Common Drug Review
Clinical Review Report

December 2014

Drug	indacaterol + glycopyrronium (Ultibro Breezhaler)
Indication	For the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema
Listing request	For the once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD (including chronic bronchitis and emphysema) who remain symptomatic despite use of monotherapy with a LABA or LAAC
Manufacturer	Novartis Pharmaceuticals Canada Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
BDI	Baseline Dyspnea Index
BMI	body mass index
CCV	cerebrovascular or cardiovascular
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRQ-SAS	Chronic Respiratory Disease Questionnaire Self-Administered Scale
DB	double-blind
FAS	full analysis set
FEV_1	forced expiratory volume in one second
FPD	fine particle dose
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
H_0	null hypothesis
H_a	alternative hypothesis
ICS	inhaled corticosteroid
LAAC	long-acting anticholinergic
LABA	long-acting beta-2 adrenergic agonist
LAMA	long-acting antimuscarinic agent
LOCF	last observation carried forward
LS	least squares
MCID	minimal clinically important difference
MD	mean difference
PPS	per-protocol set
QoL	quality of life
RCT	randomized controlled trial
SABA	short-acting beta-2 adrenergic agonist
SAE	serious adverse event
SAMA	short-acting antimuscarinic agent
SGRQ-C	St. George's Respiratory Questionnaire-COPD
TDI	Transition Dyspnea Index

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.[1,2] There is 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.[2] According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population ≥ 35 years of age.[3] 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.[1]

Management decisions are guided by disease severity (i.e., symptoms/disability and spirometry measurements) 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.[2] Bronchodilators form the mainstay of pharmacotherapy for COPD,[2] and include short-acting beta2 adrenergic agonists (SABAs) and short-acting antimuscarinic agents (SAMAs). Long-acting beta-2 adrenergic agonists (LABAs) or long-acting antimuscarinic agents (LAMAs; also referred to as long-acting anticholinergic [LAAC] drugs) as well as combinations of fixed-dose LABAs and inhaled corticosteroids (ICS) are the most commonly used treatments for COPD in Canada. Antimuscarinic and beta agonist drugs are often used in combination for maximal improvement in dyspnea and function. Inhaled steroids may not be useful for mild disease; however, they may have a greater role in the management of moderate to severe COPD, or in patients with persistent symptoms.[4-6] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, in which ICS use may be beneficial.[7-9] Inhaled medications are most commonly delivered with the use of pressurized metered-dose inhalers and dry powder inhalers.

Indacaterol maleate + glycopyrronium bromide (Ultibro Breezhaler) is a LABA + LAMA combination bronchodilator product. The recommended dose is indacaterol 110 mcg + glycopyrronium 50 mcg once daily.

Indication under review
For the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema
Listing criteria requested by sponsor
For the once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD (including chronic bronchitis and emphysema) who remain symptomatic despite use of monotherapy with a LABA or LAAC

The objective of this review was to perform a systematic review of the beneficial and harmful effects of indacaterol maleate and glycopyrronium bromide (Ultibro Breezhaler) for the treatment of patients with COPD, including chronic bronchitis and emphysema.

