was sufficient; however, the terminal elimination half-life of inhaled ACL is approximately seven hours[32] and of tiotropium, reported to be five to seven days.[33] Therefore, the washout period may have been insufficient to wash out the entire previous dose of tiotropium. The treatment period of only seven days in Study M/34273/29 may also have been inadequate to assess the true treatment effect of the study medications, especially in the case of formoterol, as steady-state concentrations would not have been achieved.
- While measures typically used in the evaluation of COPD therapies (e.g., spirometry measures, SGRQ, TDI) were included as outcomes in the trials, none of the trials were prospectively designed or adequately powered to assess treatment differences in COPD exacerbation rates, which is an important outcome for management decisions in COPD.[19] No data were available for other outcomes identified in the protocol, such as exercise tolerance or days of missed work/school. There was great heterogeneity in the manner in which COPD symptoms were measured across the trials, which complicated comparisons between trials and interpretation of the results. The use of tools developed by the manufacturer, or not validated for use in COPD (e.g., the Daily Sleep Diary[38] and Night-time Symptoms Questionnaire[39] used in Study LAS-MD-33), also complicates interpretation of the clinical significance of differences between treatments for patients with COPD.
- All included trials were designed as superiority trials, whereas a non-inferiority design versus another LAMA (e.g., tiotropium, glycopyrronium), or versus other clinically relevant comparators in Canada (e.g., LABAs or LABA + ICS combinations) would have provided valuable information for decision-making due to the similar place in therapy for these drugs.
- Treatment compliance appears to have been based upon self-reported use of study medication by patients (i.e., recorded in electronic diaries). This method could have introduced reporting bias; however, Investigators also checked the dose indicator on the inhaler devices at each study visit, so if there was poor compliance by patients, it is assumed this would have been identified early in the trials.

3.5.2 External validity

- Numerous baseline patient characteristics affect the generalizability of the results of the included trials to Canadian COPD patients. First, the mean age of enrolled patients in the trials (58 to 65 years) resulting from the inclusion criteria of patients ≥ 40 years of age represents a younger patient population than is typically treated for COPD in Canada. According to the clinical expert consulted on this review, the average age for initiation of pharmacotherapy in patients with COPD in Canada is usually 65 years of age or older. This is supported by an analysis of data from a prescription database from Quebec, where the mean age of new users of COPD medication was 78 years old

(although this study included only patients whose medications were covered by Regie de l'assurance maladie du Québec).[40] A population-based study of the epidemiology of COPD in Ontario showed the majority of COPD patients are above age 65 years.[41] There was also a very high proportion of current smokers (42.1% to 63.3%) across treatment groups in the trials. Furthermore, the percentage of patients with bronchial reversibility (10.6% to 15.7%) was also high for a COPD study, implying that a larger proportion of enrolled patients may have had an asthmatic component to their disease, which could have exaggerated the bronchodilatory effect of ACL one might expect in COPD patients. In comparison, the bronchodilator response in the large TORCH RCT comparing a LABA (salmeterol) plus a ICS (fluticasone propionate) with placebo was less than 4%.[42] The pattern of pre-study COPD medication use did not reflect medication regimens generally prescribed in Canada (i.e., low use of LABAs and LABA + ICS combinations).

- The exclusion of patients with unstable cardiac conditions from the trials is of concern, especially given the comorbid association of cardiac disease and COPD. The clinical expert noted that this is usual practice in clinical trials and that clinicians may be hesitant to initiate LAMA therapy in the presence of unstable cardiac conditions. Furthermore, the exclusion of patients on prohibited medications who did not wish to interrupt their medication to enter the trial may have introduced selection bias and also adds to uncertainty regarding the generalizability of these data to Canadian patients. Many patients with COPD who may be candidates for ACL are also likely to be on the medications that were prohibited in the trials (e.g., long-acting beta-2 agonists, ICS + LABA combinations).
- The short duration of the placebo-controlled trials (12 to 24 weeks) and active comparator trials (study periods of seven days to six weeks) are inadequate for assessment of the long-term efficacy and safety of a medication used chronically for a condition such as COPD. A trial of at least one-year's duration is important to assess seasonal variations in the COPD disease course.[10]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 11). See Appendix 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Pulmonary function tests

a) Placebo-controlled trials

The primary efficacy outcome in the three placebo-controlled trials was the change from baseline in the morning pre-dose (trough) FEV_1 at 12 weeks (M/34273/34 for the US filing, LAS-MD-33, and LAS-MD-38 Part A) and 24 weeks (M/34273/34 for the EU filing). Health Canada considered the primary end point to be 12 weeks in Study M/34273/34.[10] Detailed results are available in Table 20. At 12 weeks, the LSM differences between the ACL 400 mcg twice daily and placebo groups ranged from 0.072 L to 0.124 L, and the differences compared with placebo were statistically significant in all three trials (Table 11). At 24 weeks, in Study M/34273/34, the LSM difference was 0.128 L (95% CI: 0.085; 0.170), which was also statistically significant. The LSM differences all exceeded the lower end of the MCID (0.100 L) in Studies M/34273/34 and LAS-MD-33, but not in Study LAS-MD-38 Part A.

TABLE 11: CHANGE FROM BASELINE IN MORNING PRE-DOSE (TROUGH) FEV_1 (L) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline						
Mean (SD)	1.508 (0.525)	1.500 (0.489)	1.376 (0.570)	1.332 (0.493)	1.249 (0.519)	1.459 (0.519)
Change from baseline at Week 12						
LSM diff [vs. placebo] (95% CI); *P* value	0.105 (0.065, 0.144); $P < 0.0001$		0.124 (0.08, 0.16); $P < 0.0001$		0.072 (0.03, 0.12); $P = 0.0012$	

ACL = aclidinium bromide, CI = confidence interval; FEV_1 = forced expiratory volume in one second; ITT = intention-to-treat; LOCF = last observation carried forward; LSM diff = least squares mean difference.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

The LSM differences in trough FEV_1 by study visits ranged from 0.105 L to 0.140 L over weeks 1 to 24 in Study M/34273/34, from 0.108 L to 0.133 L over weeks 1 to 8 in Study LAS-MD-33, and from 0.065 L to 0.101 L in Study LAS-MD-38 Part A over weeks 1 to 8 (Table 22).

Statistically significant differences between the ACL 400 mcg twice daily and placebo groups were demonstrated for all other spirometry measures (i.e., peak FEV_1, FEV_1 $AUC_{0\text{-}3h}$, trough and peak FVC, and trough IC) at study end in the trials, thus supporting a consistent bronchodilatory treatment effect with ACL 400 mcg twice daily across trials (Table 22).

In Study M/34273/34, the magnitude of change from baseline in trough FEV_1 with ACL 400 mcg twice daily, as compared with placebo, appeared to be maintained from week 1 to week 24 (Figure 8). Maximal bronchodilation was achieved one to three hours after the first dose of ACL 400 mcg on day 1, which exceeded the MCID (0.100 to 0.140 L) beginning at 30 minutes (Figure 9).

b) Active comparator trials

The change from baseline in trough FEV_1 was a secondary outcome in the active comparator trials and was measured at day 1 in Studies M/34273/23 and M/34273/39, and at the end of the study period in all three trials. On day 1, the LSM differences in the change from baseline for the ACL 400 mcg twice-daily groups compared with placebo were 0.186 L (95% CI, 0.112 to 0.260) in Study M/34273/23 and 0.141 L (95% CI, 0.088 to 0.195) in Study M/34273/39. Both results were statistically significant (Table 21) and clinically important. The LSM difference in the change in trough FEV_1 on day 1 for the tiotropium 18 mcg once-daily groups compared with placebo were 0.122 L (95% CI, 0.0479 to 0.196) in Study M/34273/23 and 0.093 L (95% CI, 0.039 to 0.148) in Study M/34273/39; although they were statistically significant, only Study M/34273/23 exceeded the lower end of the MCID (0.100 L) (Table 21). The LSM differences between the ACL 400 mcg and tiotropium 18 mcg groups were 0.064 L (95% CI, –0.011 to 0.139) and 0.048 L (95% CI, 0.003 to 0.093). Only the latter result in Study M/34273/39 was statistically significant. At the end of the study period in M/34273/23 (day 7) and M/34273/29 (day 15), the LSM differences between ACL 400 mcg and placebo, tiotropium 18 mcg and placebo, or formoterol 12 mcg and placebo were all statistically significant (Table 12). In Study M/34273/39, the LSM differences between ALC 400 mcg and placebo and between tiotropium 18 mcg and placebo were also statistically significant (Table 12). However, in all three trials, the LSM differences between the active treatments ACL 400 mcg and tiotropium 18 mcg or ACL 400 mcg and formoterol 12 mcg were not statistically different. In all instances, the LSM differences for all active treatments versus placebo exceeded the

lower end of the MCID (0.100 L), but the differences between active treatments did not exceed this level.

The change in trough FEV_1 following administration of ACL 400 mcg as compared with tiotropium 18 mcg in Study M/34273/23 on day 1 is illustrated in Figure 10. The treatment effect appears to have been maintained at the end of the study period on day 15 as per Figure 11.

The primary efficacy outcome in the active comparator trials was the normalized FEV_1 AUC (i.e., the time period for which data were collected divided by the number of hours over which the data are averaged) as follows: $AUC_{0\text{-}12/12\ h}$ (M/34273/23 and M/34273/29) or $AUC_{0\text{-}24/24\ h}$ (M/34273/39) at the end of the study period. In addition, FEV_1 AUC values were measured on day 1 in Studies M/34273/23 (Table 23) and M/34273/39 (Table 25). In Study M/34273/23, statistically significant treatment differences were observed between ACL 400 mcg and placebo, and tiotropium 18 mcg and placebo, for all AUC measures (i.e., $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$ and $AUC_{12\text{-}24}$) on days 1 and 15. Similarly, statistically significant differences in favour of ACL 400 mcg compared with tiotropium 18 mcg were observed for all measures with the exception of $AUC_{0\text{-}24}$ on day 15 (Table 23). In Study M/34273/29, results were reported only at day 7 (Table 24). All differences between AUC measures for ACL 400 mcg and placebo, or formoterol 12 mcg and placebo, were statistically significant. A statistically significant difference between ACL 400 mcg and formoterol 12 mcg was observed only for FEV_1 $AUC_{0\text{-}24}$ measured on day 7. In Study M/34273/39, all comparisons between ACL 400 mcg and placebo, or tiotropium 18 mcg and placebo, were statistically significantly different on day 1 and at week 6. The only statistically significant difference between ACL 400 mcg versus tiotropium 18 mcg was for FEV_1 $AUC_{0\text{-}24}$ and $AUC_{12\text{-}24}$ on day 1 (Table 25).

In general, the treatment differences in normalized FVC $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$ and $AUC_{12\text{-}24}$ at the end of each study period followed a similar pattern as FEV_1 AUC measures in the active comparator trials (Table 26, Table 27, and Table 28). While differences in all active treatment comparisons compared with placebo were statistically significant, differences between ACL 400 mcg and tiotropium 18 mcg or formoterol 12 mcg were statistically significant only when a 24 hour time period was considered (i.e., $AUC_{0\text{-}24}$ or $AUC_{12\text{-}24}$). Statistically significant differences were demonstrated between ACL 400 mcg and tiotropium 18 mcg or formoterol 12 mcg in FVC $AUC_{12\text{-}24}$ on days 1 and 15, and day 7, in Studies M/34273/23 and M/34273/29, respectively. In Study M/34273/39, a statistically significant difference was shown for $AUC_{0\text{-}24}$ between ACL 400 mcg and tiotropium 18 mcg on day 1.

Between-treatment differences for the change from baseline in morning peak FEV_1 and FVC values were statistically significant for all active treatment comparisons compared with placebo on day 1 (M/34273/23 and M/34273/39) and at end of the study periods in all trials (Table 29, Table 30, Table 31). There were no statistically significant differences between any of the active treatment groups for these outcomes at any time point in any of the active comparator trials.

TABLE 12: CHANGE FROM BASELINE IN MORNING PRE-DOSE (TROUGH) FEV_1 (L) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): ACTIVE COMPARATOR TRIALS

	M/34273/23			M/34273/29			M/34273/39		
	ACL 400 (N = 29)	TIO 18 (N = 28)	Placebo (N = 30)	ACL 400 (N = 74)	FOR 12 (N = 74)	Placebo (N = 76)	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Baseline									
Mean (SD)	1.463 (0.500)	1.493 (0.469)	1.444 (0.444)	1.422 (0.471)	1.383 (0.458)	1.441 (0.455)	1.462 (0.481)	1.543 (0.536)	1.422 (0.521)
Change from baseline at end of study period									
Study end	**Day 15**			**Day 7**			**Week 6**		
LSM diff [ACL vs. placebo] (95% CI); *P* value	0.186 (0.124 to 0.248); *P* < 0.0001			0.154 (0.112, 0.197); *P* < 0.0001			0.141 (0.083, 0.199); *P* < 0.0001		
LSM diff [TIO vs. placebo] (95% CI); *P* value	0.150 (0.086 to 0.213); *P* < 0.0001			NA			0.102 (0.043, 0.161);*P* = 0.0008		
LSM diff [ACL vs. TIO] (95% CI); *P* value	0.036 (–0.027 to 0.099); *P* = 0.2560			NA			0.038 (–0.010, 0.087); *P* = 0.1191		
LSM diff [FOR vs. placebo] (95% CI); *P* value	NA			0.148 (0.105 to 0.190); *P* < 0.0001			NA		
LSM diff [ACL vs. FOR] (95% CI); *P* value	NA			0.007 (–0.036 to 0.050); *P* = 0.7589			NA		

ACL = aclidinium bromide, CI = confidence interval; FEV_1 = forced expiratory volume in one second; FOR = formoterol; LSM diff = least squares mean difference; NA = not applicable; TIO = tiotropium; vs. = versus.
Source: Clinical Study Reports for M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

3.6.2 Chronic obstructive pulmonary disease exacerbations

COPD exacerbations were reported only in the placebo-controlled trials (Table 32). Overall, rates of any COPD exacerbation were relatively low, ranging from 6.3% to 20.5% across treatment groups in the individual trials. The OR for COPD exacerbations of any severity when ACL 400 mcg and placebo were compared ranged from 0.51 (95% CI, 0.24 to 1.07) to 0.95 (95% CI, 0.48 to 1.88), which did not reach statistical significance in any of the trials. The rates of COPD exacerbations per patient per year were numerically lower with ACL 400 mcg compared with placebo in all trials. When the rate ratios (RR) are compared for COPD exacerbations of any severity, statistically significant differences were noted in Studies M/34273/34 (0.67; 95% CI, 0.48 to 0.94; *P* = 0.0195) and LAS-MD-33 (0.52; 95% CI, 0.32 to 0.85; *P* = 0.0094), but not LAS-MD-38 Part A (0.96; 95% CI, 0.45 to 2.05; *P* = 0.9124). Although the rates of moderate to severe COPD exacerbations were also numerically lower with ACL 400 mcg compared with placebo in all three trials, the RR did not reach statistical significance (Table 32).

HRs for the time to first COPD exacerbation of any severity were calculated for all three placebo-controlled studies (Table 33). The only statistically significant difference between ACL 400 mcg and placebo was observed in Study M/34273/34 (HR 0.64; 95% CI, 0.42 to 0.97; *P* = 0.0343).

3.6.3 Mortality

Overall, the numbers of deaths across all six included trials was very low, as expected for trials of short duration (Table 34). There were six treatment-emergent deaths reported in the placebo-controlled trials (i.e., which includes one death in the ACL 200 mcg groups of Study M/34273/34). Of these, three were reported in Study M/34273/34, one in each treatment group (ACL 200 mcg, ACL 400 mcg, and placebo). The causes of death were myocardial infarction, acute cardiac failure, and blunt chest trauma during a traffic accident. There was one death reported in Study LAS-MD-33 in the ACL 400 mcg group that was attributed to complications from cancer, and two deaths reported in Study LAS-MD-38 Part A, one with no definitive cause of death and one death in the ACL 400 mcg group due to severe cardiorespiratory arrest and respiratory failure. None of the deaths were considered related to study treatment. There were no deaths reported in the active comparator trials.

3.6.4 Health care resource utilization

The total number of days of hospitalization for COPD exacerbations was reported only in the placebo-controlled trials (Table 35). Overall, the numbers of patients who required hospitalization were very low across the three trials (i.e., approximately one to three patients per treatment group required hospitalization), and so it is not possible to draw any meaningful conclusions from these data. The only exception is for the placebo group in Study M/273/34, in which 10 patients required hospitalization for COPD exacerbations; however, no further details on these hospitalizations were available.

3.6.5 Quality of life

Health-related quality of life, as measured by the SGRQ, was a secondary end point in Study M/34273/34 and "another" efficacy end point in the other two placebo-controlled trials. The SGRQ was not administered in any of the active comparator trials. As early as week 4, the LSM change from baseline in the ACL 400 mcg groups in Studies M/34273/34 and LAS-MD-33 achieved the MCID (i.e., a reduction in total score of ≥ 4 units; Table 13). The magnitude of the LSM change from baseline continued to increase at week 12 and week 24 (M/34273/34). However, improvements were also observed in the placebo groups, and the difference in change relative to placebo exceeded the MCID only in Study M/34273/34. The LSM differences between the ACL 400 mcg and placebo groups were statistically significant in Studies M/34273/34 and LAS-MD-33 at weeks 4, 12, and 24 (M/34273/34 only). In Study LAS-MD-38 Part A, the LSM change from baseline did not reach the MCID until week 12;

however, it was achieved in both the ACL 400 mcg and placebo groups (Table 13). The LSM differences between the ACL 400 mcg and placebo groups did not reach statistical significance at either week 4 or week 12 in this study.

TABLE 13: CHANGE IN SGRQ TOTAL SCORE FROM BASELINE (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline						
Mean (SD)	47.4 (18.4)	44.9 (16.7)	48.3 (17.8)	45.1 (16.3)	50.4 (16.9)	49.2 (17.4)
Week 4						
LSM (SE)	–5.19 (0.63)	–2.60 (0.63)	–4.0(0.7)	–0.4 (0.7)	–3.3 (0.8)	–2.7 (0.7)
LSM diff [vs. placebo] (95% CI)	–2.59 (–4.30, –0.89); *P* = 0.0029		–3.6 (–5.4, –1.8); *P* = 0.0001		–0.6 (–2.7, 1.5); *P* = 0.5826	
Week 12						
LSM (SE)	–6.45 (0.72)	–2.36 (0.72)	–4.6 (0.8)	–2.0(0.8)	–5.4 (1.0)	–4.3 (1.0)
LSM diff [vs. placebo] (95% CI)	–4.10 (–6.06, –2.13); *P* < 0.0001		–2.5 (–4.7, –0.4); *P* = 0.0186		–1.1 (–3.8, 1.6); *P* = 0.4288	
Week 24						
LSM (SE)	–7.41 (0.82)	–2.79 (0.82)	-	-	-	-
LSM diff [vs. placebo] (95% CI)	–4.63 (–6.84, –2.42); *P* < 0.0001		-		-	

ACL = aclidinium bromide; CI = confidence interval; LSM diff = least squares mean difference; SGRQ = St. George's Respiratory Questionnaire; SE = standard error.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

Results for the SGRQ were also reported as the proportion of patients who achieved the MCID (Table 37). Across all trials, 37.8% to 51.7% of patients in the ACL 400 mcg groups and 27.1% to 39.1% of patients in the placebo groups achieved the MCID (≥ 4 unit reduction) in the total SGRQ score by week 4. The proportions increased to 44.4% to 56.9% in the ACL 400 mcg groups and 35.9% to 39.5% in the placebo groups at week 12. In Study M/34273/34 at week 24, 57.3% of patients in the ACL 400 mcg group versus 41.0% in the placebo group achieved the MCID. The OR (ACL 400 mcg versus placebo) for achieving the MCID on the SGRQ was statistically significant in Study M/34273/34 at all-time points (i.e., weeks 4, 12, and 24). In Study LAS-MD-33, the OR was statistically significant at week 4, but was no longer statistically significant at week 12. In Study LAS-MD-38 Part A, the OR did not reach statistical significance at either week 4 or week 12.

The EQ-5D was also administered in Studies M/34273/34 and LAS-MD-38 Part A (Table 38) to supplement the SGRQ. In Study M/34273/34, the LSM difference between ACL 400 mcg and placebo in the change in weighted index score from baseline reached statistical significance at week 24 (0.03; 95% CI, 0.00 to 0.06; *P* = 0.0414), but was not statistically significant at either week 4 or week 12, nor was it clinically significant at any time point, as the MCID for the EQ-5D ranges from 0.033 to 0.074.[43] The LSM difference between groups in the change from baseline in the visual analogue scale was not statistically significant at week 4, but did reach statistical significance at week 12 (3.30; 95% CI, 1.27 to 5.32;

P = 0.0014) and week 24 (3.13; 95% CI, 0.96 to 5.29; *P* = 0.0047). The LSM differences between-treatment groups were not statistically significant at any time point in Study LAS-MD-38 Part A.

3.6.6 Chronic obstructive pulmonary disease symptoms

There was great heterogeneity in the way COPD symptoms were recorded and evaluated across the six included studies (Table 39 to Table 45). The change in COPD symptoms from baseline was measured in two of the placebo-controlled trials (M/34273/34 and LAS-MD-33). In Study M/34273/34, changes from baseline to week 24 in the breathlessness, chest, cough and sputum, and total scores, as measured by the E-RS, were all statistically significantly reduced in the ACL 400 mcg group compared with placebo (Table 39). The LSM differences in the scores ranged from –0.44 (95% CI, –0.63 to –0.25) for the cough and sputum score to –2.02 (95% CI, 2.72 to –1.33) for the total score, the magnitude of which is of uncertain clinical significance. The percentage of days with night-time and morning symptoms (i.e., any symptom, feeling short of breath, coughing, bringing up mucous or phlegm, chest tightness or congestion) over the whole study period (24 weeks), were all statistically significantly reduced (by approximately 5% to 7%) with ACL 400 mcg compared with placebo, with the exception of the wheezing score (which was reduced by approximately 3% to 4%) as per Table 40. The change from baseline in night-time sleep disturbance score was not significantly different with ACL 400 mcg compared with placebo; however, change in night-time lung condition, morning-time disturbance, and morning lung condition scores were all statistically significantly improved with ACL 400 mcg compared with placebo (Table 41). The LSM differences in these measures ranged from –0.14 to 0.13, which is also of uncertain clinical significance.

In Study LAS-MD-33, the change from baseline in the daily average of night-time symptoms (Table 42) were all statistically significantly reduced with ACL 400 mcg compared with placebo at week 12, with the exception of night-time sputum production. The change from baseline in the daily average of early morning symptoms (i.e., severity of breathlessness for first hour on getting up and impact of breathlessness on morning activities) at week 12 were also significantly reduced with ACL 400 mcg compared with placebo (Table 43).

Changes in COPD symptoms from baseline were captured in two of the active comparator trials (M/34273/23 and M/34273/39). In Study M/34273/23, breathlessness, cough, sputum, and night-time symptom scores were assessed at week 1, week 2, and week 1 + week 2 combined. In general, LSM differences between ACL 400 mcg and placebo were statistically significant in favour of ACL for most symptom scores, with the exception of the sputum score. The clinical significance of these findings is uncertain, especially in the context of the short treatment period evaluated (i.e., 7 and 15 days). Of note, LSM differences between tiotropium 18 mcg and placebo and between ACL 400 mcg and tiotropium 18 mcg did not reach statistical significance for any of the symptom scores, possibly due to the short treatment period evaluated (Table 44). In Study M/34273/39, LSM differences in the change in the daily total E-RS score and components (e.g., breathlessness, cough and sputum, and chest domains) over six weeks were all statistically significant in favour of ACL 400 mcg or tiotropium 18 mcg compared with placebo (Table 45). LSM differences in the change from baseline in the percentage of days without morning COPD symptoms and in the severity of morning symptoms were statistically significantly reduced with both ACL 400 mcg and tiotropium 18 mcg compared with placebo. LSM differences in the severity of night-time COPD symptoms and in limitation of activity due to COPD symptoms was statistically significantly reduced with ACL 400 mcg, but not tiotropium 18 mcg, compared with placebo. There were no statistically significant changes in the number of nocturnal awakenings due to COPD symptoms for either ACL 400 mcg or tiotropium 18 mcg when compared with placebo. For all symptom

scores in Study M/34273/39, there were no statistically significant differences between ACL 400 mcg and tiotropium 18 mcg.

3.6.7 Dyspnea

Dyspnea, as measured by the BDI score at baseline and TDI focal score at weeks 4, 12, and 24 (M/34273/34 only), was a secondary end point in Study M/34273/34 and "another" efficacy end point in the other two placebo-controlled trials (Table 46). The TDI was not evaluated in any of the active comparator trials. At week 4, the LSM change from baseline (BDI) in the ACL 400 mcg groups compared with placebo in Studies M/34273/34 and LAS-MD-33 achieved the MCID (i.e., an improvement of one unit or more; Table 14). The magnitude of the LSM change from BDI continued to increase at week 12 and week 24 (M/34273/34). The LSM differences between the ACL 400 mcg and placebo groups were statistically significant in both trials at all-time points (Table 14). In Study LAS-MD-38 Part A, the LSM change from BDI was not measured at week 4, but the MCID was reached at week 12 (LSM change of 1.3) in the ACL 400 mcg group. The LSM difference between the ACL 400 mcg and placebo group in Study LAS-MD-38 Part A was also statistically significant at week 12.

TABLE 14: TRANSITION DYSPNEA INDEX FOCAL SCORE MEASUREMENTS (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline (BDI)						
Mean (SD)	6.7 (2.1)	6.7 (2.0)	6.2 (2.1)	6.5 (2.2)	6.0 (1.9)	6.2 (2.2)
Change in TDI score from BDI at week 4						
LSM (SE)	1.54 (0.17)	0.62 (0.18)	1.2 (0.2)	0.4 (0.2)	-	-
LSM diff [vs. placebo] (95% CI)	0.92 (0.44 to 1.39) *P* = 0.0002		0.9 (0.2 to 1.5); *P* = 0.0066			
Change in TDI score from BDI at week 12						
LSM (SE)	1.74 (0.19)	0.86 (0.20)	1.5 (0.2)	0.5 (0.2)	1.3 (0.2)	0.3 (0.2)
LSM diff [vs. placebo] (95% CI)	0.88 (0.35 to 1.41) *P* = 0.0012		1.0(0.4 to 1.6); *P* = 0.0021		1.0 (0.3 to 1.7) *P* = 0.0054	
Change in TDI score from BDI at week 24						
LSM (SE)	1.94 (0.21)	0.94 (0.21)	—	—	—	—
LSM diff [vs. placebo] (95% CI)	1.00 (0.43 to 1.57) *P* = 0.0006		—		—	

ACL = aclidinium bromide; BDI = Baseline Dyspnea Index; CI = confidence interval; LOCF = last observation carried forward; LSM diff = least squares mean difference; SD = standard deviation; SE = standard error; TDI = Transition Dyspnea Index; vs. = versus.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

Changes in dyspnea were also reported as the proportion of patients who achieved the MCID for the TDI focal score (Table 47). In Studies M/34273/34 and LAS-MD-33, between 50.0% to 56.8% of patients in the ACL 400 mcg groups and 31.2% to 42.0% of patients in the placebo groups achieved improvement of one unit or more in the TDI focal score by week 4. At week 12, the proportions ranged from 47.7% to 59.5% in the ACL 400 mcg groups and 32.9% to 42.4% in the placebo groups across all three trials. At week 24 in Study M/34273/34, 56.9% versus 45.5% of patients achieved the MCID, respectively. Odds

ratios (ACL 400 mcg versus placebo) for achieving an improvement of one unit or more in the TDI focal score from the BDI score were statistically significant in all studies at the different time points measured (Table 47).

3.6.8 Rescue medication

In the placebo-controlled trials, the LSM differences in the change from baseline to end of treatment in the use of total daily and daytime or morning rescue medication were statistically significantly reduced with ACL 400 mcg compared with placebo in Studies M/34273/34 and LAS-MD-33 (Table 48). Changes in use of night-time or evening rescue medication were not statistically significantly different between-treatment groups in either trial. In Study LAS-MD-38 Part A, the opposite finding was observed (Table 48). There were no statistically significant treatment differences in the use of total daily and daytime or morning rescue medication, but the LSM difference in use of night-time or evening rescue medication was statistically significantly reduced with ACL 400 mcg compared with placebo. Across all trials, the clinical significance of the LSM difference in the magnitude of the reduction (i.e., less than one puff) is unclear.

In the active comparator trials, the use of rescue medication was reported in different ways in the three trials. In Study M/34273/23 changes from baseline (i.e., established during the run-in period) in the daily (day + night) use and in the day use and night use alone of rescue medication were reported at week 1, week 2, and week 1 + week 2 combined (Table 49). In general, statistically significant reductions in use of reliever medication were observed in both the ACL 400 mcg and tiotropium 18 mcg groups when compared with placebo for various measures, with the exception of change in night-time use of reliever medication. In Study M/34273/29, LSM differences between groups in the change from baseline in daily and daytime use, but not night-time use, of reliever medication at day 7, was statistically significantly reduced for both ACL 400mcg and formoterol 12 mcg compared with placebo (Table 50). In Study M/34273/39, there were no statistically significant differences in the change from baseline in the average daily use of rescue medication between any treatment group comparisons; however, there were statistically significant reductions in the change from baseline in percentage of rescue medication-free days over six weeks when ACL 400 mcg or tiotropium 18 mcg was compared with placebo (Table 51). Across all three trials, there were no statistically significant differences between the active treatment groups (i.e., ACL 400 mcg compared with tiotropium 18 mcg or formoterol 12 mcg) for any measure of reliever medication use.

3.6.9 Patient adherence and satisfaction

The overall treatment compliance rate in all six included studies was high (i.e., > 91% across all groups) (Table 52 and Table 53). Compliance data could not be located for Study M/34273/23.

Patient satisfaction questionnaires were conducted in Studies M/34273/23 (Table 54) and M/34273/29 (Table 54); however, only descriptive statistics for the results were reported. In general, more patients in both trials found the Genuair device easier to use than either the HandiHaler or Aerolizer devices, and more patients definitively preferred the Genuair device over the HandiHaler (30.00% versus 6.67%) or the Aerolizer (62.8% versus 6.4%), although 40.0% and 14.1% of patients, respectively, did not have any preference for either of the inhalers compared. In Study M/34273/39, 80.1% of patients preferred the Genuair device across all three treatment groups compared with 10.7% of patients who preferred the HandiHaler ($P < 0.0001$); whereas, 9.2% of patients had no preference (Table 56). More patients (88.8%) were also willing to continue using the Genuair device over six weeks of treatment than the HandiHaler device (45.4%); $P < 0.0001$ (Table 57).

3.6.10 Subgroup analyses

Study M/34273/34 was the only study that reported data from pre-specified subgroup analyses. Examination of the treatment effect for the primary and various secondary end points by age (< 60, 60 to 69, and > 70 years), COPD severity (mild/moderate, severe/very severe), ICS use (yes/no), and BMI (underweight to normal, pre-obese, obese) did not find any differences in the magnitude of the treatment between ACL 400 mcg twice daily and placebo. A larger proportion of females achieved the MCID for SGRQ at week 24 in the ACL 400 mcg group: females (OR 3.47) compared with males (OR 1.42). For change from baseline in peak FEV_1 at week 24, the treatment effect for ACL 400 mcg in patients with reversibility (0.285 L) was higher than in patients with no reversibility (0.169 L). The treatment effect for this outcome was also larger in the current smoker subgroup (0.247 L) compared with the ex-smoker subgroup (0.211 L); however, according to the Health Canada reviewer, this was driven by a low peak FEV_1 observed in the placebo group for the current smokers compared with ex-smokers.[10]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

Treatment-emergent AEs are summarized in Table 15 for the placebo-controlled trials and Table 16 for the active comparator trials. Overall, the incidence of AEs in the ACL 400 mcg treatment groups of the placebo-controlled trials ranged from 44.7% to 53.5% compared with 49.5% to 57.1% in the placebo groups. The most frequently reported AEs (> 2% of patients in any treatment group) in the ACL 400 mcg groups were COPD exacerbations (7.4% to 14.1%), headache (1.6% to 12.3%), and nasopharyngitis (1.6% to 11.2%). Corresponding rates in the placebo groups were 11.5% to 20.5% for COPD exacerbations, 2.2% to 8.1% for headache, and 1.1% to 8.4% for nasopharyngitis.

In the active comparator trials, the frequency of AEs was lower than that observed in the placebo-controlled trials, likely due to the shorter duration of these trials. Overall, between 18.9% and 27.5% of patients in the ACL 400 mcg groups experienced an AE, compared with 10.7% to 29.7% of patients who received tiotropium 18 mcg, 14.9% of patients who received formoterol 12 mcg, and 21.1% to 26.7% of patients who received placebo. The most frequently reported AEs (2% or more of patients in any treatment group) in the ACL 400 mcg groups were nasopharyngitis (3.4% to 5.8%) and headache (0% to 7.0%). Corresponding rates were 3.6% to 5.7% for nasopharyngitis and 3.6% to 3.8% for headache in the tiotropium 18 mcg group, 1.4% and 2.7% in the formoterol 12 mcg group, and 0% to 2.4% and 3.3% to 6.6% in the placebo groups, respectively. COPD exacerbations were only reported in Study M/34273/39 and were 2.3% (ACL 400 mcg), 1.3% (tiotropium 18 mcg), and 4.7% (placebo).

3.7.2 Serious adverse events

In the placebo-controlled trials, the frequency of SAEs ranged from 3.2% to 5.6% in the ACL 400 mcg groups and 2.2% to 6.6% in the placebo groups (Table 15). The most frequently reported SAEs (1% or more of patients in any treatment group) were COPD exacerbation (0.7% to 2.8% in the ACL 400 mcg and 0.5% to 3.7% in the placebo groups) and acute respiratory failure (1.1% in the ACL 400 mcg group of Study LAS-MD-33 only). Please see Section 3.6.3 for details of reported deaths in these trials.

In the active comparator trials, the frequency of SAEs was low, ranging from 0% to 1.8% in the ACL 400 mcg groups, 0% to 2.5% in the tiotropium 18 mcg groups, 0% in the formoterol 12 mcg group, and 0% to 3.3% in the placebo groups (Table 16). The most frequently reported SAE (1% or more of patients in any treatment group) was COPD exacerbation (0% to 1.4% in the ACL 400 mcg groups, 0% to 0.6% in the

tiotropium 18 mcg groups, 0% in the formoterol group, and 0% to 3.3% in the placebo groups). There were no reported deaths in the active comparator trials.

3.7.3 Withdrawals due to adverse events

In the placebo-controlled trials, WDAEs ranged from 3.0% to 7.3% in the ACL 400 mcg groups and 4.0% to 7.5% in the placebo groups (Table 15). The most frequently reported reason (1% or more of patients in any treatment group) was COPD (0.5% to 3.4% in the ACL 400 mcg groups and 1.8% to 3.8% in the placebo groups). The next most frequently reported reasons were dyspnea and ventricular tachycardia (Table 15).

In the active comparator trials, WDAEs ranged from 0% to 2.7% in the ACL 400 mcg groups, 0% to 1.3% in the tiotropium 18 mcg groups, 1.4% in the formoterol group, and 3.5% to 10.0% in the placebo groups (Table 16). The most frequently reported reason (1% or more of patients in any treatment group) was COPD (0% to 2.7% in the ACL 400 mcg groups, 0% to 1.3% in the tiotropium groups, 0% in the formoterol group, and 1.3% to 3.6% in the placebo groups).

TABLE 15: HARMS: PLACEBO-CONTROLLED TRIALS (SAFETY POPULATION)

Characteristic	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)
AEs						
Patients with > 0 AEs, N (%)	144 (53.5)	156 (57.1)	85 (44.7)	97 (52.2)	90 (50.8)	90 (49.5)
Most frequent AEs (by preferred term)[a]						
COPD	38 (14.1)	56 (20.5)	14 (7.4)	23 (12.4)	23 (13.0)	21 (11.5)
Headache	33 (12.3)	22 (8.1)	3 (1.6)	4 (2.2)	6 (3.4)	6 (3.3)
Nasopharyngitis	30 (11.2)	23 (8.4)	3 (1.6)	2 (1.1)	—	—
Back pain	5 (1.9)	10 (3.7)	3 (1.6)	1 (0.5)	—	—
Hypertension	7 (2.6)	9 (3.3)	—	—	2 (1.1)	4 (2.2)
Rhinitis	9 (3.3)	7 (2.6)	—	—	—	—
Cough	7 (2.6)	5 (1.8)	4 (2.1)	5 (2.7)	8 (4.5)	4 (2.2)
Diarrhea	8 (3.0)	3 (1.1)	4 (2.1)	3 (1.6)	5 (2.8)	3 (1.6)
Arthralgia	3 (1.1)	6 (2.2)	5 (2.6)	1 (0.5)	—	—
Bronchitis	7 (2.6)	6 (2.2)	0 (0)	4 (2.2)	—	—
Influenza	5 (1.9)	6 (2.2)	—	—	—	—
Dyspepsia	1 (0.4)	6 (2.2)	—	—	—	—
Toothache	6 (2.2)	1 (0.4)	—	—	—	—
UTI	2 (0.7)	2 (0.7)	3 (1.6)	4 (2.2)	—	—
Dyspnea	—	—	5 (2.6)	6 (3.2)	2 (1.1)	4 (2.2)
Oropharyngeal pain	—	—	4 (2.1)	3 (1.6)	—	—
Fatigue	—	—	4 (2.1)	4 (2.2)	1 (0.6)	4 (2.2)
Insomnia	—	—	3 (1.6)	6 (3.2)	—	—
URTI	—	—	2 (1.1)	7 (3.8)	—	—
Nausea	—	—	2 (1.1)	4 (2.2)	3 (1.7)	5 (2.7)
Dizziness	—	—	2 (1.1)	1 (0.5)		
Sinusitis	—	—	—	—	5 (2.8)	2 (1.1)

Characteristic	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)
SAEs						
Patients with > 0 SAEs, N (%)	15 (5.6)	15 (5.5)	6 (3.2)	4 (2.2)	8 (4.5)	12 (6.6)
Most frequent SAEs (by preferred term)[b]						
COPD	2 (0.7)	10 (3.7)	3 (1.6)	1 (0.5)	5 (2.8)	6 (3.3)
Acute respiratory failure	0 (0)	0 (0)	2 (1.1)	0 (0)		
WDAEs						
WDAEs, N (%)	8 (3.0)	11 (4.0)	8 (4.2)	14 (7.5)	13 (7.3)	8 (4.4)
Most common reasons for withdrawal (by preferred term)[b]						
COPD	4 (1.5)	5 (1.8)	1 (0.5)	7 (3.8)	6 (3.4)	4 (2.2)
Dyspnea	0 (0)	1 (0.4)	2 (1.1)	2 (1.1)	—	—
Ventricular tachycardia	0 (0)	0 (0)	2 (1.1)	1 (0.5)	—	—

ACL = aclidinium bromide; AE = adverse event; COPD = chronic obstructive pulmonary disease; SAE = serious adverse event; SD = standard deviation; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Reported by at least 2% of patients in any treatment group.

[b] Reported by at least 1% of patients in any treatment group.

Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 16: HARMS: ACTIVE COMPARATOR TRIALS (SAFETY POPULATION)

Characteristic	M/34273/23			M/34273/29			M/34273/39		
	ACL 400 (N = 29)	TIO 18 (N = 28)	Placebo (N = 30)	ACL 400 (N = 74)	FOR 12 (N = 74)	Placebo (N = 76)	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Patients with > 0 AEs, N (%)	7 (24.1)	3 (10.7)	8 (26.7)	14 (18.9)	11 (14.9)	16 (21.1)	47 (27.5)	47 (29.7)	22 (25.9)
Most frequent AEs (by preferred term)[a]									
Atrial fibrillation	0 (0)	1 (3.3)	0 (0)	—	—	—	—	—	—
Diarrhea	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.6)	—	—	—
Flatulence	1 (3.4)	0 (0)	0 (0)	—	—	—	—	—	—
Toothache	0 (0)	1 (3.3)	0 (0)	2 (2.7)	0 (0)	0 (0)	—	—	—
Fatigue	1 (3.4)	0 (0)	0 (0)	—	—	—	—	—	—
Nasopharyngitis	1 (3.4)	1 (3.6)	0 (0)	3 (4.1)	1 (1.4)	1 (1.3)	10 (5.8)	9 (5.7)	2 (2.4)
Pneumonia	1 (3.4)	0 (0)	0 (0)	—	—	—	—	—	—
Rhinitis	0 (0)	0 (0)	1 (3.3)	—	—	—	—	—	—
Confusion	1 (3.4)	0 (0)	0 (0)	—	—	—	—	—	—
Back pain	1 (3.4)	1 (3.6)	0 (0)	—	—	—	3 (1.8)	2 (1.3)	2 (2.4)
Pain in extremity	1 (3.4)	0 (0)	0 (0)	—	—	—	—	—	—
Syncope	1 (3.4)	0 (0)	0 (0)	—	—	—	—	—	—
Headache	0 (0)	1 (3.6)	1 (3.3)	5 (6.8)	2 (2.7)	5 (6.6)	12 (7.0)	6 (3.8)	3 (3.5)
Cough	1 (3.4)	0 (0)	0 (0)	1 (1.4)	1 (1.4)	2 (2.6)	3 (1.8)	3 (1.9)	3 (3.5)
Oropharyngeal pain	1 (3.4)	0 (0)	1 (3.3)	—	—	—	—	—	—
COPD	0 (0)	0 (0)	3 (10.0)	—	—	—	4 (2.3)	2 (1.3)	4 (4.7)
Dyspnea	0 (0)	0 (0)	1 (3.3)	—	—	—	—	—	—
Pruritis	1 (3.4)	0 (0)	0 (0)	2 (2.7)	0 (0)	2 (2.6)	—	—	—
Hypertension	—	—	—	—	—	—	1 (0.6)	2 (1.3)	3 (3.5)
SAEs									
Patients with > 0 SAEs, N (%)	0 (0)	0 (0)	1 (3.3)	1 (1.4)	0 (0)	2 (2.6)	3 (1.8)	4 (2.5)	0 (0)

Characteristic	M/34273/23			M/34273/29			M/34273/39		
	ACL 400 (N = 29)	TIO 18 (N = 28)	Placebo (N = 30)	ACL 400 (N = 74)	FOR 12 (N = 74)	Placebo (N = 76)	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Most frequent SAEs (by preferred term)[b]									
COPD	0 (0)	0 (0)	1 (3.3)	1 (1.4)	0 (0)	1 (1.3)	0 (0)	1 (0.6)	0 (0)
WDAEs									
WDAEs, N (%)	0 (0)	0 (0)	3 (10.0)	2 (2.7)	1 (1.4)	3 (4.0)	3 (1.8)	2 (1.3)	3 (3.5)
Most common reasons for withdrawal (by preferred term)[a]									
COPD	0 (0)	0 (0)	1 (3.6)	2 (2.7)	0 (0)	1 (1.3)	2 (1.2)	2 (1.3)	2 (2.4)

ACL = aclidinium bromide; AE = adverse event; COPD = chronic obstructive pulmonary disease; FOR = formoterol; SAE = serious adverse event; TIO = tiotropium; WDAE = withdrawal due to adverse event.

[a] Reported by at least 2% of patients in any treatment group.

[b] Reported by at least 1% of patients in any treatment group.

Source: Clinical Study Reports for M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

3.7.5 Notable harms

Notable AEs identified for antimuscarinic drugs are anticholinergic AEs and cardiovascular AEs. Potential anticholinergic AEs are summarized across the three placebo-controlled trials in Table 17. Overall, the frequency of anticholinergic AEs was low and similar between ACL 400 mcg and placebo in all three trials. The incidence of AEs related to any cardiac disorders ranged from 4.0% to 4.7% in the ACL 400 mcg groups and 1.8% to 5.5% in the placebo groups. The incidence of any specific cardiac disorder (e.g., supraventricular tachycardia) did not exceed 1.1% in any treatment group.

The only active comparator trial in which potential anticholinergic or cardiac disorder AEs were reported was Study M/34273/39 (Table 18). Similarly, the incidence of these AEs was low and similar between-treatment groups. The incidence of pharyngitis (1.3% versus 0.6%), dry mouth (1.3% versus 0.6%), and constipation (1.3% versus 0%) was higher in the tiotropium 18 mcg group compared with the ACL 400 mcg group, but, given the small numbers of events, it is difficult to draw any meaningful inferences from these results.

TABLE 17: NOTABLE HARMS: PLACEBO-CONTROLLED TRIALS (SAFETY POPULATION)

Characteristic	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)
Potential[a] anticholinergic AEs (by category and preferred term), N (%)						
Cardiac						
Sinus tachycardia	0 (0)	1 (0.4)	1 (0.5)	0 (0)	—	—
Palpitations	1 (0.4)	0 (0)	—	—	0 (0)	0 (0)
Supraventricular tachycardia	—	—	2 (1.1)	2 (1.1)	—	—
Ventricular tachycardia	—	—	2 (1.1)	1 (0.5)	—	—
Heart rate increased	—	—	0 (0)	1 (0.5)	0 (0)	0 (0)
Tachycardia					1 (0.6)	0 (0)
Arrhythmia					0 (0)	1 (0.5)
Bradycardia					0 (0)	2 (1.1)
Eye disorders						
Vision blurred	0 (0)	0 (0)	—	—	—	—
Optic neuritis	—	—	—	—	1 (0.6)	0 (0)
Gastrointestinal						
Constipation	0 (0)	2 (0.7)	0 (0)	1 (0.5)	0 (0)	3 (1.6)
Dry mouth	1 (0.4)	1 (0.4)	1 (0.5)	2 (1.1)	3 (1.7)	1 (0.5)
Renal and urinary						
UTI	2 (0.7)	2 (0.7)	3 (1.6)	4 (2.2)	1 (0.6)	0 (0)
Cystitis	1 (0.4)	0 (0)	0 (0)	1 (0.5)	—	—
Dysuria	1 (0.4)	0 (0)	—	—	—	—
Urinary retention	—	—	—	—	1 (0.6)	0 (0)
Urinary incontinence	—	—	—	—	0 (0)	1 (0.5)
Respiratory						
Dysphonia	1 (0.4)	0 (0)	—	—	—	—
Oropharyngeal pain	2 (0.7)	4 (1.5)	—	—	—	—
Dry throat	0 (0)	1 (0.4)	—	—	—	—
Throat irritation	1 (0.4)	4 (1.5)	—	—	—	—

Characteristic	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)
Cardiac disorders (by preferred term)[a]						
Any cardiac disorder	11 (4.1)	5 (1.8)	9 (4.7)	8 (4.3)	7 (4.0)	10 (5.5)
AV block first degree	1 (0.4)	0 (0)	2 (1.1)	1 (0.5)	1 (0.6)	0 (0)
Supraventricular tachycardia	0 (0)	1 (0.4)	2 (1.1)	2 (1.1)	—	—
Supraventricular extrasystoles	—	—	0 (0)	2 (1.1)	—	—
Ventricular tachycardia	—	—	2 (1.1)	0 (0)	—	—
Ventricular extrasystoles	0 (0)	0 (0)	1 (0.5)	2 (1.1)	1 (0.6)	1 (0.5)
Bradycardia	—	—	0 (0)	0 (0)	0 (0)	2 (1.1)
Atrial fibrillation	—	—	0 (0)	0 (0)	1 (0.6)	2 (1.1)

ACL = aclidinium bromide; AV = atrioventricular; COPD = chronic obstructive pulmonary disease; UTI = urinary tract infection.
[a] Reported by at least 1% of patients in any group.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 18: NOTABLE HARMS: ACTIVE COMPARATOR TRIALS (SAFETY POPULATION)

	M/34273/39		
	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Potential anticholinergic AEs (by category and preferred term)			
Infections and infestations			
Pharyngitis	1 (0.6)	2 (1.3)	1 (1.2)
UTI	1 (0.6)	0 (0)	0 (0)
Respiratory, thoracic, and mediastinal disorders			
Oropharyngeal pain	1 (0.6)	1 (0.6)	1 (1.2)
Throat irritation	1 (0.6)	0 (0)	1 (1.2)
Dry throat	0 (0)	1 (0.6)	0 (0)
Gastrointestinal disorders			
Dry mouth	1 (0.6)	2 (1.3)	0 (0)
Constipation	0 (0)	2 (1.3)	0 (0)
General disorders and administration site conditions			
Pyrexia	1 (0.6)	0 (0)	0 (0)
Cardiac disorders (by Preferred Term)[a]			
Any cardiac disorder	2 (1.2)	2 (1.3)	0 (0)

ACL = aclidinium bromide; TIO = tiotropium bromide; UTI = urinary tract infection.
[a] Reported by at least 1% of patients in any group. (Note all cardiac-related AEs occurred at a frequency of 0.2% to 0.6% in individual patients.)
Source: Clinical Study Report for M/34273/39.[17]

4. DISCUSSION

4.1 Summary of Available Evidence

Six prospective, double-blind, RCTs were included in the review, of which three were placebo-controlled trials (M/34273/34 [N = 828], LAS-MD-33 [N = 561], and LAS-MD-38 Part A [N = 544])[1-3] and three were active comparator trials (M/34273/23 [N = 30], M/34273/29 [N = 79], and M/34273/39 [N = 414]).[4-6] All of the trials included patients who were at least 40 years of age, had moderate to severe COPD (according to GOLD criteria), and smoked at least 10 pack-years. The primary outcome in the placebo-controlled trials was the change from baseline in the pre-dose (trough) FEV_1 at 12 weeks, whereas in the active comparator trials it was the change from baseline in the normalized FEV_1 $AUC_{0\text{-}12/12h}$ (Studies M/34273/23 and M/34273/29) or FEV_1 $AUC_{0\text{-}24/24h}$ (Study M/34273/39). All primary end points were analyzed using the ITT population. Key limitations among the trials include baseline characteristics that affect the generalizability of the findings to Canadian COPD patients (e.g., age, smoking status, pre-study COPD medication use, proportion of patients with bronchial reversibility, and the exclusion of patients with unstable cardiac conditions), the short duration of the trials, and the fact that none of the trials were prospectively designed or powered to assess treatment differences in COPD exacerbations. Furthermore, the baseline imbalance in Study LAS-MD-38 Part A, in which a larger proportion of patients with severe COPD were included in the ACL 400 mcg group, compromises interpretation of the results from this trial and biases the results toward the null hypothesis of no treatment difference when compared with placebo.

4.2 Interpretation of Results

4.2.1 Efficacy

A number of baseline characteristics were identified that affect the generalizability of the results from the included trials to a Canadian population of COPD patients. These include the relatively young age of enrolled patients, high proportion of patients who continued to smoke during the trials, low pre-study use of ICS or LABA + ICS therapy, and the relatively high proportion of patients with bronchial reversibility. According to the clinical expert consulted for this review, the patients in the included trials are not representative of the target population for COPD treatment in Canada, as the average age for initiation of COPD therapy in patients is usually 65 years. In general, patients are most commonly treated with a combination of LABA + ICS in Canada, whereas prior use of such therapy was low in the trials, likely due to poor access. The high rate of bronchial reversibility implies that many enrolled patients may have had an asthmatic component to their COPD, which could have exaggerated the bronchodilatory benefit of ACL in COPD. In fact, in the one trial (M/34273/34) that reported pre-specified subgroup analyses, a larger treatment effect was observed in the change from baseline in peak FEV_1 at 24 weeks in patients with reversibility compared with those with no reversibility.