Results and Interpretation

Included Studies

Eight double-blind randomized controlled trials (RCTs) and one open-label RCT met the inclusion criteria for this review. All studies were multi-centre and manufacturer sponsored. One of the studies (QUANTIFY, N = 934), compared indacaterol 110 mcg + glycopyrronium 50 mcg once daily with another LAMA/LABA combination, tiotropium 18 mcg daily (LAMA) + formoterol 12 mcg twice daily (LABA), over 26 weeks. QUANTIFY tested the non-inferiority of indacaterol + glycopyrronium versus tiotropium + formoterol for the primary outcome of change in St. George's Respiratory Questionnaire-COPD (SGRQ-C) at end of study. SHINE (N = 2,135) tested the superiority of indacaterol + glycopyrronium versus the individual components of indacaterol (150 mcg once daily) and glycopyrronium (50 mcg once daily) for the primary outcome of forced expiratory volume in one second (FEV_1) at 26 weeks. SPARK (N = 2,224) tested the superiority of indacaterol + glycopyrronium versus the individual component of glycopyrronium (50 mcg once daily) for the primary outcome of the rate of moderate to severe exacerbations over the course of the 64 to 76 week study. Both SHINE and SPARK included an open-label tiotropium group as a secondary comparator. One study (ILLUMINATE, N = 523) compared indacaterol 110 mcg + glycopyrronium 50 mcg once daily with an ICS + LABA combination, fluticasone propionate 500 mcg + salmeterol 50 mcg twice daily over 26 weeks. One study (ENLIGHTEN, N = 339) compared indacaterol + glycopyrronium with placebo over 52 weeks. ENLIGHTEN identified safety and tolerability as its primary outcome. BEACON (N = 193) compared indacaterol 110 mcg + glycopyrronium 50 mcg once daily administered in the Breezhaler device with a combination of the components of the Breezhaler, indacaterol 150 mcg once daily and glycopyrronium 50 mcg once daily, over four weeks. BEACON tested the non-inferiority of indacaterol + glycopyrronium versus these components administered simultaneously for the primary outcome of trough FEV_1 at four weeks. Two crossover studies were included, BLAZE (six weeks of treatment in each period, N = 247) and BRIGHT (three weeks of treatment, N = 85), each including two treatment groups (indacaterol 110 mcg + glycopyrronium 50 mcg once daily and tiotropium 18 mcg once daily) and a placebo group. The primary outcome of BLAZE was to test the superiority of indacaterol + glycopyrronium versus placebo for dyspnea scores, and in BRIGHT the primary outcome was exercise tolerance after three weeks of treatment versus placebo. Finally, ARISE (N = 160) examined the safety of indacaterol 110 mcg + glycopyrronium 50 mcg once daily versus tiotropium 18 mcg once daily using an open-label design.

The key limitation of the included studies is the lack of blinding in ARISE and the lack of blinding of the tiotropium group in both SHINE and SPARK. QUANTIFY was the only study that compared indacaterol + glycopyrronium with another LAMA/LABA combination, tiotropium + formoterol; however, it was conducted entirely in Germany, which might limit generalizability of the findings to Canada. The included trials did not have a large enough sample nor were they of sufficient duration to assess key clinical outcomes such as mortality and mortality due to COPD.

Efficacy

Mortality or Mortality Due to Chronic Obstructive Pulmonary Disease

SPARK, the study with the longest duration of treatment (64 to 76 weeks) and patients with the most severe COPD, also had by far the most deaths, with 3% of patients dying in each of the indacaterol + glycopyrronium, glycopyrronium, and tiotropium groups. The most common cause of death was COPD, followed by cardiorespiratory arrest. In the other studies, generally no more than 1% of patients died in any single group; with this small number of events, no conclusions can be drawn regarding the impact of indacaterol + glycopyrronium on mortality or mortality due to COPD.

Exacerbations

Exacerbations were the primary outcome of only one (SPARK) of the nine included studies. In SPARK, which enrolled a population with more severe COPD and with a recent (within one year prior to enrolment) history of exacerbations, indacaterol + glycopyrronium demonstrated superiority over glycopyrronium for moderate to severe exacerbation events (ratio of rates 0.88; 95% CI, 0.77 to 0.99; *P* = 0.038). There was no statistically significant difference in event rates between indacaterol + glycopyrronium and tiotropium (ratio of rates 0.90; 95% CI, 0.79 to 1.02; *P* = 0.096). The proportion of patients in SPARK who had a moderate to severe exacerbation was 28% with indacaterol + glycopyrronium, 25% with tiotropium, and 26% with glycopyrronium, suggesting that although indacaterol + glycopyrronium may reduce the number of exacerbation events in a given patient, it may not affect the proportion of patients who have an exacerbation. In SHINE, indacaterol + glycopyrronium reduced the time to a moderate to severe exacerbation versus placebo (hazard ratio 0.56; 95% CI, 0.40 to 0.78; *P* < 0.001). In QUANTIFY, numerically fewer patients in the indacaterol + glycopyrronium (13%) than in the tiotropium + formoterol (15%) group experienced a moderate to severe exacerbation over the 26-week study period (relative risk 0.85; 95% CI, 0.62 to 1.17; *P* = 0.323). In ARISE, 22% of indacaterol + glycopyrronium patients had a moderate to severe exacerbation versus 21% with tiotropium.