The baseline imbalance in the proportion of patients with severe COPD among the treatment groups in Study LAS-MD-38 Part A complicates the interpretation of results from this trial. After investigation of multiple possible reasons for the imbalance, the manufacturer concluded that it was due to chance and to the variability that can occur in a clinical trial.[3] The imbalance resulted in a higher proportion of patients with severe COPD randomized to the ACL 400 mcg twice-daily group compared with the placebo group and may have led to a smaller treatment effect being observed with ACL 400 mcg twice daily in this trial compared with the other included trials (e.g., change in SGRQ score from baseline, COPD exacerbations of any severity). It appears that an exploratory post-hoc analysis was performed by the manufacturer to investigate whether treatment effects would be modified by applying a matching-based adjustment for the imbalanced baseline variables.[3] Although the results demonstrated that the

magnitude of trough FEV_1 improvement with ACL over placebo was increased compared with the pre-specified analysis, the difference (0.102 mL) was very close to the lower range of the MCID (0.100 L).[3] These data should be interpreted with caution as this statistical analysis was not specified a priori.

In all six trials, ACL 400 mcg twice daily resulted in statistically significantly greater bronchodilation compared with placebo as assessed by spirometry measurements (e.g., FEV_1, FVC, and IC). The LSM differences between groups in the change from baseline in the trough FEV_1 at 12 weeks (the primary efficacy end point in the placebo-controlled trials) ranged from 0.072 L to 0.124 L. The suggested MCID in the literature for trough FEV_1 is a change of 0.100 L to 0.140 L.[7,8] The difference between the ACL 400 mcg twice-daily and placebo groups at week 12 was at the lower range of the MCID in Study M/34273/34 (0.105 L) and was not reached in Study LAS-MD-38 Part A (0.072 L). The treatment effect (change of approximately 0.100 L) from baseline appeared to be maintained over 24 weeks in Study M/34273/34; however, in the long-term and extension trials reported in Appendix 6: SUMMARY OF LONG-TERM AND EXTENSION STUDIES, the mean change in trough FEV_1 with ACL 400 mcg was below the MCID, ranging from 0.030 L (40 weeks) to 0.072 L (52 weeks). In the active comparator trials, the LSM differences between ACL 400 mcg twice daily and placebo in the change from baseline in trough FEV_1 to study period end ranged from 0.141 L (week 6 in Study M/34273/39) to 0.186 L (day 15 in Study M/34273/23), both exceeding the MCID. Given the short duration of these trials, it is not known whether the treatment effect is maintained over time. In comparison, the LSM differences between tiotropium 18 mcg once daily and placebo ranged from 0.102 L (week 6 in Study M/34273/39) to 0.150 L (day 15 in Study M/34273/23) and between formoterol and placebo was 0.148 L at day 7 in Study M/34273/29.

The only statistically significant difference between active treatments for trough FEV_1 was on day 1, which was observed for the comparison of ACL 400 mcg twice daily and tiotropium 18 mcg once daily (i.e., LSM difference of 0.048 L in favour of ACL). The rapidity of action of ACL, attributed to its pharmacokinetic properties, is supported by attainment of maximal bronchodilation within one to three hours. The clinical significance of a rapid onset of action for a LAMA in COPD is uncertain, especially in the context of chronic administration. Furthermore, differences between active treatments for other spirometry measures (e.g., FEV_1 $AUC_{0\text{-}24}$ or $AUC_{12\text{-}24}$) were only statistically significant when a 24-hour period was considered, underscoring the importance of the second evening dose of ACL. Before the clinical development of ACL 400 mcg twice daily, a development program for once-daily dosing of ACL 200 mcg was undertaken. Following completion of a dose-finding study, two pivotal studies, and three efficacy profiling studies, it was concluded that the 24 hour bronchodilator efficacy of ACL 200 mcg once daily was suboptimal.[10] Of note, an ongoing clinical program is investigating the fixed combination of ACL and formoterol.[10]

None of the included trials were designed or powered to prospectively assess treatment differences in COPD exacerbations, an important measure for treatment decisions in COPD and a key health care cost driver. According to the patient input received for this review (Appendix 1: PATIENT INPUT SUMMARY), the control of COPD symptoms and prevention or minimization of the frequency and duration of exacerbations are key outcomes of importance to COPD patients. Overall, exacerbation rates or the number of hospitalizations due to COPD exacerbations that were reported in the trials were low and the trial durations too short to assess any meaningful treatment differences in these outcomes.

Statistically significant improvements in symptom-related outcomes with ACL 400 mcg twice daily as measured by the SGRQ, TDI, patient reports of morning and night-time COPD symptoms, and rescue medication use, provide support for the efficacy of ACL in the treatment of patients with moderate to

severe COPD. The SGRQ and TDI were measured only in the placebo-controlled trials, and the results do not provide robust evidence of clinically meaningful symptomatic benefit. The change from baseline in SGRQ total score or the TDI focal score was assessed only as a powered secondary outcome in Study M/34273/34 and as "another" efficacy variable in Studies LAS-MD-33 and LAS-MD-38 Part A. At week 12, although statistically significant differences were observed between ACL 400 mcg twice daily and placebo for LSM differences in the change in SGRQ total score from baseline in Studies M/34273/34 and LAS-MD-33, the MCID (reduction of four units or more) was achieved only in Study M/34273/34. At week 12 in Study LAS-MD-38 Part A, the MCID was achieved in both the ACL 400 mcg twice-daily and the placebo groups. Inconsistency between trials is also demonstrated by the OR for the proportion of patients achieving the MCID for the SGRQ. The OR was statistically significant at all-time points in Study M/34273/34, only at week 4 in Study LAS-MD-33, and at no time point in Study LAS-MD-38 Part A. Changes from baseline in the TDI focal score between treatments at week 12 were statistically significant in all three placebo-controlled trials; however, the LSM differences between ACL 400 mcg twice daily and placebo only ranged from 0.88 to 1.0, which is of uncertain clinical significance as the MCID for the TDI focal score reported in the literature is an improvement of one unit or more.[9] The OR of achieving the MCID was statistically significant in all studies at the time points measured.

There was substantial heterogeneity in the manner in which symptoms were measured and analyzed across the included trials. Patient-reported symptoms were reported in two of the placebo-controlled (M/34273/34 and LAS-MD-33) and two of the active comparator (M/34273/23 and M/34273/39) trials. In general, statistically significant improvements in various COPD symptoms were observed with ACL 400 mcg twice daily over placebo; however, the small magnitude of the change in symptom scores is of uncertain clinical relevance. Furthermore, the different tools used to measure symptoms in the trials, including some developed by the manufacturer and others not validated for use in COPD, complicate interpretation of the results and preclude meaningful comparisons among trials. Although, generally, the use of rescue medication was statistically significantly reduced in the ACL 400 mcg twice-daily group compared with placebo groups, the results between trials is inconsistent and the clinical significance of the LSM difference between groups (i.e., less than one puff of salbutamol 100 mcg) is questionable.

In keeping with these findings, Health Canada concluded that the pivotal (placebo-controlled) studies have provided substantial evidence for the efficacy of ACL 400 mcg twice daily as a bronchodilator in patients with moderate to severe COPD; however, they have not provided robust evidence for the drug's efficacy in providing symptom relief, which was reflected in the final indication.[10] The final Health Canada–approved indication for Tudorza Genuair is for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[32]

Across all trials, compliance was very high (> 91% across treatment groups). In the active comparator trials, the manufacturer captured information on patient satisfaction and perception of different inhaler attributes in the active comparator trials by administering patient questionnaires. It is not clear how the questionnaires were administered and whether potential biases could have influenced the results. Furthermore, as there are no data available on the proportions of patients who used the various devices correctly or incorrectly, there is the possibility that, although patients may have found a particular inhaler device easier to use or preferable to another, they may have been using the devices incorrectly. More patients in Studies M/34273/23 and M/34273/29 found the Genuair inhaler easier to use, and more patients definitively preferred the Genuair inhaler over the HandiHaler (30.00% versus 6.67%) or the Aerolizer (62.8% versus 6.4%) devices, although between 40.0% and 14.1% of patients, respectively, did not have any preference. In Study M/34273/39, a statistically significant higher proportion of patients preferred the Genuair inhaler over the HandiHaler (80.1% versus 10.7%) and statistically more

patients (88.8%) were also willing to continue using the Genuair device over six weeks of treatment than the HandiHaler device (45.4%). These findings are supported by the results of other manufacturer-sponsored studies summarized in Appendix 8: SUMMARY OF DRY POWDER INHALERS, which found that the Genuair inhaler was associated with greater patient preference, greater patient satisfaction, fewer critical errors, and higher peak inspiratory flow than the HandiHaler. The ease of use of the Genuair inhaler was mentioned in the patient input received for this review (Appendix 1: PATIENT INPUT SUMMARY). According to the clinical expert on the review team, the choice to prescribe Tudorza Genuair over alternative COPD therapies will likely be based, in large part, on the ease of use of the Genuair multi-dose inhaler.

The manufacturer also submitted a systematic review and network meta-analysis (summarized and critically appraised in Appendix 7: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS) that was conducted due to a lack of head-to-head RCTs designed to assess the comparative efficacy of ACL, tiotropium, and glycopyrronium. Based on the outcomes of mean change from baseline in FEV_1, SGRQ total score, TDI focal score, COPD exacerbations, and drug discontinuations, the author concluded that there is comparative efficacy among ACL, tiotropium, or glycopyrronium. However, there were numerous key limitations regarding the reporting of the manufacturer-submitted indirect comparison, including sparse details regarding sensitivity analyses, limited detail regarding conclusions and the implications of the conclusions, no network of studies diagram, and lack of reporting of the comparability of the patient populations included in the studies. In the meta-regression analysis, there was no information provided with respect to model fit, and the number of trials used in the regression (eight) is small. Furthermore, it is unclear why 10 trials comparing tiotropium with placebo were excluded from the analysis. A manufacturer-sponsored published systematic review and network meta-analysis of similar design also came to the same conclusion — that is, that maintenance treatment with ACL 400 mcg twice daily is expected to produce similar improvements in lung function, health-related quality of life, and dyspnea compared with tiotropium and glycopyrronium.[11]

4.2.2 Harms

In the placebo-controlled trials, treatment-emergent AEs, SAEs, and WDAEs occurred with similar frequency in the ACL 400 mcg twice-daily and placebo groups. The most frequently reported AEs were COPD exacerbations, headache, and nasopharyngitis. In the active comparator trials, although the incidence of these safety outcomes was lower than observed in the placebo-controlled trials, likely due to the shorter duration of the trials, the pattern and type of AEs, SAEs, and WDAEs experienced were similar. There did not appear to be any differences between active treatments in any of these safety outcomes. Notable harms included anticholinergic AEs and cardiovascular AEs, and results for these categories were available from the three placebo-controlled trials and Study M/342273/39. Overall, the incidence of both was low and similar between-treatment groups in the trials. In the active comparator trial M/34273/39, the incidence of pharyngitis (1.3% versus 0.6%), dry mouth (1.3% versus 0.6%), and constipation (1.3% versus 0%), was higher in the tiotropium 18 mcg once-daily group compared with the ACL 400 mcg twice-daily group, but, given the small numbers of events, it is difficult to draw any meaningful inferences from these results.

In keeping with the identified differences in baseline characteristics, the safety populations in the included trials may not be closely representative of the target treatment population in Canada. This is especially true with regard to the exclusion of patients with unstable cardiac conditions from all included trials, as heart disease is a comorbidity commonly associated with COPD.[19] It is anticipated that many patients with COPD will also have cardiac conditions and will require treatment for COPD.[19] According to

the Health Canada Reviewer's Report,[10] the manufacturer examined cardiovascular treatment-emergent AEs by conducting analyses of major adverse cardiovascular events (MACE) and of cardiac events of interest based on standardized MedDRA queries (SMQs). No apparent differences in MACE scores or in the incidence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke were observed.[10] An imbalance was noted for the SMQs of bradycardia, conduction defects, or sinus node disorder and of cardiac failure; however, according to the Health Canada reviewer, the manufacturer submitted a Risk Management Plan that, coupled with risk minimization activities required by other regulatory agencies and pharmacovigilance practices, adequately addresses the safety issues identified during the review.[10]

5. CONCLUSIONS

Six prospective, double-blind RCTs, including three placebo-controlled trials (N = 1,933) and three active comparator trials (N = 593), that compared ACL with placebo, tiotropium, or formoterol in patients with moderate to severe COPD were included in the review. Compared with placebo, treatment with ACL 400 mcg twice daily was associated with statistically significant improvements in trough FEV_1 ranging from 0.072 L to 0.124 L at 12 weeks in the placebo-controlled trials, and 0.141 L (week 6) to 0.186 L (day 15) in the active comparator trials. The MCID reported for this outcome in the literature is 0.100 to 0.140 L. The magnitude of the treatment effect was comparable to that of tiotropium 18 mcg once daily and formoterol 12 mcg twice daily. None of the trials were designed or powered to assess treatment differences in COPD exacerbations. Statistically significant improvements in symptom-related outcomes with ACL 400 mcg twice daily compared with placebo, as measured by the SGRQ, TDI, patient reports of morning and night-time COPD symptoms, and use of rescue medication were reported. However, the results do not provide robust evidence of clinically meaningful symptomatic benefit due to inconsistencies between trials and uncertain clinical relevance of the magnitude of the treatment effect when compared with the MCIDs for these outcomes. Overall, ACL 400 mcg twice daily was well tolerated. Treatment-emergent AEs, SAEs, and WDAEs occurred with similar frequency in treatment groups and in placebo and other active comparator groups. The most frequently reported AEs were COPD exacerbations, headache, and nasopharyngitis. Rates of anticholinergic and cardiovascular AEs were low and similar among treatment groups.

Key limitations of the evidence from the trials include baseline patient characteristics that affect the generalizability of the findings to Canadian COPD patients (e.g., age, smoking status, pre-study COPD medication use, proportion of patients with bronchial reversibility, and the exclusion of patients with unstable cardiac conditions) as well as the short duration of the trials. The baseline imbalance in the proportions of patients with severe COPD between-treatment groups in Study LAS-MD-38 Part A compromises interpretation of the results from this trial.

APPENDIX 1: PATIENT INPUT SUMMARY

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. It has been reviewed by the submitting patient groups.

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

The Ontario Lung Association (OLA) is a not-for-profit health promotion organization that provides support and education to people living with lung disease in Ontario and is concerned with the prevention and control of chronic lung disease and lung health. The OLA is run by a board of directors, employs approximately 75 people, relies on thousands of volunteers, and has invested more than $27 million in lung health research carried out in Ontario. The OLA has received funding from Pfizer, GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Merck, Novartis, Takeda, InterMune, Grifols, Actelion, and Eli Lilly. In 2013, it also received program funding from the Ontario Home Respiratory Services Association (OHRSA). No conflicts were declared in the preparation of this submission.

COPD Canada is a non-profit organization, established in 2005, with the primary mandate to assist Canadians who suffer from chronic obstructive pulmonary disease (COPD). It is an educational association and patient advocacy group. COPD Canada reviews and interprets the latest scientific and medical advances from worldwide sources and makes this information available in easy-to-understand language to Canadians who suffer from COPD. COPD Canada has received grants from AstraZeneca, GlaxoSmithKline, Novartis, Nycomed-Takeda, and ProResp Canada. No conflicts were declared in the preparation of this submission.

2. Condition and Current Therapy-Related Information

This information was gathered from conversations with patients and caregivers by phone or in group pulmonary rehabilitation settings, a certified respiratory educator, previous patient surveys, the personal experiences of members, and published scientific literature.

Patients with COPD experience many symptoms, but the most common tend to be difficulty breathing, coughing, shortness of breath, fatigue, weakness, lack of appetite, and difficulty talking. Performing everyday tasks such as carrying groceries, changing bed sheets, walking up stairs, opening doors, and showering can be difficult, and patients become limited in their ability to participate in social interactions, occupational activities, and leisure activities.

As the disease worsens, patients with COPD need to adapt their lifestyle in order to cope with their condition. This can include early retirement, walking very slowly, avoiding public places with stairs or without washrooms on the ground floor, being vigilant with respect to weather conditions, and using supplemental oxygen when walking, during pulmonary rehabilitation, or while on an aircraft. Ongoing issues include more frequent exacerbations, loss of appetite, more infections due to lowered immunity, chronic bronchitis, increased reliance on supplemental oxygen, and increased risk of hospitalization and mortality. Furthermore, patients often feel socially isolated, may suffer social stigma, feel a loss of independence, and find their relationships with loved ones are affected, leading to lower emotional well-being and depression.

Caregivers of those living with COPD are frequently the spouse or child of the patient and experience many of the same negative impacts on their lives. They experience limited time for managing their own

physical health and well-being, depression, isolation, anxiety, stress, fatigue, increased requirements for social support, a lack of independence, and reduced abilities to travel and socialize. In the case of adult children caring for their parents, the caregivers are often torn between caring for their parent and their own children. The costs associated with COPD affect the family, the health care system, and the community as a whole, with the loss of productivity and the need for additional health care services.

There is no cure for COPD, there are no medications that reverse the loss of lung function caused by COPD, and no drug has demonstrated effectiveness in halting the progression of the disease. The goals of currently available medications for COPD are to maintain control of symptoms (fatigue, shortness of breath, appetite loss, low energy, irritability, and the inability to fight infection) and prevent or minimize the frequency and duration of exacerbations. Non-medicinal interventions include pulmonary rehabilitation, exercise programs, breathing lessons, and use of supplemental oxygen. The main surgical options include lung transplantation and lung reduction surgery, options that are available only to a small group of COPD patients who qualify.

Treatments tried by those interviewed included tiotropium, fluticasone propionate plus salmeterol (Advair), budesonide plus formoterol (Symbicort), roflumilast, prednisone, salbutamol, ipratropium, and indacaterol. Typical maintenance therapy included the use of tiotropium once daily with fluticasone propionate plus salmeterol 500/50 mcg twice daily. While current treatments provide some relief, adverse effects such as palpitations, dry mouth, voice hoarseness, mouth sores, visual effects, and urinary problems need to be better managed. Exacerbations are often managed with prednisone and antibiotics. While prednisone works quickly, it can have dangerous adverse effects such as stomach upset, general swelling, and increases in the symptoms of osteoporosis and ophthalmic disease.

COPD patients need additional therapies that work to improve breathing, lung function, fatigue, and appetite, as well as reduce hospital admissions, improve quality of life, provide ease of use, and offer more than symptomatic or emergency relief. Because COPD is treated in a stepwise manner, additional treatment options are often needed to address continual disease progression, particularly as the disease becomes more severe. Long-term use of some of the available medications results in their diminishing effectiveness.

3. Related Information About the Drug Being Reviewed

The majority of patients had no experience with aclidinium bromide. One medical doctor and one patient (both of whom were confident the patient was not receiving placebo) who were involved in the clinical trial for this drug were interviewed. Both clinician and patient spoke very positively of the effectiveness of the drug and also underscored the ease of use of the inhaler, stating that it was a significant advancement over current delivery systems. No adverse effects were reported by this patient.

Patients anticipate new treatment options to lead to overall disease management improvement by reducing airflow obstruction, coughing, and the need for rescue medication while improving breathing, energy, and appetite. They would like an increased ability to fight infection and reduced hospital admissions — resulting in overall improved quality of life. Shortness of breath was the symptom they would most like to have improved, and patients would like to be less dependent on oxygen. From a patient's perspective, aclidinium bromide is of critical importance because it is a long-acting treatment that is relatively easy to use, which will encourage compliance, and will provide an additional therapeutic choice.

Patients indicated that they would be able to live with some adverse effects, but nothing worse than they are already experiencing and nothing that was irreversible. Patients do not want to travel to a health care setting to receive new treatments. They do not want to have to make additional changes to daily routines for themselves or their caregivers, do not want anyone to have to take time off work to accommodate treatments, and would like little or no cost burden associated with new treatments. Patients want to improve enough to be less of a burden to their family.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 15, 2013
Alerts:	Weekly search updates until (March 19, 2014)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	*aclidinium bromide/
2	(Tudorza* or Genuair* or Pressair* or aclidinium bromide or aclidinium* or bretaris* or eklira* or LAS-34273 or LAS34273 or LAS W-330 or LAS W330 or UQW7UF9N91 or 320345-99-1).ti,ab.
3	or/1-2
4	3 use oemezd
5	(Tudorza* or Genuair* or Pressair* or aclidinium bromide or aclidinium* or bretaris* or eklira* or LAS-34273 or LAS34273 or LAS W-330 or LAS W330 or UQW7UF9N91 or 320345-99-1).ti,ot,ab,sh,rn,hw,nm.
6	5 use pmez
7	or/4,6
8	7 not conference abstract.pt.
9	remove duplicates from 8

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	October 2013
Keywords:	Included terms for aclidinium bromide and chronic obstructive pulmonary disease
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

TABLE 19: EXCLUDED STUDIES

Reference	Reason for Exclusion
de la Motte S, et al. 2012[44]	Inappropriate dose
Maltais F, et al. 2011[45]	Inappropriate dose
Chanez P, et al. 2010[46]	Inappropriate dose
D'Urzo A, et al. 2013[47]	Inappropriate design
Gelb AF, et al. 2013[48]	Inappropriate design

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 20: CHANGE FROM BASELINE IN MORNING PRE-DOSE (TROUGH) FEV_1 (L) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline						
Mean (SD)	1.508 (0.525)	1.500 (0.489)	1.376 (0.570)	1.332 (0.493)	1.249 (0.519)	1.459 (0.519)
Change from baseline at week 12						
LSM (SE)	0.058 (0.015)	–0.047 (0.015)	0.099 (0.015)	–0.025 (0.015)	0.064 (0.016)	–0.008 (0.015)
LSM diff [vs. placebo] (95% CI); *P* value	0.105 (0.065 to 0.144); *P* < 0.0001		0.124 (0.08 to 0.16); *P* < 0.0001		0.072 (0.03 to 0.12); *P* = 0.0012	
Change from baseline at week 24						
LSM (SE)	0.055 (0.016)	–0.073 (0.016)	-	—	—	—
LSM diff [vs. placebo] (95% CI); *P* value	0.128 (0.085 to 0.170); *P* < 0.0001		-	—	—	—

ACL = aclidinium bromide, CI = confidence interval; FEV_1 = forced expiratory volume in one second; ITT = intention-to-treat; LSM diff = least squares mean difference; SD = standard deviation; SE = standard error; vs. = versus.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 21: CHANGE FROM BASELINE IN MORNING PRE-DOSE (TROUGH) FEV_1 (L) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): ACTIVE COMPARATOR TRIALS

	M/34273/23			M/34273/29			M/34273/39		
	ACL 400 (N = 29)	TIO 18 (N = 28)	Placebo (N = 30)	ACL 400 (N = 74)	FOR 12 (N = 74)	Placebo (N = 76)	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Baseline									
Mean (SD)	1.463 (0.500)	1.493 (0.469)	1.444 (0.444)	1.422 (0.471)	1.383 (0.458)	1.441 (0.455)	1.462 (0.481)	1.543 (0.536)	1.422 (0.521)
Change from baseline at day 1									
LSM (SE)	0.164 (0.048)	0.099 (0.048)	– 0.0235 (0.047)				0.072 (0.016)	0.024 (0.017)	–0.069 (0.022)
LSM diff [ACL vs. placebo] (95% CI); *P* value	0.186 (0.112 to 0.260); P<0.0001						0.141 (0.088 to 0.195); *P* < 0.0001		
LSM diff [TIO vs. placebo] (95% CI); *P* value	0.122 (0.0479 to 0.196); *P* = 0.0022						0.093 (0.039 to 0.148); *P* = 0.0009		
LSM diff [ACL vs. TIO] (95% CI); *P* value	0.064 (–0.011 to 0.139); *P* = 0.090						0.048 (0.003 to 0.093); *P* = 0.0351		
Change from baseline at day 7									
LSM (SE)				0.130 (0.023)	0.123 (0.023)	–0.025 (0.023)			
LSM diff [ACL vs. placebo] (95% CI); *P* value				0.154 (0.112 to 0.197); *P* < 0.0001					
LSM diff [FOR vs. placebo] (95% CI); *P* value				0.148 (0.105 to 0.190); *P* < 0.0001					
LSM diff [ACL vs. FOR] (95% CI); *P* value				0.007 (–0.036 to 0.050); *P* = 0.7589					
Change from baseline at day 15									
LSM (SE)	0.143 (0.079)	0.107 (0.079)	–0.043 (0.078)						
LSM Diff [ACL vs. placebo] (95% CI); *P* value	0.186 (0.124 to 0.248); *P* < 00001								
LSM diff [TIO vs. placebo]	0.150 (0.086 to 0.213); *P* < 0.0001								

	M/34273/23			M/34273/29			M/34273/39		
	ACL 400 (N = 29)	TIO 18 (N = 28)	Placebo (N = 30)	ACL 400 (N = 74)	FOR 12 (N = 74)	Placebo (N = 76)	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
(95% CI); *P* value									
LSM diff [ACL vs. TIO] (95% CI); *P* value	0.036 (–0.027 to 0.099); *P* = 0.2560								
Change from baseline at week 6									
LSM (SE)							0.029 (0.018)	–0.009 (0.018)	–0.112 (0.024)
LSM diff [ACL vs. placebo] (95% CI); *P* value							0.141 (0.083 to 0.199); *P* < 0.0001		
LSM diff [TIO vs. Placebo] (95% CI); *P* value							0.102 (0.043 to 0.161); *P* = 0.0008		
LSM diff ACL vs. TIO] (95% CI); *P* value							0.038 (–0.010 to 0.087); *P* = 0.1191		

ACL = aclidinium bromide, CI = confidence interval; FEV_1 = forced expiratory volume in one second; FOR = formoterol; LSM diff = least squares mean difference; SD = standard deviation; SE = standard error; TIO = tiotropium; vs. = versus.
Source: Clinical Study Reports for M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

TABLE 22: SUMMARY OF CHANGE FROM BASELINE IN SPIROMETRY PARAMETERS OVER TREATMENT PERIOD (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