Health-Related Quality of Life

Only five of the included studies evaluated health-related quality of life as an outcome. QUANTIFY was the only study that identified quality of life as a primary outcome, and indacaterol + glycopyrronium was non-inferior to tiotropium + formoterol for change from baseline in total SGRQ-C scores. The least squares mean difference (LS MD) between groups of –0.69 (95% CI, –2.31 to 0.92), *P* = 0.399, in the full analysis set (FAS) and –0.77 (95% CI, –2.48 to 0.93), *P* = 0.373, in the per-protocol set, met the criteria for non-inferiority, as the upper boundary of the CI was lower than the predefined margin for non-inferiority of 4 points. A 4-point change is considered to be the minimal clinically important difference (MCID) for this instrument. After 26 weeks in SHINE (LS MD –2.13; 95% CI, –3.72 to –0.54; *P* = 0.009) and after 64 to 76 weeks in SPARK (LS MD –2.69; 95% CI, –4.17 to –1.21; *P* < 0.001), indacaterol + glycopyrronium demonstrated statistically significant improvements over tiotropium for the SGRQ-C total, but these differences fall below the MCID of 4 and are therefore unlikely to be clinically significant. Tiotropium was administered open label in these studies, and this is likely to introduce bias into the assessment of a patient-reported outcome such as the SGRQ-C. When indacaterol + glycopyrronium was compared with fluticasone propionate + salmeterol, there was no statistically significant difference in SGRQ-C total scores after 26 weeks in ILLUMINATE (Table 3). No statistical analysis was reported for SGRQ-C in the open-label RCT ARISE, as this was an exploratory outcome.

Dyspnea

There was no statistically significant difference between indacaterol + glycopyrronium and tiotropium + formoterol in dyspnea scores (Table 1, Table 32) after 26 weeks in QUANTIFY. There were statistically significantly greater (improved) dyspnea scores with indacaterol + glycopyrronium than with fluticasone propionate + salmeterol at Week 26 (LS MD 0.76; 95% CI, 0.26 to 1.26; *P* = 0.003) in ILLUMINATE; however, these differences fall below the MCID of 1 identified by the manufacturer, and are thus not likely to be clinically significant. In BLAZE, there was a statistically significant improvement in Transition Dyspnea Index (TDI) focal scores for indacaterol + glycopyrronium versus placebo (LS MD 1.37; 95% CI, 0.95 to 1.79; *P* < 0.001) and versus tiotropium (LS MD 0.49; 95% CI, 0.07 to 0.91; *P* = 0.021) at six weeks; however, the difference versus tiotropium is again not likely to be clinically significant. In BRIGHT, there was no statistically significant difference in change in Borg dyspnea scores between indacaterol + glycopyrronium versus placebo or versus tiotropium at three weeks (Table 6).

Symptoms

Symptom scores were collected using a daily diary, and there is considerable debate over the reliability of this approach for assessing symptoms. There was a statistically significant improvement in symptom scores for indacaterol + glycopyrronium versus tiotropium after 64 to 76 weeks in SPARK (LS MD –0.44; 95% CI, –0.62 to –0.26; $P < 0.001$) and after 26 weeks in SHINE (–0.24; 95% CI, –0.46 to –0.01; $P = 0.043$). Indacaterol + glycopyrronium improved symptoms scores versus placebo after 52 weeks in ENLIGHTEN (LS MD –0.57; 95% CI, –1.01 to –0.13; $P = 0.011$). There does not appear to be an established MCID for this instrument; thus, it is not known whether these differences are clinically significant. There was no statistically significant difference in symptom scores after 26 weeks between indacaterol + glycopyrronium and fluticasone propionate + salmeterol (Table 3) in ILLUMINATE or between indacaterol + glycopyrronium administered in the combination device and the separate components of indacaterol plus glycopyrronium administered simultaneously with separate devices after four weeks in BEACON (Table 5). End of study symptom scores were improved at six weeks for indacaterol + glycopyrronium versus placebo in BLAZE, and this difference was statistically significant (LS MD –0.72; 95% CI, –0.94 to –0.49; $P < 0.001$). There was no statistically significant difference in symptom scores between indacaterol + glycopyrronium and tiotropium at end of study (Table 6). Symptom scores were not reported in the other studies.

Forced Expiratory Volume in One Second

Trough FEV_1 was the primary outcome in SHINE, and after 26 weeks indacaterol + glycopyrronium demonstrated superiority over its components, indacaterol (LS MD 0.07 L; 95% CI, 0.05 to 0.10; $P < 0.001$) and glycopyrronium (LS MD 0.09 L; 95% CI, 0.06 to 0.11; $P < 0.001$), the two interventions in the primary analysis. Trough FEV_1 was also improved to a greater extent with indacaterol + glycopyrronium than with tiotropium (LS MD 0.08 L; 95% CI, 0.05 to 0.10; $P < 0.001$) and with placebo (LS MD 0.21 L; 95% CI, 0.17 to 0.24; $P < 0.001$) in SHINE, and these differences were statistically significant. However, of the above comparisons, only the improvement versus placebo would be considered clinically significant. In SPARK, trough FEV_1 was also statistically significantly improved for indacaterol + glycopyrronium versus tiotropium (LS MD 0.07 L; 95% CI, 0.06 to 0.09; $P < 0.001$); however, this difference is unlikely to be clinically significant. In ILLUMINATE, after 26 weeks indacaterol + glycopyrronium demonstrated a clinically significant superiority over fluticasone propionate + salmeterol for the primary outcome of FEV_1 AUC (0 hours to 12 hours) with an LS MD of 0.14 L (95% CI, 0.10 to 0.18, $P < 0.001$). In BEACON, after four weeks indacaterol + glycopyrronium administered in the fixed-dose combination device, was non-inferior to the separate components of indacaterol plus glycopyrronium administered simultaneously with separate devices (Table 5). There was a statistically and clinically significant improvement in pre-dose FEV_1 for indacaterol + glycopyrronium versus placebo after 52 weeks in ENLIGHTEN (LS MD 0.19 L; 95% CI, 0.13 to 0.25; $P < 0.001$). After six weeks in BLAZE, there was a statistically and clinically significant improvement in FEV_1 AUC (five minutes to four hours) for indacaterol + glycopyrronium versus placebo (LS MD 0.33 L; 95% CI, 0.31 to 0.36; $P < 0.001$) and versus tiotropium (LS MD 0.11 L; 95% CI, 0.08 to 0.13; $P < 0.001$). After three weeks in BRIGHT, there was a statistically and clinically significant improvement in trough FEV_1 for indacaterol + glycopyrronium versus placebo (LS MD 0.20 L; 95% CI, 0.15 to 0.26; $P < 0.001$) and versus tiotropium (LS MD 0.10 L; 95% CI, 0.05 to 0.15; $P < 0.001$). Change in pre-dose FEV_1 was assessed in ARISE, but no statistical analysis was provided, as this was an exploratory analysis (Table 7).

Health Care Resource Utilization

In SPARK, 15% of indacaterol + glycopyrronium and 15% of glycopyrronium patients were hospitalized versus 11% of patients treated with tiotropium. The mean number of hospital admissions was 1.4 per person hospitalized in each group. In SPARK, 5% of indacaterol + glycopyrronium patients and

glycopyrronium patients had an emergency room visit, while 4% of patients treated with tiotropium had an emergency room visit. In SPARK, 76% of patients treated with indacaterol + glycopyrronium did not have an unscheduled physician visit, versus 75% of patients treated with tiotropium and 74% of patients treated with glycopyrronium (Table 33). Health care resource utilization was not reported as an efficacy outcome in the other studies.

Exercise Tolerance

In BRIGHT, there was a statistically significant increase in exercise endurance for indacaterol + glycopyrronium versus placebo (LS MD 59.5 seconds; 95% CI, 17.7 to 101.3; *P* = 0.006). There was no statistically significant difference in exercise endurance between indacaterol + glycopyrronium and tiotropium (Table 37).