Adjusted LSM diff (L) of ACL 400 mcg vs. placebo				
Trial: M/34273/34				
End points		**Range: Day 1–Week 24**	**Week 12[a]**	**Week 24[a]**
FEV_1	**Trough**	0.105 to 0.140	0.105	0.128
	AUC_{0-3h}	0.180 to 0.210	0.187	0.210
	Peak	0.187 to 0.211	0.191	0.209
FVC	**Trough**	0.184 to 0.224	0.184	0.224
	Peak	0.257 to 0.295	0.257	0.292
IC	**Trough**	0.109 to 0.133	0.133	0.119
Trial LAS-MD-33				
End points		**Range: Week 1–Week 8**	**Week 12[b]**	**Week 24**
FEV_1	**Trough**	0.108 to 0.133	0.124	NA
	AUC_{0-3h}	0.186 to 0.196	0.192	NA
	Peak	0.185 to 0.189	0.192	NA
FVC	**Trough**	0.196 to 0.213	0.219	NA
	Peak	0.259 to 0.303	0.279	NA
IC	**Trough**	0.113 to 0.128	0.138	NA
Trial LAS-MD-38 Part A				
End points		**Range: Week 1–Week 8**	**Week 12[c]**	**Week 24**
FEV_1	**Trough**	0.065 to 0.101	0.072	NA
	AUC_{0-3h}	0.215 to 0.337	0.215	NA
	Peak	0.175 to 0.186	0.125	NA
FVC	**Trough**	0.157 to 0.196	0.120	NA
	Peak	0.296 to 0.338	0.212	NA
IC	**Trough**	0.090 to 0.126	0.113	NA

ACL = aclidinium bromide, AUC = area under the curve; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IC = inspiratory capacity; LSM diff = least squares mean difference; NA = not applicable.
[a] All treatment differences were $P \leq 0.0001$ for FEV_1, $P < 0.001$ for FVC and $P < 0.05$ for IC compared with placebo.
[b] All treatment differences were $P < 0.0001$ for FEV_1 and FVC, $P < 0.01$ for IC compared with placebo.
[c] All treatment differences were $P < 0.0001$ for peak FEV_1 and FVC, $P < 0.05$ for trough FEV_1 and IC and $P < 0.01$ for trough FVC compared with placebo.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 23: STUDY M/34273/23: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN NORMALIZED FEV_1 AUC (L) ON DAYS 1 AND 15 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Normalized FEV_1 AUC_{0-12} on day 1				
ACL 400	Placebo	0.214 (0.024)	(0.166 to 0.263)	< 0.0001
TIO 18	Placebo	0.163 (0.024)	(0.133 to 0.212)	< 0.0001
ACL 400	TIO 18	0.052 (0.024)	(0.002 to 0.101)	0.0411
Normalized FEV_1 AUC_{0-12} on day 15				
ACL 400	Placebo	0.221 (0.041)	(0.136 to 0.306)	< 0.0001
TIO 18	Placebo	0.244 (0.042)	(0.159 to 0.330)	< 0.0001
ACL 400	TIO 18	–0.023 (0.041)	(–0.108 to 0.061)	0.5723
Normalized FEV_1 AUC_{0-24} on day 1				
ACL 400	Placebo	0.235 (0.026)	(0.183 to 0.288)	< 0.0001
TIO 18	Placebo	0.162 (0.026)	(0.109 to 0.216)	< 0.0001
ACL 400	TIO 18	0.073 (0.026)	(0.020 to 0.126)	0.0080
Normalized FEV_1 AUC_{0-24} on day 15				
ACL 400	Placebo	0.232 (0.029)	(0.174 to 0.291)	< 0.0001
TIO 18	Placebo	0.185 (0.029)	(0.127 to 0.243)	< 0.0001
ACL 400	TIO 18	0.048 (0.029)	(–0.010 to 0.106)	0.1038
Normalized FEV_1 AUC_{12-24} on day 1				
ACL 400	Placebo	0.262 (0.029)	(0.203 to 0.322)	< 0.0001
TIO 18	Placebo	0.161 (0.030)	(0.101 to 0.221)	< 0.0001
ACL 400	TIO 18	0.101 (0.030)	(0.041 to 0.162)	0.0017
Normalized FEV_1 AUC_{12-24} on day 15				
ACL 400	Placebo	0.207 (0.032)	(0.142 to 0.272)	< 0.0001
TIO 18	Placebo	0.129 (0.032)	(0.064 to 0.193)	0.0003
ACL 400	TIO 18	0.078 (0.032)	(0.013 to 0.143)	0.0202

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FEV_1 = forced expiratory volume in one second; LSM diff = least squares mean difference; SE = standard error; TIO = tiotropium.
Source: Clinical Study Report for M/34273/23.[15]

TABLE 24: STUDY M/34273/29: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN NORMALIZED FEV_1 AUC (L) ON DAY 7 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Normalized FEV_1 AUC_{0-12} on day 7				
ACL 400	Placebo	0.208 (0.020)	(0.170 to 0.247)	< 0.0001
FOR 12	Placebo	0.210 (0.020)	(0.172 to 0.249)	< 0.0001
ACL 400	FOR 12	–0.002 (0.020)	(–0.040 to 0.037)	0.9237
Normalized FEV_1 AUC_{0-24} on day 7				
ACL 400	Placebo	0.195 (0.019)	(0.158 to 0.231)	< 0.0001
FOR 12	Placebo	0.225 (0.018)	(0.189 to 0.261)	< 0.0001
ACL 400	FOR 12	–0.031 (0.018)	(–0.067 to 0.006)	0.0995
Normalized FEV_1 AUC_{12-24} on day 7				
ACL 400	Placebo	0.189 (0.020)	(0.149 to 0.228)	< 0.0001
FOR 12	Placebo	0.244 (0.020)	(0.204 to 0.284)	< 0.0001
ACL 400	FOR 12	–0.056 (0.020)	(–0.096 to –0.016)	0.0065

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FOR = formoterol; LSM diff = least squares mean difference; SE = standard error.
Source: Clinical Study Report for M/34273/29.[16]

TABLE 25: STUDY M/34273/39: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN NORMALIZED FEV_1 AUC (L) ON DAY 1 AND WEEK 6 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B	95% CI	*P* value
Normalized FEV_1 AUC_{0-12} at day 1				
ACL 400	Placebo	0.149	(0.105 to 0.192)	< 0.0001
TIO 18	Placebo	0.136	(0.092 to 0.181)	< 0.0001
ACL 400	TIO 18	0.013	(–0.024 to 0.049)	0.4975
Normalized FEV_1 AUC_{0-12} at week 6				
ACL 400	Placebo	0.138	(0.080 to 0.196)	< 0.0001
TIO 18	Placebo	0.156	(0.096 to 0.215)	< 0.0001
ACL 400	TIO 18	–0.018	(–0.066 to 0.031)	0.4755
Normalized FEV_1 AUC_{0-24} at day 1				
ACL 400	Placebo	0.156	(0.111 to 0.201)	< 0.0001
TIO 18	Placebo	0.117	(0.071 to 0.162)	< 0.0001
ACL 400	TIO 18	0.040	(0.002 to 0.077)	0.0366
Normalized FEV_1 AUC_{0-24} at week 6				
ACL 400	Placebo	0.150	(0.094 to 0.205)	< 0.0001
TIO 18	Placebo	0.140	(0.083 to 0.196)	< 0.0001
ACL 400	TIO 18	0.010	(–0.036 to 0.056)	0.6721
Normalized FEV_1 AUC_{12-24} on day 1				
ACL 400	Placebo	0.168	(0.117 to 0.219)	< 0.0001
TIO 18	Placebo	0.100	(0.049 to 0.152)	0.0002
ACL 400	TIO 18	0.067	(0.025 to 0.110)	0.0018
Normalized FEV_1 AUC_{12-24} at week 6				
ACL 400	Placebo	0.160	(0.103 to 0.217)	< 0.0001
TIO 18	Placebo	0.123	(0.065 to 0.181)	< 0.0001
ACL 400	TIO 18	0.037	(–0.010 to 0.084)	0.1242

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FEV_1 = forced expiratory volume in one second; LSM diff = least squares mean difference; SE = standard error; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/39.[17]

TABLE 26: STUDY M/34273/23: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN NORMALIZED FVC AUC (L) ON DAY 1 AND 15 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Normalized FVC AUC_{0-12} on day 1				
ACL 400	Placebo	0.326 (0.049)	(0.227 to 0.425)	< 0.0001
TIO 18	Placebo	0.284 (0.050)	(0.183 to 0.385)	< 0.0001
ACL 400	TIO 18	0.042 (0.050)	(–0.059 to 0.143)	0.4059
Normalized FVC AUC_{0-12} on day 15				
ACL 400	Placebo	0.288 (0.065)	(0.156 to 0.421)	0.0001
TIO 18	Placebo	0.336 (0.065)	(0.203 to 0.469)	< 0.0001
ACL 400	TIO 18	–0.048 (0.064)	(–0.179 to 0.083)	0.4623
Normalized FVC AUC_{0-24} on day 1				
ACL 400	Placebo	0.360 (0.046)	(0.266 to 0.455)	< 0.0001
TIO 18	Placebo	0.266 (0.047)	(0.170 to 0.362)	< 0.0001
ACL 400	TIO 18	0.094 (0.046)	(–0.000 to 0.189)	0.0506
Normalized FVC AUC_{0-24} on day 15				
ACL 400	Placebo	0.321 (0.055)	(0.205 to 0.436)	< 0.0001
TIO 18	Placebo	0.259 (0.054)	(0.144 to 0.373)	0.0002
ACL 400	TIO 18	0.062 (0.054)	(–0.052 to 0.176)	0.2684
Normalized FVC AUC_{12-24} on day 1				
ACL 400	Placebo	0.420 (0.051)	(0.316 to 0.525)	< 0.0001
TIO 18	Placebo	0.277 (0.052)	(0.171 to 0.383)	< 0.0001
ACL 400	TIO 18	0.143 (0.052)	(0.037 to 0.249)	0.0101
Normalized FVC AUC_{12-24} on day 15				
ACL 400	Placebo	0.318 (0.060)	(0.195 to 0.442)	< 0.0001
TIO 18	Placebo	0.182 (0.060)	(0.059 to 0.304)	0.0050
ACL 400	TIO 18	0.137 (0.060)	(0.015 to 0.259)	0.0293

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FEV_1 = forced expiratory volume in one second; LSM diff = least squares mean difference; SE = standard error; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/23.[15]

TABLE 27: STUDY M/34273/29: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN NORMALIZED FVC AUC (L) ON DAY 7 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Normalized FVC AUC_{0-12} on day 7				
ACL 400	Placebo	0.274 (0.036)	(0.203 to 0.345)	< 0.0001
FOR 12	Placebo	0.301 (0.036)	(0.230 to 0.371)	< 0.0001
ACL 400	FOR 12	–0.026 (0.036)	(–0.097 to 0.045)	0.4653
Normalized FVC AUC_{0-24} on day 7				
ACL 400	Placebo	0.283 (0.035)	(0.214 to 0.351)	< 0.0001
FOR 12	Placebo	0.338 (0.035)	(0.270 to 0.407)	< 0.0001
ACL 400	FOR 12	–0.056 (0.035)	(–0.124 to 0.013)	0.1101
Normalized FVC AUC_{12-24} on day 7				
ACL 400	Placebo	0.302 (0.038)	(0.227 to 0.378)	< 0.0001
FOR 12	Placebo	0.383 (0.038)	(0.308 to 0.459)	< 0.0001
ACL 400	FOR 12	–0.081 (0.038)	(–0.157 to –0.005)	0.0358

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FVC = forced vital capacity; FOR = formoterol; LSM diff = least squares mean difference; SE = standard error.
Source: Clinical Study Report for M/34273/29.[16]

TABLE 28: STUDY M/34273/39: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN NORMALIZED FVC AUC (L) ON DAY 1 AND WEEK 6 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B	95% CI	*P* value
Normalized FVC AUC_{0-12} on day 1				
ACL 400	Placebo	0.192	(0.120 to 0.264)	< 0.0001
TIO 18	Placebo	0.154	(0.080 to 0.227)	< 0.0001
ACL 400	TIO 18	0.038	(–0.022 to 0.098)	0.2099
Normalized FVC AUC_{0-12} at week 6				
ACL 400	Placebo	0.187	(0.094 to 0.279)	< 0.0001
TIO 18	Placebo	0.165	(0.071 to 0.259)	0.0006
ACL 400	TIO 18	0.021	(–0.055 to 0.098)	0.5821
Normalized FVC AUC_{0-24} on day 1				
ACL 400	Placebo	0.211	(0.139 to 0.284)	< 0.0001
TIO 18	Placebo	0.146	(0.072 to 0.219)	0.0001
ACL 400	TIO 18	0.065	(0.005 to 0.125)	0.0333
Normalized FVC AUC_{0-24} at week 6				
ACL 400	Placebo	0.207	(0.119 to 0.296)	< 0.0001
TIO 18	Placebo	0.161	(0.071 to 0.251)	0.0005
ACL 400	TIO 18	0.047	(–0.027 to 0.120)	0.2141

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FVC = forced vital capacity; LSM diff = least squares mean difference; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/39.[17]

TABLE 29: STUDY M/34273/23: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN MORNING PEAK FEV_1 AND FVC VALUES (L) ON DAYS 1 AND 15 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Morning peak FEV_1 on day 1				
ACL 400	Placebo	0.218 (0.024)	(0.169 to 0.267)	< 0.0001
TIO 18	Placebo	0.170 (0.025)	(0.120 to 0.220)	< 0.0001
ACL 400	TIO 18	0.048 (0.025)	(–0.002 to 0.098)	0.0586
Morning peak FEV_1 on day 15				
ACL 400	Placebo	0.277 (0.046)	(0.181 to 0.374)	< 0.0001
TIO 18	Placebo	0.252 (0.047)	(0.153 to 0.350)	< 0.0001
ACL 400	TIO 18	0.026 (0.047)	(–0.072 to 0.124)	0.5862
Morning peak FVC on day 1				
ACL 400	Placebo	0.300 (0.058)	(0.182 to 0.418)	< 0.0001
TIO 18	Placebo	0.242 (0.059)	(0.123 to 0.361)	0.0002
ACL 400	TIO 18	0.058 (0.059)	(–0.062 to 0.177)	0.3365
Morning peak FVC on day 15				
ACL 400	Placebo	0.297 (0.072)	(0.153 to 0.442)	0.0002
TIO 18	Placebo	0.337 (0.073)	(0.191 to 0.484)	< 0.0001
ACL 400	TIO 18	–0.040 (0.073)	(–0.187 to 0.107)	0.5864

ACL = aclidinium bromide, AUC = area under the curve; CI = confidence interval; FVC = forced vital capacity; LSM diff = least squares mean difference; SE = standard error; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/23.[15]

TABLE 30: STUDY M/34273/29: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN MORNING PEAK FEV_1 AND FVC VALUES (L) ON DAYS 1 AND 7 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Morning peak FEV_1 on day 1				
ACL 400	Placebo	0.223 (0.018)	(0.187 to 0.259)	< 0.0001
FOR 12	Placebo	0.221 (0.018)	(0.185 to 0.258)	< 0.0001
ACL 400	FOR 12	0.001 (0.018)	(–0.035 to 0.038)	0.9446
Morning peak FEV_1 on day 7				
ACL 400	Placebo	0.242 (0.022)	(0.199 to 0.285)	< 0.0001
FOR 12	Placebo	0.246 (0.022)	(0.203 to 0.289)	< 0.0001
ACL 400	FOR 12	–0.004 (0.022)	(–0.047 to 0.039)	0.8496
Morning peak FVC on day 1				
ACL 400	Placebo	0.304 (0.032)	(0.240 to 0.368)	< 0.0001
FOR 12	Placebo	0.292 (0.032)	(0.229 to 0.356)	< 0.0001
ACL 400	FOR 12	0.012 (0.033)	(–0.053 to 0.076)	0.7242
Morning peak FVC on day 7				
ACL 400	Placebo	0.275 (0.042)	(0.192 to 0.357)	< 0.0001
FOR 12	Placebo	0.358 (0.042)	(0.276 to 0.440)	< 0.0001
ACL 400	FOR 12	–0.083 (0.042)	(–0.166 to –0.001)	0.0478

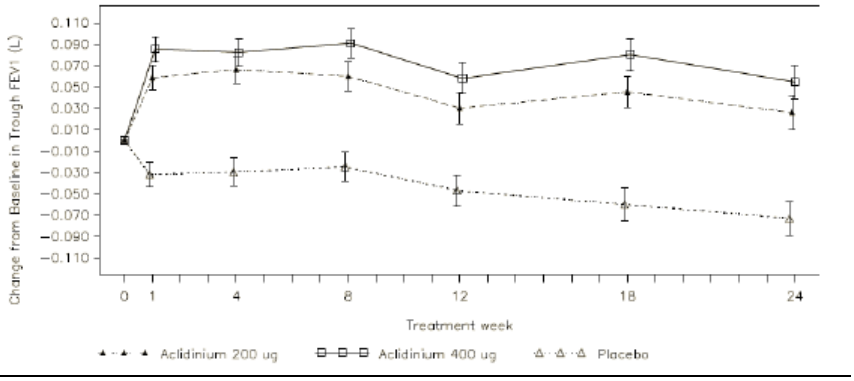
ACL = aclidinium bromide, CI = confidence interval; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; FOR = formoterol; LSM diff = least squares mean difference; SE = standard error.
Source: Clinical Study Report for M/34273/29.[16]

TABLE 31: STUDY M/34273/39: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN MORNING PEAK FEV_1 AND FVC VALUES (L) ON DAYS 1 AND 7 (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B	95% CI	*P* value
Morning peak FEV_1 on day 1				
ACL 400	Placebo	0.154	(0.112 to 0.196)	< 0.0001
TIO 18	Placebo	0.139	(0.096 to 0.182)	< 0.0001
ACL 400	TIO 18	0.014	(–0.021 to 0.049)	0.4196
Morning peak FEV_1 at week 6				
ACL 400	Placebo	0.180	(0.119 to 0.241)	< 0.0001
TIO 18	Placebo	0.172	(0.110 to 0.235)	< 0.0001
ACL 400	TIO 18	0.008	(–0.043 to 0.058)	0.7686
Morning peak FVC on day 1				
ACL 400	Placebo	0.201	(0.129 to 0.272)	< 0.0001
TIO 18	Placebo	0.146	(0.074 to 0.219)	< 0.0001
ACL 400	TIO 18	0.054	(–0.005 to 0.113)	0.0729
Morning peak FVC at week 6				
ACL 400	Placebo	0.212	(0.112 to 0.312)	< 0.0001
TIO 18	Placebo	0.170	(0.068 to 0.271)	0.0011
ACL 400	TIO 18	0.042	(–0.041 to 0.125)	0.3181

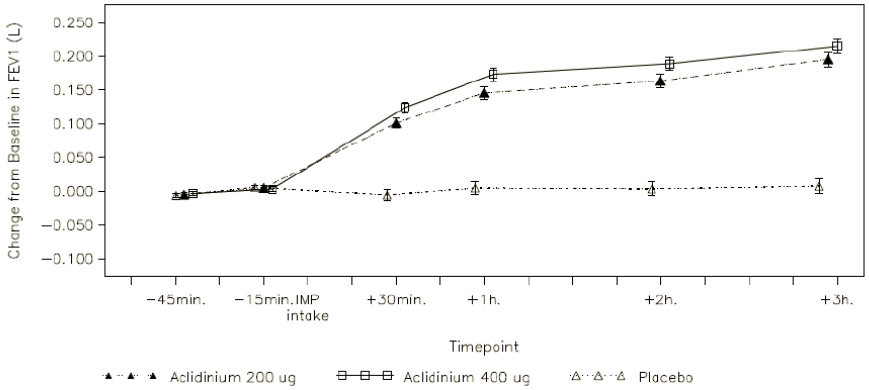
ACL = aclidinium bromide, CI = confidence interval; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LSM diff = least squares mean difference; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/39.[17]

FIGURE 8: STUDY M/34273/34 CHANGE FROM BASELINE IN MORNING PRE-DOSE (TROUGH) FEV_1 (L) BY VISIT OVER 24 WEEKS (LSM ± SE) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)



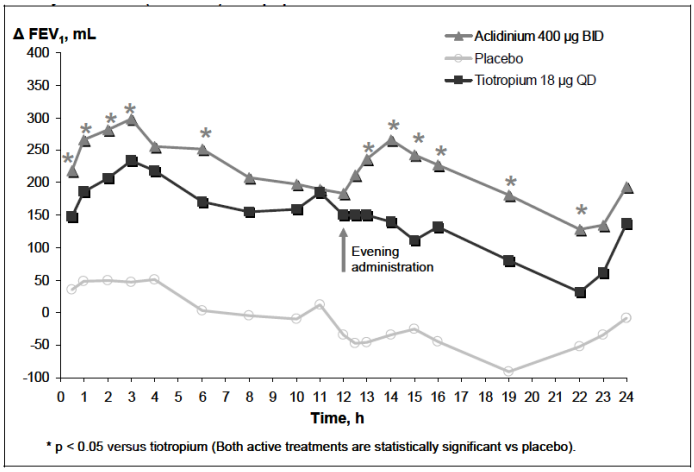
FEV_1 = forced expiratory volume in one second; LSM = least squares mean; SE = standard error.
Source: Clinical Study Report for M/34273/34.[12]

FIGURE 9: STUDY M/34273/34 CHANGE FROM BASELINE IN FEV_1 (L) BY TIME POINT ON DAY 1 (LSM ± SE) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)



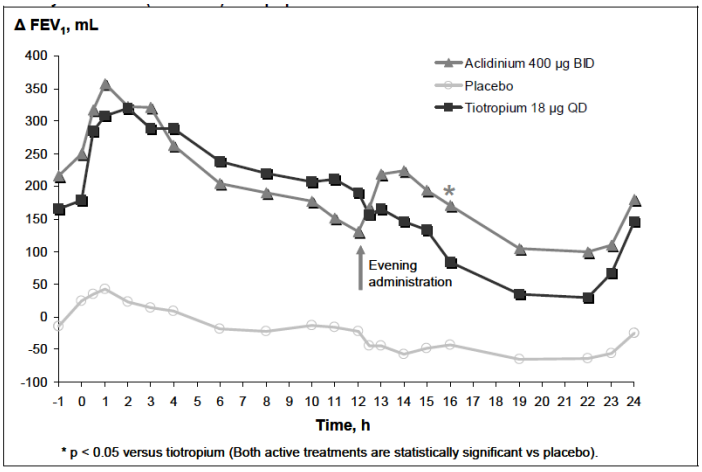
FEV_1 = forced expiratory volume in one second; LSM = least squares mean; SE = standard error.
Source: Clinical Study Report for M/34273/34.[12]

FIGURE 10: STUDY M/34273/23 CHANGE FROM BASELINE IN FEV_1 (ML) BY TIME POINT ON DAY 1 (LSM) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)



FEV_1 = forced expiratory volume in one second; LSM = least squares mean.
Source: Clinical Study Report for M/34273/23.[15]

FIGURE 11: STUDY M/34273/23 CHANGE FROM BASELINE IN FEV_1 (ML) BY TIME POINT ON DAY 15 (LSM) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)



FEV_1 = forced expiratory volume in one second; LSM = least squares mean.
Source: Clinical Study Report for M/34273/23.[15]

TABLE 32: NUMBER (%) OF PATIENTS WHO EXPERIENCED AT LEAST ONE COPD EXACERBATION DURING STUDY BASED ON THE HEALTH RESOURCE UTILIZATION (ECRF FORM) (ITT POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Any exacerbation, n (%)	38 (14.1)	56 (20.5)	12 (6.3)	22 (11.9)	19 (10.7)	19 (10.4)
OR (95% CI); *P* value	0.64 (0.41 to 1.00); *P* = 0.0513		0.51 (0.24 to 1.07); *P* = 0.0733		0.95 (0.48 to 1.88); *P* = 0.8790	
Rate of exacerbations per pt/year (95% CI)	0.40 (0.31 to 0.52)	0.60 (0.48 to 0.75)	0.41 (0.23 to 0.74)	0.79 (0.46 to 1.33)	0.48 (0.28 to 0.82)	0.50 (0.29 to 0.85)
RR (95% CI); *P* value	0.67 (0.48 to 0.94); *P* = 0.0195		0.52 (0.32 to 0.85); *P* = 0.0094		0.96 (0.45 to 2.05); *P* = 0.9124	
Duration (days) of exacerbation, mean (SD)	11.7 (8.2)	14.9 (13.4)	16.3 (11.0)	10.8 (8.1)	8.9 (5.1)	10.4 (8.6)
Moderate or severe, n (%)	33 (12.3)	44 (16.1)	11 (5.8)	16 (8.6)	16 (9.0)	19 (10.4)
Rate of exacerbations per pt/year (95% CI)	0.34 (0.26 to 0.44)	0.47 (0.38 to 0.60)	0.42 (0.24 to 0.71)	0.63 (0.38 to 1.03)	0.47 (0.26 to 0.83)	0.52 (0.30 to 0.90)
RR (95% CI); *P* value	0.72 (0.51 to 1.02); *P* = 0.0629		0.66 (0.41 to 1.07); *P* = 0.0912		0.89 (0.40 to 1.98); *P* = 0.7752	
Duration (days) of exacerbation, mean (SD)	11.7 (8.0)	16.5 (14.2)	14.8 (10.3)	12.1 (8.5)	8.5 (4.6)	10.4 (8.6)

ACL = aclidinium bromide; CI = confidence interval; eCRF = electronic case report form; ITT = intention-to-treat; OR = odds ratio; pt = patient; RR = rate ratio; SD = standard deviation.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 33: TIME (DAYS) TO FIRST COPD EXACERBATION BASED ON HEALTH RESOURCE UTILIZATION (ECRF) (INTENTION-TO-TREAT POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33[a]		LAS-MD-39 Part A[a]	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
N (%)	38 (14.1)	56 (20.5)	11 (5.7)	16 (8.6)	16 ((9.0)	19 (10.4)
HR (95% CI); *P* value	0.64 (0.42 to 0.97); *P* = 0.0342		0.7 (0.3 to 1.4); *P* = 0.3086		0.8 (0.4 to 1.6); *P* = 0.5048	

ACL = aclidinium bromide; CI = confidence interval; COPD = chronic obstructive coronary disease; eCRF = electronic case report form; HR = hazard ratio.
[a] Results were only available for moderate or severe COPD exacerbations in these trials, whereas in Study M/34273/34 the results are for any COPD exacerbations.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 34: TREATMENT-EMERGENT DEATHS (SAFETY POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Deaths, n (%)	1 (0.37)	1 (0.37)	1 (0.53)	0 (0)	1 (0.56)	1 (0.55)

ACL = aclidinium bromide.
Note: No deaths occurred in any of the active comparator trials.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 35: TOTAL NUMBER OF DAYS OF HOSPITALIZATION FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS (INTENTION-TO-TREAT POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-39 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
N (%)	2 (0.7)	10 (3.7)	2 (1.1)	1 (0.5)	1 (0.6)	3 (1.6)
At any unit, mean (SD)	5.0 (1.4))	15.5 (20.0)	6.0 (4.24)	4.0 (NA)	1.0 (NA)	2.3 (2.3)
Emergency room, mean (SD)	0 (0)	6.0 (NA)	0 (0)	0 (0)	0 (0)	1.0 (NA)
ICU or hospitalization, mean (SD)	5.0 (1.4)	16.6 (20.9)	0 (0)	0 (0)	0 (0)	0 (0)

ACL = aclidinium bromide; ICU = intensive care unit; NA = not available; SD = standard deviation.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 36: CHANGE IN SGRQ TOTAL SCORE FROM BASELINE (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline						
Mean (SD)	47.4 (18.4)	44.9 (16.7)	48.3 (17.8)	45.1 (16.3)	50.4 (16.9)	49.2 (17.4)
Week 4						
LSM (SE)	–5.19 (0.63)	–2.60 (0.63)	–4.0 (0.7)	–0.4 (0.7)	–3.3 (0.8)	–2.7 (0.7)
LSM diff [vs. placebo] (95% CI); *P* value	–2.59 (–4.30 to –0.89); *P* = 0.0029		–3.6 (–5.4 to –1.8); *P* = 0.0001		–0.6 (–2.7 to 1.5); *P* = 0.5826	
Week 12						
LSM (SE)	–6.45 (0.72)	–2.36 (0.72)	–4.6 (0.8)	–2.0 (0.8)	–5.4 (1.0)	–4.3 (1.0)
LSM diff [vs. placebo] (95% CI); *P* value	–4.10 (–6.06 to –2.13); *P* < 0.0001		–2.5 (–4.7 to –0.4); *P* = 0.0186		–1.1 (–3.8 to 1.6); *P* = 0.4288	
Week 24						
LSM (SE)	–7.41 (0.82)	–2.79 (0.82)	—	—	—	—
LSM diff [vs. Placebo] (95% CI); *P* value	–4.63 (–6.84 to –2.42); *P* < 0.0001		—		—	

ACL = aclidinium bromide; CI = confidence interval; LSM diff = least squares mean difference; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; SE = standard error; vs. = versus.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 37: NUMBER (%) OF PATIENTS WITH IMPROVEMENT IN SGRQ (4-POINT OR MORE REDUCTION IN TOTAL SCORE) (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 189)	Placebo (N = 181)	ACL 400 (N = 172)	Placebo (N = 178)
Week 4, n (%)						
Yes No	139 (51.7) 130 (48.3)	106 (39.1) 165 (60.9)	77 (40.7) 112 (59.3)	49 (27.1) 132 (72.9)	65 (37.8) 107 (62.2)	56 (31.5) 122 (68.5)
OR (diff vs. placebo) (95% CI); *P* value	1.60 (1.117 to 2.287); *P* = 0.0104		1.75 (1.12 to 2.73) *P* = 0.0146		1.30 (0.83 to 2.06); *P* = 0.2564	
Week 12, n (%)						
Yes No	153 (56.9) 116 (43.1)	107 (39.5) 164 (60.5)	84 (44.4) 105 (55.6)	65 (35.9) 116 (64.1)	77 (44.8) 95 (55.2)	69 (38.8) 109 (61.2)
OR (diff vs. placebo) (95% CI); *P* value	1.96 (1.375 to 2.802); *P* = 0.0002		1.37 (0.90 to 2.09) *P* = 0.1390		1.28 (0.83 to 1.97); *P* = 0.2596	
Week 24, n (%)						
Yes No	154 (57.3) 115 (42.8)	111 (41.0) 160 (59.0)	-	-	-	-
OR (diff vs. placebo) (95% CI); *P* value	1.87 (1.320 to 2.660); *P* = 0.0004		-		-	-

ACL = aclidinium bromide; CI = confidence interval; OR = odds ratio; SGRQ = St. George's Respiratory Questionnaire; vs. = versus.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 38: TREATMENT COMPARISONS IN CHANGE IN EQ-5D SCORES OVER TREATMENT PERIOD (LAST OBSERVATION CARRIED FORWARD) (INTENTION-TO-TREAT POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 177)	Placebo (N = 182)
Weighted index score				
Baseline				
Mean (SD)	0.8 (0.2)	0.8 (0.2)	0.7591 (0.1564)	0.7648 (0.1627)
Change from baseline at week 4				
LSM (SE)	0.033 (0.010)	0.029 (0.010)	0.0168 (0.0085)	0.0081 (0.0083)
LSM diff [vs. placebo] (95% CI); *P* value	0.004 (–0.02 to 0.03); *P* = 0.7477		0.0087 (–0.0146 to 0.0321); *P* = 0.4638	
Change from baseline at week 12				
LSM (SE)	0.041 (0.011)	0.019 (0.011)	0.0199 (0.0088)	0.0234 (0.0087)
LSM diff [vs. placebo] (95% CI); *P* value	0.02 (–0.01 to 0.05); *P* = 0.1368		–0.0035 (–0.0278 to 0.0208); *P* = 0.7782	
Change from baseline at week 24				
LSM (SE)	0.055 (0.011)	0.024 (0.011)	—	—
LSM diff [vs. placebo] (95% CI); *P* value	0.03 (0.00 to 0.06); *P* = 0.0414		—	
Visual analogue scale				
Baseline				
Mean (SD)	61.6 (15.2)	62.3 (15.3)	64.1 (18.3)	64.9 (18.8)
Change from baseline at week 4				
LSM (SE)	2.17 (0.74)	1.93 (0.75)	1.2 (1.0)	2.9 (1.0)
LSM diff [vs. placebo] (95% CI); *P* value	0.24 (–1.78 to 2.25); *P* = 0.8187		–1.6 (–4.4 to 1.1); *P* = 0.2388	
Change from baseline at week 12				
LSM (SE)	4.03 (0.75)	0.73 (0.75)	2.5 (1.1)	4.1 (1.1)
LSM diff [vs. placebo] (95% CI); *P* value	3.30 (1.27 to 5.32); *P* = 0.0014		–1.6 (–4.6 to 1.4); *P* = 0.2861	
Change from baseline at week 24				
LSM (SE)	4.87 (0.80)	1.74 (0.80)	—	—
LSM diff [vs. placebo] (95% CI); *P* value	3.13 (0.96 to 5.29); *P* = 0.0047		—	

ACL = aclidinium bromide; CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; LSM = least squares mean; LSM diff = least squares mean difference; SD = standard deviation; SE = standard error; vs. = versus.
Note: EQ-5D was not performed in Study LAS-MD-33.
Source: Clinical Study Reports for M/34273/34,[12] and LAS-MD-38 Part A.[14]

TABLE 39: STUDY M34273/34: CHANGE FROM BASELINE IN EXACT-RS TOTAL SCORE, BREATHLESSNESS, CHEST, AND COUGH AND SPUTUM DOMAIN SCORES OVER 24 WEEKS (INTENTION-TO-TREAT POPULATION) (LOCF)

	M/34273/34	
	ACL 400 (N = 269)	Placebo (N = 273)
Baseline, mean (SD)		
Total score	14.1 (6.4)	13.6 (6.6)
Breathlessness score	6.8 (3.5)	6.5 (3.5)
Chest score	3.4 (1.9)	3.3 (1.9)
Cough and sputum score	3.9 (1.8)	3.8 (1.9)
Change from baseline to end of treatment (24 weeks), LSM diff (95% CI); *P* value		
Total score	–2.02 (–2.72 to –1.33); *P* < 0.0001	
Breathlessness score	–1.05 (–1.43 to –0.68); *P* < 0.0001	
Chest score	–0.52 (–0.74 to –0.30); *P* < 0.0001	
Cough and sputum score	–0.44 (–0.63 to –0.25); *P* < 0.0001	

ACL = aclidinium bromide; CI = confidence interval; EXACT-RS = Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; LOCF = last observation carried forward; LSM diff = least squares mean difference; SD = standard deviation.
Source: Clinical Study Report for M/34273/34.[12]

TABLE 40: STUDY M34273/34: PERCENTAGE OF DAYS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE SYMPTOMS OVER 24 WEEKS (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

	M/34273/34
	Comparison vs. placebo, LSM diff (95% CI); *P* value
Night-time	
Any symptom	–7.21 (–11.28 to –3.13); *P* = 0.0005
Feeling short of breath	–6.97 (–11.50 to –2.45); *P* = 0.0026
Coughing	–6.99 (–11.48 to –2.50); *P* = 0.0023
Bringing up mucous or phlegm	–7.96 (–12.90 to –3.02); *P* = 0.0016
Chest tightness or congestion	–4.55 (–8.64 to –0.47); *P* = 0.0291
Wheezing	–2.88 (–7.20 to 1.44); *P* = 0.1908
Morning	
Any symptom	–5.81 (–8.85 to –2.77); *P* = 0.0002
Feeling short of breath	–6.93 (–11.52 to –2.33); *P* = 0.0032
Coughing	–5.39 (–9.25 to –1.54); *P* = 0.0061
Bringing up mucous or phlegm	–8.67 (–12.91 to –4.43); *P* < 0.0001
Chest tightness or congestion	–5.94 (–10.15 to –1.74); *P* = 0.0057
Wheezing	–4.34 (–8.72 to 0.05); *P* = 0.0526

CI = confidence interval; COPD = chronic obstructive pulmonary disease; LSM diff = least squares mean difference.
Source: Clinical Study Report for M/34273/34.[12]

TABLE 41: STUDY M/34273/34: CHANGE FROM BASELINE IN SLEEP DISTURBANCE, MORNING-TIME DISTURBANCE AND NIGHT-TIME AND MORNING LUNG FUNCTION CONDITION OVER 24 WEEKS FROM NIGHT-TIME AND MORNING SYMPTOMS QUESTIONNAIRE (ITT POPULATION) (LOCF)

	M/34273/34	
	ACL 400 (N = 269)	Placebo (N = 273)
Night-time		
Baseline, mean (SD)		
Sleep disturbed[a]	0.8 (0.6)	0.8 (0.7)
Night-time lung condition	3.3 (0.5)	3.4 (0.5)
Change from baseline over 24 weeks, LSM (SE)		
Sleep disturbed	–0.14 (0.03)	–0.07 (0.03)
LSM diff [vs. placebo] (95% CI); *P* value	–0.06 (–0.14 to 0.02); *P* = 0.1289	
Night-time lung condition	0.14 (0.03)	0.02 (0.03)
LSM diff [vs. placebo] (95% CI); *P* value	0.12 (0.05 to 0.18); *P* = 0.0006	
Morning		
Baseline, Mean (SD)		
Morning-time disturbance	0.9 (0.7)	0.9 (0.7)
Morning lung condition	3.3 (0.5)	3.3 (05)
Change from baseline over 24 weeks, LSM (SE)		
Morning-time disturbance	–0.13 (0.03)	0.01 (0.03)
LSM diff [vs. placebo] (95% CI); *P* value	–0.14 (–0.23 to –0.06); *P* = 0.0011	
Morning lung condition	0.14 (0.02)	0.01 (0.02)
LSM diff [vs. placebo] (95% CI); *P* value	0.13 (0.06 to 0.20); *P* = 0.0001	

CI = confidence interval; ITT = intention-to-treat; LOCF = last observation carried forward; LSM = least squares mean; LSM diff = least squares mean difference; SD = standard deviation; SE = standard error; vs. = versus.
Note: Sleep disturbed: 0 = No, it not disturbed by these symptoms; 1 = Slightly disturbed by these symptoms; 2 = Moderately disturbed by these symptoms, but I still able to get some sleep; 3 = Severely disturbed by these symptoms; 4 = Extremely disturbed by these symptoms, these symptoms kept me awake most of the night.
Lung condition: 1 = Very poor; 2 = Poor; 3 = Fair; 4 = Good; 5 = Very good.
Morning-time disturbance: 0 = These symptoms did not limit what wanted to do this morning; 1 = Slightly limited what I wanted to do this morning; 2 = Moderately limited what I wanted to do this morning; 3 = Severely limited what I wanted to do this morning; 4 = Extremely limited in what I wanted to do, I was unable to do what I wanted to do this morning.
Source: Clinical Study Report for M/34273/34.[12]

TABLE 42: STUDY LAS-MD-33: CHANGE FROM BASELINE IN DAILY AVERAGE OF NIGHT-TIME SYMPTOMS (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

	Placebo (N = 185)		ACL 400 (N = 190)		
Mean (SD)	**Baseline**	**Change at Week 12**	**Baseline**	**Change at Week 12**	***P* value**
Frequency					
Breathlessness	1.41 (1.199)	–0.13 (0.920)	1.41 (1.272)	–0.44 (1.116)	0.0023
Cough	2.06 (1.501)	0.10 (1.355)	1.92 (1.612)	–0.36 (1.286)	0.0002
Sputum production	1.33 (1.434)	0.05 (0.982)	1.35 (0.918)	–0.37 (0.918)	< 0.0001
Wheezing	1.33 (1.468)	–0.00 (1.145)	1.25 (1.465)	–0.53 (1.272)	< 0.0001
Quantity of sputum production					
Night-time production	0.68 (0.763)	–0.12 (0.523)	0.72 (0.804)	–0.24 (0.624)	0.0578
24 hour production	1.56 (1.049)	0.04 (0.607)	1.49 (1.061)	–0.14 (0.665)	0.0051
Severity and impact of symptoms on activity					
Breathlessness	1.82 (0.922)	–0.19 (0.695)	1.72 (0.918)	–0.44 (0.858)	0.0004
Cough	1.49 (0.877)	–0.10 (0.784)	1.39 (0.971)	–0.24 (0.572)	0.0251
Severity and impact of symptoms on sleep					
Breathing symptoms	0.82 (0.720)	–0.06 (0.587)	0.85 (0.766)	–0.24 (0.572)	0.0045

ACL = aclidinium bromide; SD = standard deviation.
Note: Frequency: 0 = never; 1 = 1–2 times; 2 = 3–4 times; 3 = 5–6 times; 4 = 7 or more times.
Quantity of sputum production: 0 = none; 1 = amount of 1 teaspoon; 2 = amount of 1 tablespoon; 3 = more than 1 tablespoon.
Activity: 0 = none; 1 = symptoms present, but caused little or no discomfort; 2 = mild symptoms that were unpleasant, but caused little or no discomfort; 3 = moderate symptoms that caused discomfort, but did not affect normal daily activities; 4 = severe symptoms that interfered with normal daily activities.
Sleep: 0 = none; 1 = symptoms causing early awakening or awakening once during the night; 2 = symptoms causing early awakening or awakening two or more times during the night; 3 = symptoms causing awakening for most times during the night; 4 = symptoms which were so severe that I could not sleep at all.
Source: Clinical Study Report for LAS-MD-33.[13]

TABLE 43: STUDY LAS-MD-33: CHANGE FROM BASELINE IN DAILY AVERAGE OF EARLY MORNING SYMPTOMS (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

	Placebo (N = 185)		ACL 400 (N = 190)		
Mean (SD)	Baseline	Change at Week 12	Baseline	Change at Week 12	*P* value
Severity of breathlessness for first hour on getting up	1.57 (0.916)	–0.09 (0.607)	1.51 (0.923)	–0.32 (0.788)	0.0009
Impact of breathlessness on morning activities	1.42 (0.867)	–0.03 (0.561)	1.39 (0.879)	–0.28 (0.756)	0.0002

ACL = aclidinium bromide; SD = standard deviation.
Note: Daily average rating of severity of breathless for the first hour on getting up in the morning during week 12 (0 = none; 1 = symptoms present, but caused little or no discomfort; 2 = mild symptoms that were unpleasant, but caused little or no discomfort; 3 = moderate symptoms that caused discomfort, but did not affect normal activities; 4 = severe symptoms that interfered with normal activities).
Daily average rating of usual activities that were restricted by breathlessness in the morning during week 12 (0 = none; 1 = symptoms present, but caused little or no restriction on morning activities; 2 = mild symptoms that were unpleasant, but caused little restriction on morning activities; 3 = moderate symptoms that caused discomfort and moderately restricted morning activities; 4 = severe symptoms that interfered greatly with morning activities).
Source: Clinical Study Report for LAS-MD-33.[13]

TABLE 44: STUDY M/34273/23: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN COPD SYMPTOM SCORES (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Breathlessness (week 1)				
ACL 400	Placebo	–0.324 (0.128)	(–0.580 to –0.067)	0.0143
TIO 18	Placebo	–0.225 (0.130)	(–0.485 to 0.035)	0.0882
ACL 400	TIO 18	–0.099 (0.130)	(–0.360 to 0.162)	0.4504
Breathlessness (week 2)				
ACL 400	Placebo	–0.287 (0.153)	(–0.594 to 0.019)	0.0652
TIO 18	Placebo	–0.204 (0.155)	(–0.514 to 0.107)	0.1940
ACL 400	TIO 18	–0.084 (0.155)	(–0.396 to 0.228)	0.5916
Breathlessness (week 1 + week 2)				
ACL 400	Placebo	–0.309 (0.135)	(–0.579 to –0.039)	0.0255
TIO 18	Placebo	–0.217 (0.136)	(–0.490 to 0.056)	0.1174
ACL 400	TIO 18	–0.092 (0.137)	(–0.367 to 0.182)	0.5038
Cough (week1)				
ACL 400	Placebo	–0.273 (0.131)	(–0.537 to –0.100)	0.0421
TIO 18	Placebo	–0.142 (0.133)	(–0.409 to 0.124)	0.2892
ACL 400	TIO 18	–0.131 (0.134)	(–0.399 to 0.137)	0.3316
Cough (week 2)				
ACL 400	Placebo	–0.296 (0.150)	(–0.597 to 0.006)	0.0543
TIO 18	Placebo	–0.165 (0.152)	(–0.471 to 0.140)	0.2824
ACL 400	TIO 18	–0.130 (0.153)	(–0.437 to 0.177)	0.3979
Cough (week 1 + week 2)				
ACL 400	Placebo	–0.284 (0.134)	(–0.553 to –0.015)	0.0387

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
TIO 18	Placebo	–0.154 (0.136)	(–0.427 to 0.119)	0.2624
ACL 400	TIO 18	–0.130 (0.137)	(–0.404 to 0.144)	0.3444
Sputum (week 1)				
ACL 400	Placebo	–0.030 (0.086)	(–203 to 0.142)	0.7255
TIO 18	Placebo	0.076 (0.087)	(–0.099 to 0.251)	0.3893
ACL 400	TIO 18	–0.106 (0.088)	(–0.282 to 0.070)	0.2315
Sputum (week 2)				
ACL 400	Placebo	–0.060 (0.114)	(–0.289 to 0.169)	0.5992
TIO 18	Placebo	0.120 (0.116)	(–0.112 to 0.352)	0.3045
ACL 400	TIO 18	–0.180 (0.116)	(–0.413 to 0.053)	0.1269
Sputum (week 1 + week 2)				
ACL 400	Placebo	–0.045 (0.092)	(–230 to 0.140)	0.6272
TIO 18	Placebo	0.094 (0.094)	(–0.093 to 0.282)	0.3177
ACL 400	TIO 18	–0.139 (0.094)	(–0.328 to 0.049)	0.1438
Night-time symptoms (week 1)				
ACL 400	Placebo	–0.207 (0.086)	(–0.379 to –0.036)	0.0190
TIO 18	Placebo	–0.073 (0.087)	(–0.247 to 0.101)	0.4053
ACL 400	TIO 18	–0.135 (0.087)	(–0.309 to 0.040)	0.1285
Night-time symptoms (week 2)				
ACL 400	Placebo	–0.160 (0.105)	(–0.371 to 0.051)	0.1340
TIO 18	Placebo	–0.071 (0.106)	(–0.285 to 0.142)	0.5063
ACL 400	TIO 18	–0.089 (0.107)	(–0.303 to 0.126)	0.4102
Night-time symptoms (week 1 + week 2)				
ACL 400	Placebo	–0.184 (0.091)	(–0.367 to –0.001)	0.0485
TIO 18	Placebo	–0.072 (0.092)	(–0.257 to 0.114)	0.4397
ACL 400	TIO 18	–0.112 (0.093)	(–0.299 to 0.074)	0.2312

ACL = aclidinium bromide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; LSM diff = least squares mean difference; SE = standard error; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/23.[15]

TABLE 45: STUDY M/34273/39: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN DAILY EXACT-RS SCORE AND COMPONENTS OVER SIX WEEKS (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD)

Treatment (A)	Treatment (B)	LSM diff A-B	95% CI	*P* value
Change from baseline in daily total E-RS score over 6 weeks				
ACL 400	Placebo	–2.0	(–3.0 to –1.0)	< 0.0001
TIO 18	Placebo	–1.2	(–2.2 to –0.2)	0.0166
ACL 400	TIO 18	–0.7	(–1.6 to 0.1)	0.0744
Change from baseline in daily breathlessness domain E-RS score over 6 weeks				
ACL 400	Placebo	–1.1	(–1.6 to –0.5)	< 0.0001
TIO 18	Placebo	–0.7	(–1.2 to –0.2)	0.0094
ACL 400	TIO 18	–0.4	(–0.8 to 0.1)	0.0896
Change from baseline in daily cough and sputum domain E-RS score over 6 weeks				
ACL 400	Placebo	–0.4	(–0.7 to –0.2)	0.0020
TIO 18	Placebo	–0.2	(–0.5 to 0.1)	0.1092
ACL 400	TIO 18	–0.2	(–0.4 to 0.0)	0.0791
Change from baseline in daily chest domain E-RS score over 6 weeks				
ACL 400	Placebo	–0.5	(–0.7 to –0.2)	0.0026
TIO 18	Placebo	–0.3	(–0.6 to –0.0)	0.0432
ACL 400	TIO 18	–0.1	(–0.4 to 0.1)	0.2563
Change from baseline in per cent of days without morning COPD symptoms over 6 weeks				
ACL 400	Placebo	8.9	(4.1 to 13.8)	0.0004
TIO 18	Placebo	5.6	(0.6 to 10.6)	0.0291
ACL 400	TIO 18	3.4	(–0.8 to 7.5)	0.1084
Change from baseline in severity of night-time COPD symptoms over 6 weeks				
ACL 400	Placebo	–0.14	(–0.25 to –0.03)	0.0099
TIO 18	Placebo	–0.07	(–0.18 to 0.04)	0.1948
ACL 400	TIO 18	–0.07	(–0.16 to 0.02)	0.1327
Change from baseline in severity of morning COPD symptoms over 6 weeks				
ACL 400	Placebo	–0.22	(–0.33 to –0.11)	0.0001
TIO 18	Placebo	–0.12	(–0.24 to –0.01)	0.0320
ACL 400	TIO 18	–0.09	(–0.19 to 0.00)	0.0524
Change from baseline in number of nocturnal awakenings due to COPD symptoms over 6 weeks				
ACL 400	Placebo	–0.12	(–0.30 to 0.05)	0.1748
TIO 18	Placebo	–0.06	(–0.24 to 0.12)	0.5054
ACL 400	TIO 18	–0.06	(–0.21 to 0.09)	0.4217
Change from baseline in limitation of activity due to COPD symptoms over 6 weeks				
ACL 400	Placebo	–0.18	(–0.29 to –0.07)	0.0016
TIO 18	Placebo	–0.08	(–0.19 to 0.03)	0.1636
ACL 400	TIO 18	–0.10	(–0.19 to –0.01)	0.0372

ACL = aclidinium bromide; COPD = chronic obstructive pulmonary disease; EXACT-RS = Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; LSM diff = least squares mean difference; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/39.[17]

TABLE 46: TDI FOCAL SCORE CHANGE FROM BDI (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline (BDI)						
Mean (SD)	6.7 (2.1)	6.7 (2.0)	6.2 (2.1)	6.5 (2.2)	6.0 (1.9)	6.2 (2.2)
Change in TDI score from BDI at week 4						
LSM (SE)	1.54 (0.17)	0.62 (0.18)	1.2 (0.2)	0.4 (0.2)	—	—
LSM diff [vs. placebo] (95% CI); *P* value	0.92 (0.44 to 1.39); *P* = 0.0002		0.9 (0.2 to 1.5); *P* = 0.0066		—	
Change in TDI score from BDI at week 12						
LSM (SE)	1.74 (0.19)	0.86 (0.20)	1.5 (0.2)	0.5 (0.2)	1.3 (0.2)	0.3 (0.2)
LSM diff [vs. placebo] (95% CI); *P* value	0.88 (0.35 to 1.41); *P* = 0.0012		1.0 (0.4 to 1.6); *P* = 0.0021		1.0 (0.3 to 1.7); *P* = 0.0054	
Change in TDI score from BDI at week 24						
LSM (SE)	1.94 (0.21)	0.94 (0.21)	—	—	—	—
LSM diff [vs. placebo] (95% CI); *P* value	1.00 (0.43 to 1.57); *P* = 0.0006		—		—	

ACL = aclidinium bromide; BDI = Baseline Dyspnea Index; CI = confidence interval; LSM diff = least squares mean difference; SD = standard deviation; TDI = Transition Dyspnea Index; SE = standard error; vs. = versus.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 47: NUMBER (%) OF PATIENTS WITH IMPROVEMENT IN TDI (1 UNIT OR MORE IN FOCAL SCORE): (INTENTION-TO-TREAT POPULATION) (LAST OBSERVATION CARRIED FORWARD) PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Week 4						
Yes No	147 (56.8) 112 (43.2)	107 (42.0) 148 (58.0)	85 (50.0) 85 (50.0)	49 (31.2) 108 (68.8)	—	—
OR (diff vs. placebo) (95% CI); *P* value	1.89 (1.326 to 2.699); *P* = 0.0004		2.16 (1.36 to 3.42); *P* = 0.0011		—	—
Week 12						
Yes No	156 (59.5) 106 (40.5)	109 (42.4) 148 (57.6)	82 (47.7) 90 (52.3)	53 (32.9) 108 (67.1)	72 (50.7) 70 (49.3)	51 (34.5) 97 (65.5)
OR (diff vs. placebo) (95% CI); *P* value	2.06 (1.444 to 2.935); *P* < 0.0001		1.77 (1.12 to 2.79); *P* = 0.0136		1.84 (1.13 to 3.00); *P* = 0.0150	
Week 24						
Yes No	149 (56.9) 113 (43.1)	117 (45.5) 140 (54.5)	—	—	—	—
OR (diff vs. placebo) (95% CI); *P* value	1.68 (1.183 to 2.399); *P* = 0.0038		—		—	

ACL = aclidinium bromide, CI = confidence interval; diff = difference; OR = odds ratio; vs. = versus.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[14]

TABLE 48: CHANGE FROM BASELINE IN DAY, NIGHT, AND TOTAL DAILY RESCUE MEDICATION (NUMBER OF PUFFS) — ANCOVA MODEL TREATMENT COMPARISONS (LOCF) (ITT POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33	LAS-MD-38 Part A		
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 185)	ACL 400 (N = 177)	Placebo (N = 182)
Baseline						
Total daily rescue medication, mean (SD)	3.5 (3.0)	3.8 (4.3)	4.4 (4.5)	3.9 (3.6)	4.91 (4.74)	4.23 (4.20)
Daytime or morning rescue medication, mean (SD)	2.4 (2.2)	2.6 (2.8)	3.6 (3.9)	3.3 (3.2)	3.26 (3.21)	2.88 (3.24)
Night-time or evening rescue medication, mean (SD)	1.1 (1.3)	1.2 (1.8)	0.8 (1.6)	0.6 (1.3)	2.16 (2.39)	1.96 (1.95)
Change from baseline to end of treatment						
Total daily rescue medication, LSM (SE)	–1.20 (0.241)	–0.25 (0.242)	–1.5 (0.2)	–0.9 (0.2)	–1.65 (0.22)	–1.23 (0.23)
LSM diff vs. placebo (95% CI); *P* value	–0.95 (–1.60 to –0.30) *P* = 0.0045		–0.6 (–1.1 to –0.1) *P* = 0.0243		–0.42 (–1.05 to 0.20) *P* = 0.1866	
Daytime or morning rescue medication, LSM (SE)	–0.88 (0.137)	–0.23 (0.137)	–1.2 (0.2)	–0.6 (0.2)	–1.04 (0.15)	–0.90 (0.16)
LSM diff vs. placebo (95% CI); *P* value	–0.65 (–1.02 to –0.28) *P* = 0.0006		–0.6 (–1.1 to –0.1) *P* = 0.0209		–0.13 (–0.56 to 0.30) *P* = 0.5411	
Night-time or evening rescue medication, LSM (SE)	–0.32 (0.117)	–0.03 (0.117)	–0.3 (0.1)	–0.3 (0.1)	–0.75 (0.12)	–0.40 (0.12)
LSM diff vs. placebo (95% CI); *P* value	–0.29 (–0.61 to 0.03) *P* = 0.0709		0.0 (–0.2 to 0.2) *P* = 0.9268		–0.35 (–0.69 to –0.01) *P* = 0.0422	

ACL = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention-to-treat; LOCF = last observation carried forward; LSM = least squares mean; LSM diff = LSM difference; SD = standard deviation; SE = standard error; vs. = versus.

Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A[14]

TABLE 49: STUDY M/34273/23: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN DAY AND NIGHT USE OF RESCUE MEDICATION (NUMBER OF PUFFS) RECORDED BY PATIENT (ITT POPULATION) (LOCF)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Change in daily (day + night) use of rescue medication (week 1)				
ACL 400	Placebo	–2.031 (0.442)	(–2.916 to –1.146)	< 0.0001
TIO 18	Placebo	–1.245 (0.446)	(–2.140 to –0.351)	0.0072
ACL 400	TIO 18	–0.786 (0.450)	(–1.687 to 0.116)	0.0864
Change in daily (day + night) use of rescue medication (week 2)				
ACL 400	Placebo	–1.970 (0.466)	(–2.904 to –1.036)	< 0.0001
TIO 18	Placebo	–1.400 (0.471)	(–2.344 to –0.455)	0.0044
ACL 400	TIO 18	–0.570 (0.474)	(–1.521 to 0.381)	0.2343
Change in daily (day + night) use of rescue medication (week 1 + week 2)				
ACL 400	Placebo	–2.031 (0.442)	(–2.900 to –1.127)	< 0.0001
TIO 18	Placebo	–1.321 (0.447)	(–2.217 to –0.425)	0.0046
ACL 400	TIO 18	–0.692 (0.450)	(–1.595 to 0.211)	0.1303
Change in day use of rescue medication (week 1)				
ACL 400	Placebo	–1.827 (0.408)	(–2.644 to –1.009)	< 0.0001
TIO 18	Placebo	–1.055 (0.412)	(–1.882 to –0.229)	0.0133
ACL 400	TIO 18	–0.772 (0.415)	(–1.604 to 0.061)	0.0686
Change in day use of rescue medication (week 2)				
ACL 400	Placebo	–1.782 (0.420)	(–2.624 to –0.940)	< 0.0001
TIO 18	Placebo	–1.177 (0.425)	(–2.028 to –0.325)	0.0077
ACL 400	TIO 18	–0.605 (0.427)	(–1.462 to 0.252)	0.1624
Change in day use of rescue mediation (week 1 + week 2)				
ACL 400	Placebo	–1.809 (0.404)	(–2.619 to –0.999)	< 0.0001
TIO 18	Placebo	–1.113 (0.409)	(–1.933 to –0.294)	0.0086
ACL 400	TIO 18	–0.696 (0.411)	(–1.520 to 0.129)	0.0966
Change in night use of rescue medication (week 1)				
ACL 400	Placebo	–0.195 (0.099)	(–0.394 to 0.005)	0.0553
TIO 18	Placebo	–0.180 (0.100)	(–0.381 to 0.022)	0.0792
ACL 400	TIO 18	–0.015 (0.101)	(–0.218 to 0.188)	0.8829
Change in night use of rescue medication (week 2)				
ACL 400	Placebo	–0.175 (0.108)	(–0.392 to 0.042)	0.1120
TIO 18	Placebo	–0.211 (0.109)	(–0.431 to 0.009)	0.0594
ACL 400	TIO 18	0.036 (0.110)	(–0.185 to 0.257)	0.7436
Change in night use of rescue medication (week 1 + week 2)				
ACL 400	Placebo	–0.193 (0.099)	(–0.391 to 0.004)	0.0550
TIO 18	Placebo	–0.197 (0.100)	(–0.397 to 0.003)	0.0533
ACL 400	TIO 18	0.004 (0.100)	(–0.197 to 0.205)	0.9710

ACL = aclidinium bromide; CI = confidence interval; ITT = intention-to-treat; LOCF = last observation carried forward; LSM diff = least squares mean difference; SE = standard error; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/23.[15]

TABLE 50: STUDY M/34273/29: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN DAY AND NIGHT AND DAILY USE OF RESCUE MEDICATION (NUMBER OF PUFFS) RECORDED BY PATIENT (ITT POPULATION) (LOCF)

Treatment (A)	Treatment (B)	LSM diff A-B (SE)	95% CI	*P* value
Change in daily use of rescue medication (day 7)				
ACL 400	Placebo	–0.48 (0.17)	(–0.82 to –0.15)	0.0051
FOR 12	Placebo	–0.67 (0.17)	(–1.00 to –0.33)	0.0001
ACL 400	FOR 12	0.18 (0.17)	(–0.16 to 0.52)	0.2887
Change in daytime use of rescue medication (day 7)				
ACL 400	Placebo	–0.39 (0.14)	(–0.67 to –0.12)	0.0056
FOR 12	Placebo	–0.54 (0.14)	(–0.82 to –0.27)	0.0001
ACL 400	FOR 12	0.15 (0.14)	(–0.13 to 0.43)	0.2908
Change in night-time use of rescue medication (day 7)				
ACL 400	Placebo	–0.09 (0.05)	(–0.19 to 0.02)	0.1063
FOR 12	Placebo	–0.12 (0.05)	(–0.23 to –0.02)	0.0244
ACL 400	FOR 12	0.03 (0.05)	(–0.07 to 0.14)	0.5273

ACL = aclidinium bromide; CI = confidence interval; FOR = formoterol; ITT = intention-to-treat; LOCF = last observation carried forward; LSM diff = least squares mean difference; SE = standard error.
Source: Clinical Study Report for M/34273/29.[16]

TABLE 51: STUDY M/34273/39: TREATMENT COMPARISONS OF CHANGE FROM BASELINE IN AVERAGE DAILY USE OF RESCUE MEDICATION (NUMBER OF PUFFS) (INTENTION-TO-TREAT POPULATION) (LOCF)

Treatment (A)	Treatment (B)	LSM diff A-B	95% CI	*P* value
Change from baseline over 6 weeks				
ACL 400	Placebo	–0.4	(–1.0 to 0.2)	0.1532
TIO 18	Placebo	–0.4	(–0.9 to 0.2)	0.2104
ACL 400	TIO 18	–0.0	(–0.5 to 0.4)	0.8575
Change from baseline in percentage of rescue medication-free days over 6 weeks				
ACL 400	Placebo	9.6	(1.3 to 17.8)	0.0229
TIO 18	Placebo	8.9	(0.6 to 17.3)	0.0366
ACL 400	TIO 18	0.6	(–6.3 to 7.5)	0.8613

ACL = aclidinium bromide; CI = confidence interval; FOR = formoterol; LOCF = last observation carried forward; LSM diff = least squares mean difference.
Source: Clinical Study Report for M/34273/39.[17]

TABLE 52: TREATMENT COMPLIANCE (SAFETY POPULATION): PLACEBO-CONTROLLED TRIALS

	M/34273/34		LAS-MD-33		LAS-MD-38 Part A	
	ACL 400 (N = 269)	Placebo (N = 273)	ACL 400 (N = 190)	Placebo (N = 186)	ACL 400 (N = 177)	Placebo (N = 182)
Overall compliance						
Mean (SD)	93.7 (13.6)	91.7 (14.3)	99.3 (1.2)	98.7 (4.9)	95.2 (21.6)	93.0 (12.0)
Median	94.2	93.6	99.4	99.4	94.5	94.0
Range (Min, Max)	21.4, 168.2	5.6, 150.0	89, 100	54, 107	0, 274	61, 173
Patients compliant, n (%)						
Yes	250 (93.3)	251 (91.9)	190 (100)	184 (98.9)	175 (98.9)	177 (97.8)
No	18 (6.7)	22 (8.1)	0 (0)	2 (1.1)	2 (1.1)	4 (2.2)

ACL = aclidinium bromide; Max = maximum; Min = minimum; SD = standard deviation.
Source: Clinical Study Reports for M/34273/34,[12] LAS-MD-33,[13] and LAS-MD-38 Part A.[1.4]

TABLE 53: TREATMENT COMPLIANCE (SAFETY POPULATION): ACTIVE COMPARATOR TRIALS

	M/34273/23			M/34273/29			M/34273/39		
	ACL 400 (N = 30)	TIO 18 (N = 30)	Placebo (N = 30)	ACL 400 (N = 74)	FOR 12 (N = 74)	Placebo (N = 76)	ACL 400 (N = 171)	TIO 18 (N = 158)	Placebo (N = 85)
Overall compliance									
Patients compliant, n (%)									
Yes	NR	NR	NR	73 (98.7)	74 (100.0)	73 (96.1)	166 (98.2)	153 (96.8)	80 (94.1)
No	NR	NR	NR	1 (1.4)	0 (0)	3 (4.0)	3 (1.8)	5 (3.2)	5 (5.9)

ACL = aclidinium bromide, FOR = formoterol; NR = not reported; TIO = tiotropium bromide.
Source: Clinical Study Reports for M/34273/23,[15] M/34273/29,[16] and M/34273/39.[17]

TABLE 54: STUDY M/34273/23 QUESTIONS ON CONVENIENCE OF THE DEVICE (SAFETY POPULATION)

Question No.	Question	Answer	Genuair (N = 30) n (%)	HandiHaler (N = 30) N (%)
1/2	How easy has the patient considered the use of Genuair/HandiHaler?	Very easy	24 (80.0)	16 (53.33)
		Easy	5 (16.67)	9 (30.00)
		Normal	0 (0)	5 (16.67)
		Difficult	0 (0)	0 (0)
		Very difficult	1 (3.33)	0 (0)
		Not done	0 (0)	0 (0)
3/4	How easy was the dose preparation of Genuair/HandiHaler?	Very easy	25 (83.33)	14 (46.67)
		Easy	4 (13.33)	12 (40.00)
		Normal	1 (3.33)	4 (13.33)
		difficult	0 (0)	0 (0)
		Very difficult	0 (0)	0 (0)
		Not done	0 (0)	0 (0)
5/6	Is there any particular feature that you liked the most about Genuair/HandiHaler?	No	27 (90.00)	29 (96.67)
		Yes	3 (10.00)	1 (3.33)
		Not done	0 (0)	0 (0)
7/8	Is there any particular feature that you disliked about Genuair/HandiHaler?	No	27 (90.0)	26 (86.67)
		Yes	2 (6.67)	4 (13.33)
		Not done	1 (3.33)	0 (0)
9/10	Did you taste or feel anything while inhaling with Genuair/HandiHaler?	I did not taste or feel anything	7 (23.33)	15 (50.00)
		I did not taste anything but I felt something in my mouth	10 (33.33)	6 (20.00)
		I did not feel anything but I tasted something	5 (16.67)	6 (20.00)
		I felt and tasted something	8 (26.67)	3 (10.00)
		Not done	0 (0)	0 (0)
11	Which device do you prefer the most?	I definitively prefer Genuair/HandiHaler	9 (30.00)	2 (6.67)
		I somewhat prefer Genuair/HandiHaler	6 (20.00)	1 (3.33)
		I do not have any preference for either of the 2 inhalers	12 (40.00)	
		Not done	0 (0)	

Source: Clinical Study Report for M/34273/23.[15]

TABLE 55: STUDY M/34273/29 QUESTIONS ON CONVENIENCE OF THE DEVICE (SAFETY POPULATION)

Question No.	Question	Answer	Genuair (N = 79) n (%)	Aerolizer (N = 79) n (%)
1/2	How easy has the patient considered the use of Genuair/Aerolizer?	Very easy	51 (65.4)	19 (24.4)
		Easy	19 (24.4)	19 (24.4)
		Normal	7 (9.0)	26 (33.3)
		difficult	1 (1.3)	12 (15.4)
		Very difficult	0 (0)	2 (2.6)
		Not done	0 (0)	0 (0)
		Missing	1	1
3/4	How easy was the dose preparation of Genuair/Aerolizer?	Very easy	57 (73.1)	15 (19.2)
		Easy	15 (19.2)	26 (33.3)
		Normal	5 (6.4)	21 (26.9)
		difficult	1 (1.3)	15 (19.2)
		Very difficult	0 (0)	1 (1.3)
		Not done	0 (0)	0 (0)
		Missing	1	1
5/6	How clearly does the Genuair/Aerolizer indicate that the dose was correctly inhaled?	Very easy	29 (37.2)	18 (23.1)
		Easy	23 (29.5)	22 (28.2)
		Normal	15 (19.2)	26 (33.3)
		difficult	9 (11.5)	12 (15.4)
		Very difficult	2 (2.6)	0 (0)
		Not done	0 (0)	0 (0)
		Missing	1	1
7	Which device do you prefer the most?	I definitively prefer Genuair/HandiHaler	49 (62.8)	5 (6.4)
		I somewhat prefer Genuair/HandiHaler	10 (12.8)	3 (3.9)
		I do not have any preference for either of the 2 inhalers	11 (14.1)	
		Not done	0 (0)	
		Missing	1	

Source: Clinical Study Report for M/34273/29.[16]

TABLE 56: STUDY M/34273/39 PERCENTAGE OF PATIENTS WHO PREFERRED GENUAIR, HANDIHALER, OR NEITHER OVER 6 WEEKS (INTENTION-TO-TREAT POPULATION)

Device preference	Placebo (N = 85)	ACL 400 (N = 171)	TIO 18 (N = 158)	Total (N = 414)
Genuair				
n (%)	68 (80.0)	135 (79.4)	127 (80.9)	330 (80.1)
95% CI	69.9, 87.9	72.5, 85.2	73.9, 86.7	75.9, 83.8
HandiHaler				
n (%)	9 (10.6)	21 (12.4)	14 (8.9)	44 (10.7)
95% CI	5.0, 19.2	7.8, 18.3	5.0, 14.5	7.9, 14.1
No preference				
n (%)	8 (9.4)	14 (8.2)	16 (10.2)	38 (9.2)
95% CI	4.2, 17.7	4.6, 13.4	5.9, 16.0	6.6, 12.4
Comparison between patients who preferred Genuair to HandiHaler				
***P* value**	< 0.0001	< 0.0001	< 0.0001	< 0.0001

ACL = aclidinium bromide; CI = confidence interval; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/39.[17]

TABLE 57: STUDY M/34273/39 SCORE OF WILLINGNESS TO CONTINUE USING GENUAIR OR HANDIHALER DEVICE OVER 6 WEEKS OF TREATMENT (INTENTION-TO-TREAT POPULATION)

		Willingness to Continue Score			
Device	**Statistic**	**Placebo (N = 85)**	**ACL 400 (N = 171)**	**TIO 18 (N = 158)**	**Total (N = 414)**
Score over 6 weeks					
Genuair	n	85	170	157	412
	Mean (SD)	89.9 (19.9)	86.7 (26.0)	90.6 (18.2)	88.8 (22.1)
HandiHaler	n	85	169	156	410
	Mean (SD)	39.2 (36.2)	47.4 (35.5)	46.7 (34.9)	45.4 (35.5)
Comparison between Genuair and HandiHaler					
	N	85	169	156	410
	Mean (95% CI)	50.7 (41.3 to 60.2)	39.3 (31.9 to 46.6)	43.8 (37.6 to 50.0)	43.4 (39.1 to 47.7)
	P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001

ACL = aclidinium bromide; CI = confidence interval; SD = standard deviation; TIO = tiotropium bromide.
Source: Clinical Study Report for M/34273/39.[17]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To provide background information on forced expiratory volume in one second (FEV_1), the respiratory symptoms component of EXACT-PRO, SGRQ, BDI/TDI, and EQ-5D.

Forced Expiratory Volume in One Second

FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second. It is commonly used both in clinical practice and in clinical trials and is generally thought to correlate with chronic obstructive pulmonary disease (COPD) outcomes.[8] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[49] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L.[7] There is evidence that, for patients who are undergoing COPD exacerbation, a two-day increase of 0.10 L reduced the relative risk of treatment failure by 20%.[8] However, changes of the same magnitude are not always associated with clinically important differences in all studies.

While both pre- and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and measure of severity in COPD, the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) criteria indicate that post-bronchodilator values should be used.[49] This is supported by evidence from a prospective study of 300 COPD patients who were followed for at least 1.5 years and who were evaluated every three months until the end of the study.[49] Predictors of mortality were analyzed. While FEV_1, body mass index, dyspnea score, and several other factors were shown to be predictors of mortality, multivariate analyses showed that post-bronchodilator per cent predicted FEV_1 was a significant independent predictor of both all-cause mortality and respiratory-cause mortality; whereas the pre-bronchodilator per cent predicted FEV_1 was not (all-cause mortality $P = 0.008$ versus 0.126; respiratory-cause mortality $P = 0.0016$ versus 0.302). Furthermore, with respect to GOLD classifications of disease severity, the discriminative ability of the GOLD severity classification was higher using post-bronchodilator than using pre-bronchodilator per cent predicted FEV_1 ($P = 0.009$ versus 0.131).

Normalized area under the curve (AUC) FEV_1 is an average of the measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation.[50] No information regarding the validity of this outcome or the minimal clinically important difference (MCID) was identified.

Exacerbation of Chronic Pulmonary Disease Tool — Patient-Reported Outcomes Respiratory Symptoms

Exacerbation of Chronic Pulmonary Disease Tool — Patient-Reported Outcomes (EXACT-PRO) is an instrument that measures frequency, severity, and duration of exacerbations of COPD.[51] It is a 14-item questionnaire that evaluates the effects of pharmacological treatment on COPD exacerbations by capturing the primary COPD complaints (dyspnea, cough, and sputum production).[12,52] EXACT-PRO is designed to capture and standardize the dynamic process and fluctuations associated with exacerbations.[53] It is not a diagnostic tool but is rather a daily diary-like tool for patients to track symptoms. Patients fill it out at the end of the day and are asked to rate their symptoms from that particular day. Changes are examined over the duration of treatment.[53] Each item is scored on either a 5- or a 6-point ordinal scale (from “not at all” to “extremely” for most items), and are summed to create a total score that ranges from 0 to 100, with higher scores indicating more severe symptoms.[52]

The user manual for the EXACT-PRO defines an exacerbation event as a 12-point increase from baseline in total score over the course of two days or a nine-point increase from baseline over the course of three days.[54] Recovery from an event has been defined as the time taken (in days) to return from the exacerbation score to baseline.

The EXACT-PRO has been shown to have both content and construct validity;[53] however, while it has been shown to be an effective method to evaluate the severity of and to assess recovery from a COPD exacerbation, it is not clear if it accurately detects an exacerbation.[54] As EXACT was initially developed as a potential way to identify unreported exacerbations in clinical trials, it is likely not equivalent to a physician's examination.[54]

The EXACT-Respiratory Symptoms (E-RS) score is composed of the breathlessness, cough and sputum, and chest respiratory symptom subscales of the EXACT-PRO and is calculated using 11 of the total 14 EXACT items.[12] Scores range from 0 to 40, with higher scores indicating more severe symptoms. The E-RS has three symptom subscales: RS-Breathlessness (five items), RS-Cough and Sputum (three items), and RS-Chest Symptoms (three items).The EXACT breathlessness domain has been most highly correlated with clinical outcome measures (per cent predicted FEV_1, modified medical research council dyspnea scale, and rescue medication use).[52] In trials sponsored by pharmaceutical companies, the E-RS (and the EXACT) was shown to have construct and content validity for its intended use as an outcome measure in randomized placebo-controlled trials.[53] As of 2013, its use in medical product development trials of COPD were under qualification review by the US Food and Drug Administration and the European Medicines Association.[53] No specific information regarding MCID was identified.

The EXACT-PRO questionnaire was developed by United BioSource Corporation, and the EXACT-PRO initiative was sponsored by AstraZeneca, Novartis, GlaxoSmithKline, Pfizer, and MPex Pharmaceuticals.[55]

St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a disease-specific measure of health-related quality of life (HRQoL) that consists of 50 items and was specifically developed for patients with chronic airflow limitation.[56] It was developed in 1992 to measure impaired health and perceived well-being in patients with airway disease, and to meet the need for a sensitive measure of HRQoL.[57] The instrument has been used worldwide in studies and in clinical settings.[57] The SGRQ includes questions regarding sleep disturbances, public embarrassment, and panic (which can be signs of depression or anxiety) as well as employment, recreation activities, and feeling like a nuisance to friends and family (which are indicative of social impact).[58]

The 50 items of the questionnaire are divided into three dimensions: symptoms (eight items measuring the distress due to respiratory symptoms), activity (16 items measuring the effect of disturbances on mobility and physical activity), and impacts (26 items measuring the psychosocial impact of the disease).[59] Items are weighted using empirically derived weights in order to determine the total SGRQ, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[59,60] The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units of change; a decrease in scores indicates an increase in HRQoL.[51] These have been examined as within-group measures, not between-group measures. As all estimates of clinical significance are subject to measurement error and sample error and require value judgments, MCID should be interpreted with caution.[51] It is unclear what between-group MCID would be appropriate.

Component scores for the symptoms, activity, and impact domains can be calculated (also ranging from 0 to 100), in addition to the total score. In the symptoms domain, patients are asked to rate the appearance, frequency, and severity of respiratory symptoms (wheeze, breathlessness, cough, etc.) on a 5-point scale where the low scores indicate no symptoms and high scores indicate more severe symptoms.[59] A number of items in the symptoms component relate to the frequency of symptoms over the previous year.[61] Responses on the other two domains are mostly yes-no in nature. The activity domain deals with mobility and physical activity problems that either cause or are limited by breathlessness.[59] Impacts covers aspects involved in social functioning, and psychosocial disturbances resulting from obstructive airways disease (employment, panic, medication, and side effects).[59] Social functioning and psychosocial disturbances have been identified by patients as particularly troubling aspects of COPD.

A COPD-specific version of the SGRQ (the SGRQ-C) has been developed;[62] however, it was unclear whether this was the version used in the included trials.

Baseline and Transition Dyspnea Indices

The Baseline Dyspnea Index (BDI) is a discriminative measure used to determine the severity of dyspnea at baseline, and the Transition Dyspnea Index (TDI) is a transitional measure used during the treatment period to assess changes from baseline.[7] The BDI and TDI each have three domains: functional impairment, magnitude of task, and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired), and the scores are summed to create the baseline focal score, which ranges from 0 to 12; the lower the score the greater the severity of dyspnea. The TDI domains are rated from –3 (major deterioration) to 3 (major improvement), and the scores are summed to create the transition focal score, which ranges from –9 to 9. Negative scores indicate deterioration.[7] Scores for the BDI and TDI can be obtained through interviews, or through self-administered computerized versions.[7] Both BDI and TDI have been found to have a normal distribution in patients with COPD and have been found to be reproducible in both the short (two days to two weeks) and longer term.[7]

Factor analysis has shown that dyspnea scores are separate and distinct from lung function, exercise capacity, and other outcomes in COPD patients in randomized controlled trials (RCTs). Improvements in TDI have been associated with pharmacotherapy (versus placebo), and, in an observational study, both BDI and TDI have been shown to be valid and responsive measures of acute changes in COPD-related dyspnea.[7]

Witek and Mahler[9] conducted a retrospective analysis of a cohort of COPD patients (N = 997) to assess the concurrent and construct validity and MCID for the TDI. BDI was strongly correlated with Physician's Global Evaluation (PGE), SGRQ, and FEV_1 at baseline, and one-year TDI following six months of therapy was correlated with PGE and SGRQ. Patients with a 1-unit change in TDI had fewer exacerbations, improved health status, and greater spirometric improvement than those who did not achieve a one-unit improvement in TDI. Thus, the authors concluded that the MCID for the TDI is 1 unit. The authors also concluded that there is evidence to suggest that the BDI and TDI have good concurrent and construct validity, for both the English-language versions and translations.

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D)[63,64] is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[63,64] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day.

Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The EQ-5D demonstrated convergent validity with the MRC Dyspnoea Scale in both primary and specialist care settings within the UK and US and across five European Union countries.[65] The MCID for the EQ-5D ranges from 0.033 to 0.074.[43]

Summary

FEV_1, EXACT-PRO, E-RS, SGRQ, BDI/TDI, and EQ-5D have all been shown to be valid outcome measure for patients with COPD.

Validated MCIDs were identified for SGRQ (four units from baseline), BDI/TDI (one-unit change), and EQ-5D (0.033 to 0.074). No validated value was available for FEV_1 or normalized FEV_1 AUC. However, the generally accepted clinically important change in FEV_1 is 0.10 L to 0.14 L, and one of the trials included in the main report used a value of 0.07 L as the MCID for normalized FEV_1 AUC.

No information regarding MCID for EXACT-PRO or E-RS was identified. While EXACT-PRO has been shown to be an effective method to evaluate the severity of and to assess recovery from a COPD exacerbation, it is not clear if it accurately detects an exacerbation.

APPENDIX 6: SUMMARY OF LONG-TERM AND EXTENSION STUDIES

Aim

To provide a brief summary of studies LAS-MD-35,[48] LAS-MD-36 Extension,[47] and LAS-MD-38 Part B,[35] which examined the long-term efficacy and safety of aclidinium bromide (ACL) 400 mcg twice daily in patients with moderate to severe chronic obstructive pulmonary disease (COPD) over 52 weeks (LAS-MD-35 and LAS-MD-36 Extension) or 40 weeks (LAS-MD-38 Part B).

Study Characteristics

LAS-MD-35 (Study 35) was a randomized, double-blind, parallel group, controlled trial that compared ACL 200 mcg versus ACL 400 mcg twice daily for 52 weeks. It was not included in the main report because the comparison was between two doses of ACL; only results for the 400 mcg group are examined here. The study randomized 293 patients to 400 mcg twice daily, 162 of whom completed the study.[48] Change from baseline was measured from the beginning of the study to the end of the study (total number of weeks = 52).

LAS-MD-36 Extension (Study 36) was a double-blind 52 week extension study of the 12-week placebo-controlled LAS-MD-36 study.[47] Patients who were randomized to active treatment (ACL 200 or 400 mcg twice daily) during LAS-MD-36 continued on active treatment, and patients randomized to placebo were re-randomized to one of the active treatment options. Ninety patients (60% of the original group) from the placebo group (46 of whom were re-randomized to 400 mcg) and 104 patients (64% of the original group) from the 400 mcg group continued on to the extension study. A total of 103 patients completed the extension (53% of those initially starting the extension). Change from baseline was measured from the baseline of the lead-in study to the end of the extension study (total number of weeks = 64).

LAS-MD-38 Part B (Study 38 B) was an open-label extension of the double-blind, placebo-controlled LAS-MD-38 Part A study.[35] All patients who continued from the 12-week Part A into the 40-week Part B — 147 (81% of original group) from the placebo group, 154 (84% from the original group) from the 200 mcg group, and 147 (83% from the original group) from the 400 mcg group — received 400 mcg twice daily for the duration of the extension study. Change from baseline was measured from the baseline of the lead-in study to the end of the extension study (total number of weeks = 52).

Table 58 contains key baseline characteristics of the study groups. Overall, the mean age of patients was relatively similar in the extension studies; however, those in Study 38 B were on average one (in the active treatment groups) to four (in the placebo group) years younger. Baseline lung function scores were relatively similar across the studies. Mean baseline St. George's Respiratory Questionnaire (SGRQ) scores were lowest in Study 36 (44.6 and 47.0) and similar (approximately 50) in Studies 35 and 38 B.

Findings

Effectiveness

Lung function: At the final follow-up, the mean improvement in pre-bronchodilator (trough) forced expiratory volume in one second (FEV_1) measurements ranged from 0.03 L (at the week 40 follow-up for the Study 38 B group that crossed over from ACL 200 to 400 mcg) to 0.072 L in Study 35 (at the week 52 follow-up). The mean change in peak FEV_1 was not reported in Study 36 but ranged from 0.172 L in the ACL 400 mcg extension group in Study 38 B to 0.214 L in Study 35. Table 58 contains further details.

Health status: At the final follow-up, mean improvements in the SGRQ total scores ranged from 5.2 (after 52 weeks) in Study 35 to 8.25 (after 40 weeks) in the patients who crossed over from placebo-to-ACL 400 mcg in Study 38 B). Changes in all groups were larger than the 4-point improvement considered to be the minimal clinically important difference (MCID). Rescue medication use decreased in all groups, and the mean number of puffs per day needed ranged from 1.4 in Study 35 to 2.8 in Study 38 B. Table 58 contains further detail.

Safety

Adverse events: The percentage of patients who experienced at least one treatment-emergent adverse event (AE) ranged from 62.6% in the placebo-to-ACL 400 mcg group in Study 38 B to 76.2% in the placebo-to-ACL 400 mcg group in Study 36. The most commonly reported treatment-emergent AE in all of the studies was an exacerbation in COPD. The percentage of patients with this event (19.8% to 26.1%) tended to be higher in the extension studies than in the trials included in the main review, which is expected, as more follow-up time has been accrued for events to occur. Table 58 contains further detail.

Anticholinergic events: AEs associated with anticholinergic use (dry mouth, urinary tract infection [UTI], and/or constipation) were reported in all of the studies. UTI was the most common event in Studies 36 (6.6% in the ACL 400 mcg extension and 4.3% in the placebo-to-ACL 400 mcg group) and 38 B (2.5% overall) and dry mouth (which was not reported in Study 36) was most common in Study 35 (2.5% versus 2.1% and 1.7% for UTI and constipation). Table 56 contains further detail.

Cardiac events: Cardiac events were reported in all three studies. The percentage of patients who experienced any treatment-emergent cardiac event ranged from 2.2% in the placebo-to-ACL 400 mcg patients in Study 36 to 8.5% in the ACL 400 mcg group in the same study. In general, the percentage of patients with cardiac events was higher in the extension studies than in the studies included in the main review, which is expected, as more follow-up time has been accrued for events to occur. Table 58 contains further detail.

Conclusion

Overall, ACL 400 mcg twice daily administered for up to 64 weeks (i.e., 12 weeks initial trial and 52 weeks extension) was found to be safe in patients with moderate to severe COPD. Treatment effects were lower after 52 weeks than after the initial 12 to 24 week results, with none of the studies maintaining a MCID of 0.100 L (trough) FEV_1; however, attrition of patients between the lead-in studies and the extension studies may partially or fully explain the reduction in efficacy.

TABLE 58: SUMMARY OF LONG-TERM AND EXTENSION STUDIES

Measure/ component	Study LAS-MD-35[48]	Study LAS-MD-36 Extension[47]		Study LAS-MD-38 Part B[35]		
Study design; other study details	RCT, double-blind, parallel group, in patients with moderate to severe COPD ACL 200 mcg vs. ACL 400 mcg[a] BID 52-week follow-up	Double-blind, extension study in which COPD patients previously treated with ACL 200 mcg or 400 mcg BID for 12-week lead-in study continued the same treatment. Patients previously receiving placebo re-randomized (1:1) to ACL 200 mcg or 400 mcg[a] BID 52-week follow-up		Multi-centre, open-label, treatment continuation of patients enrolled in Part A. Part A included ACL 200 mcg, 400 mcg BID, and placebo. In Part B, all patients who continued received 400 mcg BID. 40-week follow-up		
Number of patients	293 patients randomized to ACL 400 mcg; 162 completed	106/166 patients who completed the 400 mcg group of the RCT enrolled in the extension study; 74 completed	90/149 patients who completed the placebo group of the RCT enrolled in the extension study; 46 were randomized to 400 mcg, 29 completed	147/182 pts who completed the placebo group continued 344 total pts completed Part B	154/184 pts who completed ACL 200 mcg group continued	147/178 pts who completed ACL 400 mcg group continued
Safety analysis (n)	291	106	46	147	154	147
ITT (n)	290 (efficacy analysis, not ITT)	91	41	134	139	132
Baseline characteristics	Mean age: 64.2 years % male: 57.4 Current smoker: 50.2% Baseline ICS use: 36.1% Post-bronchodilator % predicted FEV_1: 51.2 Baseline mean (SD) FEV_1: 1.37 (0.61) SGRQ mean (SD) total score: 49.8 (18.9) Rescue medication use (mean; SD): 2.9 (3.2) puffs/day	Mean age: 64.1 years % male: 49.1% Current smoker: 44.3% Baseline ICS use: NR Post-bronchodilator % predicted FEV_1: 53.7% Baseline mean (SD) FEV_1: 1.33 (0.58) SGRQ mean (SD) total score: 47.0 (16.3) Rescue medication use (mean; SD): 4.4 (5.4) puffs/day [g]	Mean age: 65.0 years % male: 52.2% Current smoker: 41.3% Baseline ICS use: NR Post-bronchodilator % predicted FEV_1: 53.2% Baseline mean (SD) FEV_1: 1.31 (0.47) SGRQ mean (SD) total score: 44.6 (17.7) Rescue medication use (mean; SD): 3.7 (4.4) puffs/day [g]	Baseline characteristics reported in the main study and main body of this report. Characteristics of patients at start of extension study similar to part A with exception of age: younger mean age in placebo-to-400 mcg (61.3 years) vs. 200 mcg-to-400 mcg (63.8 years) and 400 mcg extension (63.1). Distribution of Stage III: placebo-to-400 mcg 37.4%; 200 mcg-to-400 mcg 45.5%; 400 mcg extension 53.1%		

Measure/ component	Study LAS-MD-35[48]	Study LAS-MD-36 Extension[47]		Study LAS-MD-38 Part B[35]		
Efficacy outcomes	400 mcg	400 mcg extension	Placebo-to-400 mcg	Placebo-to-400 mcg	200 mcg-to-400 mcg	400 mcg extension
Lung function, mean change in trough FEV_1	Week 1: 0.091 L Week 24: 0.101 L Week 52: 0.072 L	Week 52[d]: 0.056 L[b]	Week 52[d]: exact values NR,[b] statement that similar to the 400 mcg extension, graph indicates ~ 0.060 L	Week 40[b]: 0.045 L[e]	Week 40[b]: 0.030 L[e]	Week 40[b]: 0.048 L[e]
Lung function, mean change in peak FEV_1	Day 1: 0.235 L Week 52: 0.214 L	NR	NR	Week 52: 0.185 L	Week 52: 0.176 L	Week 52: 0.172 L
Health status, mean improvement[b] in SGRQ	Total: 5.2 Symptoms: 5.8–7.6 Activity: 3.8–5.5 Impact: 5.5–7.1	Total: 7.9	Total: 5.7	Total: 8.25	Total: 6.19	Total: 6.82
Health status, use of rescue medication	Mean: 1.4 puffs/day (SD not reported)	Mean: 2.2 puffs/day (SD not reported)	Mean: 2.7 puffs/day (SD not reported)	Mean: 2.8 puffs/day (SD not reported)	Mean: 2.8 puffs/day (SD not reported)	Mean: 2.8 puffs/day (SD not reported)
Treatment-emergent adverse events	TEAE most frequently leading to study discontinuation was COPD exacerbation	1 death; not thought to be treatment-related		3 deaths; 2 in placebo-to-400 mcg, 1 in 400 mcg; all cardiac or cardiorespiratory, none thought to be treatment-related		
Adverse events						
At least 1	192 (66.0%)	77 (72.6%)	35 (76.2%)	62.6%	65.6%	65.3%
COPD exacerbation	58 (19.9%)	21 (19.8%)	12 (26.1%)	≥5%		
Nasopharyngitis	13 (4.5%)	10 (9.4%)	2 (4.3%)	NR	NR	NR
URTI	8 (2.7%)	6 (5.7%)	2 (4.3%)	≥5%		
Sinusitis	12 (4.1%)	3 (2.8%)	1 (2.2%)	NR	NR	NR
Cough	11 (3.8%)	2 (1.9%)	3 (6.5%)	NR	NR	NR
Headache	11 (3/8%)	3 (2.8%)	1 (2.2%)	NR	NR	NR
Back pain	10 (3.4%)	4 (3.8%)	0	NR	NR	NR
Dyspnea	2 (0.7%)	2 (1.9%)	2 (4.3%)	NR	NR	NR
Anticholinergic	Dry mouth: 8 (2.7%) UTI: 6 (2.1%) Constipation: 5 (1.7%)	UTI: 7 (6.6%) Constipation: 2 (1.9%)	UTI: 2 (4.3%) Constipation: 0	Dry mouth: small numbers (NR)[f] UTI: 2.5% overall[f] Constipation: 1.3% overall[f]		

Measure/ component	Study LAS-MD-35[48]	Study LAS-MD-36 Extension[47]		Study LAS-MD-38 Part B[35]
Cardiac	Any cardiac: 12 (4.1%) Acute MI: 2 (0.7%) Atrial fibrillation: 2 (0.7%) Angina pectoris: 2 (0.7%) L/R BBB: 2 (0.7%) VE: 2 (0.7%) Palpitations: 1 (0.3%) Extrasystoles: 1 (0.3%)	Any cardiac: 9 (8.5%) L/R BBB: 3 (2.8%) AV block: 1 (0.9%) CAD: 1 (0.9%) CCF: 1 (0.9%) VE: 0	Any cardiac: 1 (2.2%) L/R BBB: 0 AV block: 1 (2.2%) CAD: 0 CCF: 0 VE: 0	Any cardiac: 26 patients (6.5%) Cerebrovascular accident: 2 patients Carotid artery occlusion: 1 Subarachnoid hemorrhage: 1

ACL = aclidinium bromide; AV = atrioventricular; BBB = bundle branch block; BID = twice daily; CAD = coronary artery disease; CCF = congestive cardiac failure; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; ITT = intention-to-treat; L/R = left/right; MI = myocardial infarction; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection; VE = ventricular extrasystoles; vs. = versus.

[a] Only the 400 mcg group is reported, as the 200 mcg dose is not relevant to this report.

[b] Based on change from baseline in Part A.

[c] Reported by ≥ 3%.

[d] Week 52 of the extension, week 64 if original study duration is included in total time.

[e] Adjusted mean change.

[f] Comparable across groups.

[g] Characteristics at baseline; characteristics of patients at start of extension study not reported.

APPENDIX 7: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS

Objective

The objective of this review is to summarize the methods and results, and to conduct a critical appraisal of the manufacturer-provided network meta-analysis (NMA) comparing the efficacy of aclidinium bromide with tiotropium bromide and glycopyrronium bromide.

Summary of Network Meta-analysis

Rationale

The manufacturer indicated that the systematic review and NMA were undertaken because none of the identified randomized controlled trials (RCTs) were designed to assess the comparative efficacy of aclidinium bromide, tiotropium bromide, and glycopyrronium bromide. Comparative data were needed in order to inform the cost-minimization analysis.

Methods

Eligibility criteria

To be eligible for inclusion, trials had to include patients with chronic obstructive pulmonary disease (COPD), be at least 12 weeks in duration, have a randomized parallel design, include at least 25 patients, and compare one of the aforementioned active comparators to placebo. As well, in order to be eligible for inclusion, studies were required to have a primary or secondary end point of change in forced expiratory volume in one second (FEV_1) and patient-reported outcomes using validated COPD scales.

Intervention and Comparators

The included interventions and doses were 400 mcg twice daily for aclidinium bromide, 18 mcg once daily for tiotropium bromide, and 50 mcg once daily for glycopyrronium bromide. These were compared with placebo.

Outcomes

The main outcomes of interest for the NMA included a mean change from baseline in FEV_1 (expressed as standard mean difference), improvement in St. George's Respiratory Questionnaire (SGRQ) score (where a change of 4 points was considered minimally important) and improvement in the Transition Dyspnea Index (TDI) score (where a change of one point was considered minimally important). Other outcomes included were COPD exacerbations and drug discontinuation.

Analysis

The quality of the included studies was assessed using the National Institute for Health and Care Excellence (NICE) checklist for study quality assessment. This scale does not provide a numerical value of quality assessment but rather indicates whether randomization, concealment, prognostic similarity between groups, double-blinding, imbalances in dropouts between groups, non-reporting of outcomes, and intention-to-treat (ITT) analysis were present, absent, or unclear. Authors stated that studies of lower quality would be excluded from the analysis but did not indicate what they considered to be lower quality using this particular tool.

Indirect comparisons were undertaken using two approaches. The first was meta-regression, which was used to determine the effects of aclidinium bromide relative to either tiotropium bromide or to glycopyrronium bromide. The active drug was the independent variable in the regression model, and

other variables considered were year of study publication, geographic region where the trial was conducted, use of a double-blind design, number of participating centres, FEV_1 inclusion criteria (e.g., $FEV_1 < 65\%$), long-acting inhaled beta-2 agonists (LABAs) allowed at the start of the trial, study duration, and time point of final FEV_1 measurement. Random effects models were used in cases of significant heterogeneity (if the Q-statistic was statistically significant or where I^2 was greater than 20%), and fixed-effects models were used when significant heterogeneity was not present. The standardized mean differences (SMDs) were calculated from the ratio of treatment effect to the pooled SD of the differences. Authors stated that SMD was used to indicate the degree of benefit for a therapy after the placebo effect has been accounted for.

The second method used was the Bucher method, where the common comparator (i.e., placebo) was used to statistically link the competing treatments. The outcomes calculated were the absolute differences and relative effect sizes between aclidinium bromide and tiotropium bromide or between aclidinium bromide and glycopyrronium bromide, with the associated *P* values and confidence intervals (CIs).

Results

Study and patient characteristics

A total of 18 relevant placebo-controlled RCTs (N = 11,959) — two comparing aclidinium bromide with placebo, two comparing glycopyrronium bromide with placebo, and 14 comparing tiotropium bromide with placebo — were identified and included in the NMA. Seventeen of the 18 trials were double-blind, the number of patients per study group ranged from 46 to 515, and the median treatment duration was 26 weeks (range 12 to 52). Trough FEV_1 inclusion criteria varied from < 0.080 L to > 0.050 L, and six of the 18 trials allowed concomitant LABA medications to be used.

For 15 of the 18 included studies, it was unclear whether randomization was appropriate, and for 12 of the 18 studies, it was unclear whether allocation concealment was adequate. The groups were deemed prognostically similar in all of the studies, and all but two of the studies were double-blind. It was either unclear or there were imbalances between discontinuation rates between groups in all but two of the included studies. It was unclear which of these items were key factors in determining whether the authors considered the study to be of lower quality.

Results of the Network Meta-analysis

The key end point in all of the trials examining the efficacy of LAMA in patients with COPD was change from baseline in the trough FEV_1.

Meta-Regression Analysis: The results of the pooled SMD for the trough FEV_1 versus placebo using meta-regression resulted in all three drugs being comparable to placebo (Table 59).

TABLE 59: META-REGRESSION: POOLED STANDARD MEAN DIFFERENCE FOR TROUGH FEV_1 VERSUS PLACEBO

Intervention	SMD[a]	95% CI; *P* Value	Trough FEV_1, L Equivalent	95% CI
Aclidinium bromide (pooled estimate from 2 trial groups)	0.63	0.31 to 0.95; < 0.001	0.127	0.101 to 0.153 L
Tiotropium bromide (pooled estimate from 4 trial groups)	0.50	0.31 to 0.69; < 0.001	0.149	0.114 to 0.184 L
Glycopyrronium bromide (pooled estimate from two trial groups)	0.31	0.09 to 0.52; 0.006	0.125	0 to 0.283 L

CI = confidence interval; FEV_1 = forced expiratory volume in one second; SMD = standard mean difference.
[a] For SMD values, < 0.2 is usually considered trivial; > 0.2 to 0.5 small; > 0.5 to 0.8 moderate; > 0.8 to 1.2 important; > 1.2 as very important.
Source: Manufacturer's submission.[35]

In the indirect comparison using meta-regression, there were no statistically significant differences between aclidinium bromide and tiotropium bromide or aclidinium bromide and glycopyrronium bromide with respect to FEV_1, improvement in SGRQ, improvement in TDI, occurrence of at least one COPD exacerbation, or drug discontinuation. The pooled estimates of all active comparators versus placebo did result in statistically significant differences (Table 60). It was unclear why only four of 14 trials comparing tiotropium bromide with placebo were pooled.

TABLE 60: META-REGRESSION SUMMARY OF RESULTS

Comparison	Estimate	95% CI; *P* value
FEV_1		
All vs. placebo	SMD = 0.48	0.34 to 0.62; < 0.001
ACL vs. TIO	–0.13 (regression coefficient)	–0.57 to 0.31;0.49
ACL vs. GLYB	–0.32 (regression coefficient)	–0.82 to 0.18; 0.16
4 unit improvement in SGRQ		
All vs. placebo	RR = 1.36	1.26 to 1.47; < 0.001
ACL vs. TIO[a]	RR = 0.81	0.62 to 1.07; NS
ACL vs. GLYB[a]	RR = 0.83	0.64 to 1.07; NS
1 unit improvement in TDI		
All vs. placebo	RR = 1.42	1.32 to 1.52; < 0.001
ACL vs. TIO[a]	RR = 1.00	0.52 to 2.16; NS
ACL vs. GLYB[a]	RR = 0.94	0.45 to 1.99; NS
At least 1 COPD exacerbation		
All vs. placebo	RR = 0.82	0.77 to 0.87; < 0.001
ACL vs. TIO[b]	RR = 1.28	0.89 to 1.88; NS
ACL vs. GLYB[b]	RR = 1.15	0.76 to 1.75; NS
Drug discontinuation		
All vs. placebo	RR = 0.63	0.52 to 0.75; < 0.001
ACL vs. TIO[b]	RR = 0.70	0.29 to 1.68; NS
ACL vs. GLYB[b]	RR = 0.90	0.34 to 2.41; NS
Point estimates for drug discontinuation rates		
ACL	3.2%	1.6% to 4.8%[c]
TIO	5.6%	3.6% to 7.5%[c]
GLYB	6.8%	4.7% to 8.9%[c]

ACL = aclidinium bromide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV^1 = forced expiratory volume in one second; GLYB = glycopyrronium; NS = not significant; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire; SMD = standard mean difference; TDI = Transition Dyspnea Index; TIO = tiotropium bromide; vs. = versus.
[a] RR > 1 favours aclidinium bromide (indicates an increased likelihood of improvement in SGRQ or TDI).
[b] RR < 1 favours aclidinium bromide (indicates a reduced risk of COPD exacerbation or drug discontinuation).
[c] *P* value not reported.
Source: Manufacturer's submission.[35]

Bucher Method Analysis: Similar to the results of the meta-regression, the analysis of indirect comparisons using the Bucher method did not identify any significant differences in the efficacy of aclidinium bromide when compared with glycopyrronium bromide and tiotropium bromide. Improvements in patient-rated scales were also not statistically significantly different. The proportion of patients with at least one COPD exacerbation was higher for patients taking aclidinium bromide versus tiotropium bromide; however, this result was not statistically significant. While the rate of drug discontinuation was higher for patients taking aclidinium bromide (compared to both tiotropium bromide and glycopyrronium bromide), the differences were not statistically significant. Further detail is provided in Table 61.

TABLE 61: SUMMARY OF INDIRECT COMPARISON RESULTS USING BUCHER METHOD

Outcome	Estimate	95% CI; *P* value
ACL vs. TIO		
Difference in trough FEV_1	–0.022 L	–66 to 21; 0.62
At least 4 unit improvement in SGRQ[a]	RR = 1.04	0.92 to 1.17; 0.96
At least 1 unit improvement in TDI[a]	RR = 0.91	0.75 to 1.11; 0.94
At least 1 COPD exacerbation[b]	RR = 0.77	0.56 to 1.08; 0.64
Drug discontinuation[b]	RR = 1.41	0.73 to 2.75; 0.72
ACL vs. GLYB		
Difference in trough FEV_1	0.003 L	–158 to 164; 0.92
At least 4 unit improvement in SGRQ[a]	RR = 1.14	0.96 to 1.46; 0.43
At least 1 unit improvement in TDI[a]	RR = 1.04	0.86 to 1.27; 0.98
At least 1 COPD exacerbation[b]	RR = 0.87	0.61 to 1.23; 0.60
Drug discontinuation[b]	RR = 1.11	0.55 to 2.25; 0.92

ACL = aclidinium bromide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; GLYB = glycopyrronium; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire; SMD = standard mean difference; TDI = Transition Dyspnea Index; TIO = tiotropium bromide; vs. = versus.
[a] RR >1 favours aclidinium bromide (indicates an increased likelihood of improvement in SGRQ or TDI).
[b] RR <1 favours aclidinium bromide (indicates a reduced risk of COPD exacerbation or drug discontinuation).
Source: Manufacturer's submission.[35]

While none of the differences were statistically significant, overall, the point estimates of the relative risk (RR) tended to favour aclidinium bromide using the Bucher method, whereas the point estimates from the meta-regression favoured the comparators. With respect to at least one COPD exacerbation, however, the point estimate of the relative risk using the Bucher method showed RR of less than one for both aclidinium bromide versus tiotropium bromide and versus glycopyrronium bromide, whereas for both comparisons using meta-regression, the RR was higher than one. With respect to drug discontinuation, point estimates in the meta-regression indicated that patients were more likely to discontinue aclidinium bromide than tiotropium bromide or than glycopyrronium bromide, whereas the Bucher method showed the opposite; however, none of the results were statistically significant.

Critical Appraisal of Network Meta-analysis

The quality of manufacturer's NMA was assessed according the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[66] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 62.

Limitations

Some of the limitations of the indirect comparison analysis related to reporting. It was unclear whether duplicate study selection, appraisal, and data extraction occurred. Few details regarding sensitivity analyses were presented, and limited detail was presented regarding conclusions and the implications of the conclusions. No network of studies diagram was presented, and the comparability of the patient populations included in the studies is not reported.

With respect to the included studies, their duration ranged from 12 to 52 weeks. Due to the differences in length of follow-up, outcomes such as exacerbation and drug discontinuation may not be comparable across studies, as the likelihood of an exacerbation increases over time. It is also unclear in the analysis which follow-up time points were used in the pooled calculations. Six of the included studies were

conducted in North America; however, it was unclear whether any of them were conducted in Canada or included Canadian patients. This may limit the generalizability to findings to the Canadian population.

In the meta-regression analysis, there is no information provided with respect to model fit, and the number of trials used in the regression (eight) is small. Furthermore, it is unclear why 10 trials comparing tiotropium bromide with placebo were excluded from the analysis.

The contradictory findings between the point estimates calculated using the meta-regression versus those using the Bucher method are problematic as well.

In the context of the relevance of these findings to drug programs participating in the CADTH Common Drug Review process, the fact that this NMA did not include ipratropium as a comparator may limit the usefulness of the analysis, as it is missing a comparator.

Strengths

Some strengths of the manufacturer-provided NMA include quality assessment of the included studies; as well, the data were analyzed using both meta-regression and the Bucher method.

TABLE 62: CRITICAL APPRAISAL BASED ON ISPOR NETWORK META-ANALYSIS CHECKLIST

Checklist Item	Details and Comments
Are the rationale for the study and the study objectives stated clearly?	• Rationale clearly stated — no head-to-head trials, need to determine the comparative effectiveness and safety for a CMA.
Does the methods section include the following? • Description of eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction (validity/quality assessment of individual studies)	• Literature search methods, search terms, and dates presented. • Search strategy not presented. • Inclusion criteria presented. • Critical appraisal performed, lower-quality studies not included in the analysis; however, it is unclear which studies were excluded and for which reason. • Details provided with respect to the critical appraisal; however, no detail provided with respect to which items were deemed important enough to exclude a study from the analysis. • Data extraction items clearly presented; however, no detail provided with respect to patient characteristics. • Unclear whether duplicate study selection, appraisal, and data extraction occurred.
Are the outcome measures described?	• Outcome measures clearly described with the exception of the timing of the assessment.
Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Description of analysis methods and models, description of statistics used and justification for their use. • Description of how bias, inconsistency, heterogeneity was dealt with. • Meta-regression used for the LAMA and common comparator (placebo). • Bucher method used for the indirect comparisons.

Checklist Item	Details and Comments
Are sensitivity analyses presented?	• Sensitivity analysis of study publication, region where the trial was conducted, double-blinding of the trial, the FEV_1 inclusion criteria, use of LABAs allowed during the trial, and overall treatment duration performed, but limited data presented. • Description of analysis with respect to publication bias included.
Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Table/list of studies with information regarding study design and patient characteristics presented. • No network of studies diagram presented.
Does the study describe an assessment of model fit? Are competing models being compared?	• The NMA fitted both fixed and random effects models; however, full details regarding both outcomes were not included.
Are the results of the evidence synthesis (ITC/MTC) presented clearly?	• Tables with results for the pairwise comparisons presented. • Point estimates and measure of uncertainty (95% CIs) presented.
Sensitivity/scenario analyses	• Limited description of the results of the sensitivity analyses – just statement that only year of publication had an impact on results. • Sensitivity analysis based on study quality not presented.
Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	• Includes consideration for study publication, region where the trial was conducted, double-blinding of the trial, the FEV_1 inclusion criteria, use of LABAs allowed during the trial, and overall treatment duration. • No discussion of external validity. • Implications framed for use in the planned CMA.

CI = confidence interval; CMA = cost-minimization analysis; FEV_1 = forced expiratory volume in one second; ISPOR = International Society of Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; LABA = long-acting inhaled beta-2 agonist; NMA = network meta-analysis; MTC = mixed treatment comparison.
Source: Jansen et al., 2011.[66]

Summary

Due to the absence of head-to-head trials of sufficient length to include in their analysis comparing aclidinium bromide with glycopyrronium or with tiotropium bromide, the manufacturer undertook a systematic review of RCTs and performed a NMA. Overall, the efficacy of aclidinium bromide was not superior to that of either tiotropium bromide or glycopyrronium bromide. There were no significant differences found with respect to changes in FEV_1, improvements in patient-rated scales (SGRQ and TDI), COPD exacerbations, or rates of drug discontinuation found in either the meta-regression analysis or the Bucher method analysis. Some important limitations of the NMA include contradictory findings between the point estimates calculated using the meta-regression versus those using the Bucher method, lack of inclusion of ipratropium as a comparator, a small number of trials used in the meta-regression with no explanation provided as to the reasons for exclusion, and overall limited detail presented in the description of the analysis. The results and conclusions of the analysis are similar to the trends and conclusions identified in an industry-sponsored NMA published in 2013.[11]

APPENDIX 8: SUMMARY OF DRY POWDER INHALERS

Aim

To describe the characteristics of the Genuair (aclidinium bromide [ACL]), HandiHaler (tiotropium bromide), and Breezhaler (glycopyrronium bromide) inhalers and to summarize identified studies regarding ease of use, correct use, and patient satisfaction with the inhalers.

Characteristics of the Inhalers

Aclidinium bromide is delivered through the multi-dose Tudorza Genuair inhaler.[32] The inhaler comes pre-loaded; in order to load a single dose into the chamber for use, the patient must remove the cap, push and release a button, fully exhale, then inhale the dry powder. There is a visual indicator that signals that the dose has been released properly into the chamber before use and both an auditory and a visual signal that the dose has been properly inhaled.

Tiotropium bromide is delivered through the HandiHaler.[33] The patient must open the dust cap, open the mouthpiece, remove a capsule from a blister package, place the capsule in the inhaler, push and release a button to crush the capsule, fully exhale, then inhale the dry powder. In order to ensure the full dose is achieved, the patient must then fully exhale and inhale any remaining dry powder. There is no indicator that tells a patient that the dose has been properly loaded and is ready to inhale, but the patient should be able to hear the capsule vibrating as an indicator that the dose has been properly inhaled.

Glycopyrronium is delivered through the Breezhaler.[67] The patient must remove the cap from the inhaler, tilt the mouthpiece open, remove a capsule from a blister package, place the capsule in the inhaler, push and release a button on each side of the inhaler to crush the capsule, fully exhale, then inhale the dry powder. The patient may need to repeat the final two steps to ensure the dose was fully delivered. There is an auditory signal that signals that the dose has been properly loaded and is ready to inhale and the patient should be able to hear a “whirring” that indicates that the dose has been properly inhaled.

More details regarding the characteristics of each inhaler are included in Table 63.

TABLE 63: INHALER CHARACTERISTICS

Characteristic	Genuair[32]	HandiHaler[33]	Breezhaler[67]
Pre-loaded/multi-dose	Yes — multiple doses come loaded in inhaler, patient must push button to load single dose into the chamber.	No — patient must remove tablet from blister package and insert into inhaler.[a]	No — patient must remove tablet from blister package and insert into inhaler.[a]
Confirmation that dose is ready	Visual — indicator changes from red to green.	No — auditory click that the mouthpiece has been properly secured, but nothing to indicate dose is ready.	Auditory — "click" tells patient dose is ready.
Confirmation of dose delivery	Yes — audible "click" when dose is delivered, may taste sweet; visual indicator changes from green to red.	Yes — can hear and feel capsule vibrate in the device chamber, may taste sweet.	Yes — can hear capsule "whirring," may taste sweet.
Number of inhalations required	1[b]	2	1 to 2
Requires step after inhalation	No	Yes — must remove used capsule from the chamber after use.	Yes — must remove used capsule from the chamber after use.
Inhaler requires cleaning	No (should not be exposed to water).	Once per month.	No — should not be exposed to water.

[a] Requires patient to peel the outer foil off the package, not push pill through the package.
[b] If used correctly.

Patient Use of Inhalers

In a randomized, open-label, multi-centre crossover study, patients used the Genuair inhaler and the HandiHaler; preference, satisfaction, and errors in use were evaluated.[68] Patients ≥ 40 years old (mean 65.9 years) had moderate to severe chronic obstructive pulmonary disease (COPD), were trained on the use of both inhalers, and used each device once a day, one after another (randomized to the order of use) for two weeks. Patients were asked which device they preferred. Of the patients who had a preference for one device over the other (91 of 105 patents; intention-to-treat population), 79.1% preferred the Genuair inhaler versus 20.9% who preferred the HandiHaler ($P < 0.0001$). Patient satisfaction was rated on a five-point Likert scale (1 = very dissatisfied, 5 = very satisfied), and satisfaction was significantly higher for the Genuair inhaler versus the HandiHaler (mean score 4.6 versus 3.8; standard deviations [SDs] not reported; $P < 0.0001$). Critical errors in the use of the Genuair inhaler included:

- failure to remove the cap
- not holding the device in the correct direction during dose loading
- shaking the inhaler with the mouthpiece facing down before use
- the control window not showing "green" before use
- the control window showing as "green" following use
- not holding breath following use.

Critical errors in the use of the HandiHaler included:

- not opening the device correctly
- not loading the capsule properly
- not closing the mouthpiece properly
- shaking the inhaler with the mouthpiece facing down before use
- the capsule not piercing properly
- not hearing the capsule rattle
- not taking a second inhalation
- not holding breath following use.

Critical errors were observed and recorded by a designated inhaler trainer after two weeks of daily use of the inhalers. Significantly fewer patients made at least one critical error when using the Genuair inhaler versus the HandiHaler (10.5% versus 26.7%; $P < 0.0001$). Dose inhalation errors were more common with Genuair inhaler use, whereas dose preparation errors were more common when using the HandiHaler.

A randomized, open-label, crossover study examined the inspiratory flow characteristics of the Genuair inhaler versus the HandiHaler A and the HandiHaler B.[69] Patients ≥40 years old, 24 with moderate (mean age 63 years, SD 8.0) and 24 with severe (mean age 65 years, SD 6.7) COPD were trained to use the HandiHaler A, HandiHaler B, and the Genuair inhaler. The use of HandiHaler A was to follow the manufacturer's instructions (two inhalations), whereas the use of HandiHaler B mimicked the inhalation used for Genuair (one inhalation, as fast and hard as possible). Patients used all three devices. The average peak inspiratory flow using the Genuair inhaler was 92.0 ± 15.4 L/min, 46.1 ± 9.6 L/min for the HandiHaler A, and 61.5 ± 8.9 L/min for HandiHaler B. Successful inhalation (defined as sufficient to activate the trigger and change the window colour from green to red) occurred 97.2% of the time with the Genuair.

No studies were identified that compared the Breezhaler with either the HandiHaler or the Genuair inhaler.

Limitations

The primary limitation of the patient satisfaction and ease of use studies is that they were sponsored by Almirall, the manufacturer of the Genuair inhaler. Furthermore, the investigators were not blinded to the inhalers being used. No information was provided regarding comorbid conditions that may affect the use of the devices, such as arthritis or cognitive difficulties. No studies were identified that compared the Breezhaler with either the HandiHaler or the Genuair inhaler.

Summary

The Genuair inhaler is a multi-dose, pre-loaded inhaler, whereas the HandiHaler and the Breezhaler require the patient to load each dose capsule into the inhaler before use. The HandiHaler requires two inhalations, the Breezhaler often requires two inhalations, and the Genuair inhaler requires one inhalation of the dry powder. Overall, in manufacturer-sponsored, open-label studies, the Genuair inhaler was found to be associated with greater patient preference, greater patient satisfaction, fewer critical errors in its use, and higher peak inspiratory flow when inhaling the powder than HandiHaler. No studies were identified that compared the Breezhaler with either the HandiHaler or the Genuair inhaler.

REFERENCES

1. Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miquel G, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J. 2012 Oct;40 (4):830-6.
2. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia GE, Caracta CF, et al. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). COPD. 2012 Apr;9 (2):90-101.
3. Rennard SI, Scanlon PD, Ferguson GT, Rekeda L, Maurer BT, Garcia GE, et al. ACCORD COPD II: a randomized clinical trial to evaluate the 12-week efficacy and safety of twice-daily aclidinium bromide in chronic obstructive pulmonary disease patients. Clin Drug Investig. 2013 Dec;33 (12):893-904.
4. Fuhr R, Magnussen H, Sarem K, Llovera AR, Kirsten AM, Falques M, et al. Efficacy of aclidinium bromide 400 ug twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. Chest [Internet]. 2012 Mar [cited 2013 Oct 18];141 (3):745-52. Available from: http://journal.publications.chestnet.org/data/Journals/CHEST/23444/110406.pdf
5. Singh D, Magnussen H, Kirsten A, Mindt S, Caracta C, Seoane B, et al. A randomised, placebo- and active-controlled dose-finding study of aclidinium bromide administered twice a day in COPD patients. Pulm Pharmacol Ther. 2012 Jun;25 (3):248-53.
6. Beier J, Kirsten AM, Mruz R, Segarra R, Chuecos F, Caracta C, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled phase IIIb study. COPD. 2013 Aug;10 (4):511-22.
7. Cazzola M, Macnee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J [Internet]. 2008 Feb [cited 2014 Jan 14];31 (2):416-68. Available from: http://erj.ersjournals.com/content/31/2/416.full.pdf+html
8. Niewoehner DE, Collins D, Erbland ML. Relation of FEV(1) to clinical outcomes during exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. Am J Respir Crit Care Med [Internet]. 2000 Apr [cited 2013 Dec 5];161 (4 Pt 1):1201-5. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm.161.4.9907143
9. Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J. 2003 Feb;21 (2):267-72.
10. Health Canada reviewer's report: Tudorza Genuair (aclidinium bromide) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutic Products Directorate, Health Canada; 2013 Jul 24.
11. Karabis A, Lindner L, Mocarski M, Huisman E, Greening A. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. Int J Chron Obstruct Pulmon Dis [Internet]. 2013 [cited 2013 Oct 18];8:405-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3772873/pdf/copd-8-405.pdf
12. Clinical study report M/34273/34. Efficacy and safety of aclidinium bromide at two dose levels vs placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD) [**CONFIDENTIAL** internal manufacturer's report]. Barcelona: Almirall, S.A.; 2012 Jan 27.

13. Clinical study report LAS-MD-33. Efficacy and safety of aclidinium bromide at two dose levels (200 µg twice daily, 400 µg twice daily) vs. placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD) [**CONFIDENTIAL** internal manufacturer's report]. Jersey City (NJ): Forest Research Institute, Inc.; 2011 Jan 21.

14. Clinical study report LAS-MD-38 (Part A). A randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of 2 doses of aclidinium bromide compared with placebo for 12 weeks in patients with moderate to severe, stable chronic obstructive pulmonary disease followed by a 40-week evaluation of the higher aclidinium bromide dose [**CONFIDENTIAL** internal manufacturer's report]. Jersey City (NJ): Forest Research Institute, Inc.; 2011 Mar 16.

15. Clinical study report M/34273/23. A multiple dose, double blind, double-dummy, two-week 3 way cross-over, placebo controlled clinical trial to assess the efficacy and safety of twice daily inhaled aclidinium bromide 400 µg compared to placebo and to an active comparator in patients with stable moderate to severe chronic obstructive pulmonary disease (COPD) [**CONFIDENTIAL** internal manufacturer's report]. Barcelona: Almirall, S.A.; 2010 Apr 22.

16. Clinical study report M/34273/29. Efficacy and safety of three doses of aclidinium bromide compared to placebo and to an active comparator all administered twice daily by inhalation in patients with stable moderate and severe chronic obstructive pulmonary disease (COPD) [**CONFIDENTIAL** internal manufacturer's report]. Barcelona: Almirall, S.A.; 2011 Jan 31.

17. Clinical study report M/34273/39. Multiple dose, double-blind, double-dummy, placebo controlled, parallel clinical trial to assess the efficacy and safety of twice daily inhaled aclidinium bromide 400 µg compared to placebo and to tiotropium bromide in patients with stable moderate to severe chronic obstructive pulmonary disease (COPD) [**CONFIDENTIAL** internal manufacturer's report]. Barcelona: Almirall, S.A.; 2012 Aug 31.

18. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J [Internet]. 2007 Sep [cited 2014 Jan 3];14 Suppl B:5B-32B. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806792

19. O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. Can Respir J [Internet]. 2008 Jan [cited 2014 Jan 3];15 Suppl A:1A-8A. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802325

20. Rennard S. Chronic obstructive pulmonary disease: definition, clinical manifestations, diagnosis, and staging. 2013 Mar 12 [cited 2014 Jan 3]. In: UpToDate [Internet]. Version 15.0. Waltham (MA): UpToDate; 1992 - . Available from: http://www.uptodate.com Subscription required.

21. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD [Internet]. London (UK): GOLD; 2014. [cited 2014 Jan 20]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf

22. Chronic obstructive pulmonary disease, 2009 [Internet]. Ottawa: Statistics Canada; 2009. [cited 2014 Jan 3]. Available from: http://www.statcan.gc.ca/pub/82-625-x/2010002/article/11273-eng.htm

23. Chronic obstructive pulmonary disease in Canadians, 2009 to 2011 [Internet]. Ottawa: Statistics Canada; 2012. [cited 2014 Jan 3]. (Health fact sheet). Available from: http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11709-eng.htm

24. Canadian Institute for Health Information. Health indicators 2008 [Internet]. Ottawa: CIHI; 2008. [cited 2014 Jan 3]. Available from: https://secure.cihi.ca/estore/productFamily.htm?pf = PFC1019&lang = fr&media = 0

25. Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, FitzGerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respir Med. 2008 Mar;102 (3):413-21.
26. Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001 Aug 15;164 (4):580-4.
27. Sin DD, Man SF, Tu JV. Inhaled glucocorticoids in COPD: immortal time bias. Am J Respir Crit Care Med. 2003 Jul 1;168(1):126-7.
28. Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. Am J Respir Crit Care Med. 2003 Jul 1;168(1):49-53.
29. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. Am J Respir Crit Care Med. 1998 Nov;158(5 Pt 1):1511-7.
30. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2000 Oct 28;356 (9240):1480-5.
31. Leigh R, Pizzichini MM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J. 2006 May;27 (5):964-71.
32. [Pr]Tudorza™ Genuair™ (aclidinium bromide inhalation powder) 400 mcg aclidinium bromide [product monograph]. Barcelona: Almira S.A.; 2013 Jul 26.
33. [Pr]Spiriva®: tiotropium capsules for oral inhalation (18 µg tiotropium per capsule as tiotropium bromide monohydrate). Capsules to be used only with the supplied HandiHaler® inhalation device [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2012 Aug 21.
34. [Pr]Seebri Breezhaler (glycopyrronium bromide) 50 mcg hard capsules [product monograph]. Dorval: Novartis Pharmaceuticals Canada Inc.; 2012 Dec 10.
35. CDR submission binder: Tudorza Genuair (aclidinium bromide); Company: Almirall Canada Ltd. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Almirall Canada Ltd.; 2013 Aug.
36. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Tudorza Pressair (aclidinium bromide) Inhalation Powder. Company: Forest Laboratories, Inc. Application No.: 202450. Approval Date: 07/23/2012. Rockville (MD): The Center; 2012 [cited 2013 Sep 13]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000TOC.cfm.
37. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Tudorza Pressair (aclidinium bromide) Inhalation Powder. Company: Forest Laboratories, Inc. Application No.: 202450. Approval Date: 07/23/2012. Rockville (MD): The Center; 2012 [cited 2013 Sep 13]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000TOC.cfm.
38. Haythornthwaite JA, Hegel MT, Kerns RD. Development of a sleep diary for chronic pain patients. J Pain Symptom Manage. 1991 Feb;6 (2):65-72.
39. Welte T, Metzenauer P, Hartmann U. Once versus twice daily formoterol via Novolizer for patients with moderate to severe COPD--a double-blind, randomised, controlled trial. Pulm Pharmacol Ther. 2008;21 (1):4-13.
40. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013 Nov;68(11):1029-36.

41. Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in ontario, Canada, 1996 to 2007: a population-based study. Arch Intern Med. 2010 Mar 22;170 (6):560-5.

42. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 Feb 22;356 (8):775-89.

43. Sinnott PL, Joyce VR, Barnett PG. Preference measurement in economic analysis. Guidebook [Internet]. Menlo Park (CA): Health Economics Resource Center (HERC); 2007 Mar. [cited 2013 Nov 12]. Available from: http://www.herc.research.va.gov/files/BOOK_419.pdf

44. de la Motte S, Beier J, Schmid K, Pascual S, Jansat JM, Gil EG. Pharmacokinetics and safety of aclidinium bromide in younger and elderly patients with chronic obstructive pulmonary disease. Int J Clin Pharmacol Ther. 2012 Jun;50 (6):403-12.

45. Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, et al. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. Respir Med. 2011 Apr;105 (4):580-7.

46. Chanez P, Burge PS, Dahl R, Creemers J, Chuchalin A, Lamarca R, et al. Aclidinium bromide provides long-acting bronchodilation in patients with COPD. Pulm Pharmacol Ther. 2010 Feb;23 (1):15-21.

47. D'Urzo A, Kerwin E, Rennard S, He T, Gil EG, Caracta C. One-year extension study of ACCORD COPD I: safety and efficacy of two doses of twice-daily aclidinium bromide in patients with COPD. COPD. 2013 Aug;10 (4):500-10.

48. Gelb AF, Tashkin DP, Make BJ, Zhong X, Garcia GE, Caracta C, et al. Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD. Respir Med. 2013 Dec;107 (12):1957-65.

49. Chen CZ, Ou CY, Wang WL, Lee CH, Lin CC, Chang HY, et al. Using post-bronchodilator FEV1 is better than pre-bronchodilator FEV1 in evaluation of COPD severity. COPD. 2012 Jun;9 (3):276-80.

50. Committee for Medicinal Products for Human Use (CHMP). Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents [Internet]. London: European Medicines Agency; 2009 Jan 22. [cited 2014 Jan 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003504.pdf

51. Leidy NK, Wilcox TK, Jones PW, Murray L, Winnette R, Howard K, et al. Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO) measure. Value Health. 2010 Dec;13 (8):965-75.

52. Leidy NK, Wilcox TK, Jones PW, Roberts L, Powers JH, Sethi S, et al. Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. Am J Respir Crit Care Med [Internet]. 2011 Feb 1 [cited 2013 Dec 11];183 (3):323-9. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201005–0762OC

53. Leidy NK, Murray LT. Patient-reported outcome (PRO) measures for clinical trials of COPD: the EXACT and E-RS. COPD. 2013 Jun;10 (3):393-8.

54. Mackay AJ, Donaldson GC, Patel AR, Singh R, Kowlessar B, Wedzicha JA. Detection and severity grading of COPD exacerbations using the exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT). Eur Respir J. 2014;43 (3):735-44.

55. EXACT-PRO initiative [Internet]. [Blue Bell (PA)]: United BioSource Corporation. 2010 [cited 2013 Dec 12]. Available from: http://www.exactproinitiative.com/default.php

56. Menn P, Weber N, Holle R. Health-related quality of life in patients with severe COPD hospitalized for exacerbations - comparing EQ-5D, SF-12 and SGRQ. Health Qual Life Outcomes [Internet]. 2010 [cited 2013 Dec 11];8:39. Available from: http://www.hqlo.com/content/pdf/1477-7525-8-39.pdf

57. Bourbeau J, Maltais F, Rouleau M, Guimont C. French-Canadian version of the Chronic Respiratory and St George's Respiratory questionnaires: an assessment of their psychometric properties in patients with chronic obstructive pulmonary disease. Can Respir J. 2004 Oct;11 (7):480-6.

58. Jones PW. St. George's respiratory questionnaire original English version [Internet]. London: St. George's University of London; 2003. [cited 2013 Dec 19]. Available from: http://www.healthstatus.sgul.ac.uk/SGRQ_download/Original%20English%20version.pdf

59. Maly M, Vondra V. Generic versus disease-specific instruments in quality-of-life assessment of chronic obstructive pulmonary disease. Methods Inf Med. 2006;45 (2):211-5.

60. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George Respiratory Questionnaire. Chest. 2007 Aug;132 (2):456-63.

61. Shukla V, Husereau D, Boucher M, Mensinkai S, Dales R. Long-acting ß2-agonists for maintenance therapy of stable chronic obstructive pulmonary disease: a systematic review [Internet]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2002. [cited 2014 Jan 15]. (Technology report no.27). Available from: http://www.cadth.ca/media/pdf/124_laba_tr_e.pdf

62. Jones PW, Forde Y. St George's Respiratory Questionnaire for COPD patients (SGRQ-C): manual [Internet]. Version No.1.1. London: St George's, University of London; 2008 Dec 11. [cited 2014 Jan 15]. Available from: http://www.meetinstrumentenzorg.nl/Portals/0/bestanden/76_2_N.pdf

63. Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37 (1):53-72.

64. EuroQol -- a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy. 1990 Dec;16 (3):199-208.

65. Punekar YS, Rodriguez-Roisin R, Sculpher M, Jones P, Spencer M. Implications of chronic obstructive pulmonary disease (COPD) on patients' health status: a western view. Respir Med. 2007 Mar;101 (3):661-9.

66. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14 (4):417-28.

67. [Pr]Onbrez Breezhaler (imaleate inhalation powder hard capsules) 75 mcg indacaterol [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2013 Oct 16.

68. van der Palen J, Ginko T, Kroker A, van der Valk P, Goosens M, Padulles L, et al. Preference, satisfaction and errors with two dry powder inhalers in patients with COPD. Expert Opin Drug Deliv. 2013 Aug;10 (8):1023-31.

69. Magnussen H, Watz H, Zimmermann I, Macht S, Greguletz R, Falques M, et al. Peak inspiratory flow through the Genuair inhaler in patients with moderate or severe COPD. Respir Med. 2009 Dec;103 (12):1832-7.