Harms

Adverse Events

In QUANTIFY, [redacted]% of indacaterol + glycopyrronium patients and [redacted]% of tiotropium + formoterol patients reported an adverse event (Table 39). Nasopharyngitis was the most commonly reported adverse event. Exacerbations were not included in the adverse events in this study. Adverse events were reported in 55% of indacaterol + glycopyrronium, 61% of indacaterol, 61% of glycopyrronium, 57% of tiotropium, and 58% of placebo patients in SHINE and 93% indacaterol + glycopyrronium and tiotropium patients and 94% of glycopyrronium patients in SPARK (Table 40). COPD was the most common adverse event in both studies. In ILLUMINATE, 55% of indacaterol + glycopyrronium patients and 60% of fluticasone propionate + salmeterol patients reported an adverse event (Table 41). COPD was the most common adverse event, occurring in 17% of indacaterol + glycopyrronium patients and 24% of fluticasone propionate + salmeterol patients. In ENLIGHTEN, a study designed to assess safety and tolerability as its primary outcome, 58% of indacaterol + glycopyrronium patients and 57% of placebo patients reported an adverse event (Table 42). The most common adverse event was COPD. In BEACON, 26% of patients treated with the fixed-dose combination of indacaterol + glycopyrronium and 25% of patients treated with the separate combination of these two components experienced an adverse event (Table 43). In BLAZE, 35% of indacaterol + glycopyrronium patients, 36% of tiotropium patients, and 39% of placebo patients experienced an adverse event while taking these interventions. In BRIGHT, 38% of indacaterol + glycopyrronium patients, 28% of tiotropium patients, and 36% of placebo patients experienced an adverse event while taking these interventions (Table 44). In ARISE, 85% of indacaterol + glycopyrronium–treated patients and 72% of tiotropium-treated patients experienced an adverse event (Table 45).

Serious Adverse Events

In QUANTIFY, [redacted]% of indacaterol + glycopyrronium patients and [redacted]% of tiotropium + formoterol patients reported a serious adverse event (SAE; Table 39). The most common SAEs were pneumonia (zero patients in the indacaterol + glycopyrronium group and four patients in the tiotropium + formoterol group) and myocardial infarction (three indacaterol + glycopyrronium patients and one tiotropium + formoterol patient).

The proportion of patients with SAEs ranged from 4% to 6% in SHINE and from 22% to 24% in SPARK (Table 40). The most common SAE in each study was "COPD worsening," which occurred in 2% to 3% of patients in SHINE and 12% to 15% of patients in SPARK. In SHINE, two indacaterol + glycopyrronium patients, three tiotropium patients, and three placebo patients had pneumonia as an SAE. In ILLUMINATE, 5% of patients had at least one SAE in each of the indacaterol + glycopyrronium and fluticasone propionate + salmeterol groups (Table 41). The most common SAE was COPD (one patient in

indacaterol + glycopyrronium and three patients in fluticasone propionate + salmeterol). In ENLIGHTEN, 16% of patients treated with indacaterol + glycopyrronium and 11% of patients treated with placebo had an SAE (Table 42). The most common SAEs were COPD (5% with indacaterol + glycopyrronium and 4% with placebo) and pneumonia (4% with indacaterol + glycopyrronium and none with placebo). In BEACON, 4% of patients treated with indacaterol + glycopyrronium and 6% of patients treated with the individual components of indacaterol and glycopyrronium experienced an SAE (Table 43). In BLAZE, 3% of patients in each of the indacaterol + glycopyrronium and tiotropium groups had an SAE, and 2% of placebo patients. In BRIGHT, one patient in each of the indacaterol + glycopyrronium, tiotropium, and placebo groups had an SAE (Table 44). In ARISE, 16% of indacaterol + glycopyrronium–treated and 5% of tiotropium-treated patients had an SAE. The most common events were colon polyp and COPD (3% in indacaterol + glycopyrronium, and none with tiotropium; Table 45).

Withdrawals Due to Adverse Events

In QUANTIFY, [redacted]% of indacaterol + glycopyrronium patients and [redacted]% of tiotropium + formoterol patients withdrew due to an adverse event (AE; Table 39). The most common reason in either group was pneumonia ([redacted] with indacaterol + glycopyrronium and [redacted] with tiotropium + formoterol). In SHINE, 1% of patients treated with indacaterol + glycopyrronium, 2% of patients treated with tiotropium, and 4% of patients treated with placebo withdrew due to an AE (Table 40). In SPARK, 11% of indacaterol + glycopyrronium-treated patients and 9% of tiotropium-treated patients withdrew due to an AE (Table 40). In ILLUMINATE, 9% of indacaterol + glycopyrronium-treated and 10% of fluticasone propionate + salmeterol–treated patients withdrew due to an AE (Table 41). The most common reason was COPD (6% versus 8%, respectively). In ENLIGHTEN, 6% of patients in each of the indacaterol + glycopyrronium-treated and placebo-treated groups withdrew due to an AE (Table 42). The most common reason was COPD, in 2% of indacaterol + glycopyrronium and 1% placebo-treated patients. In BEACON, 1% of patients in each group withdrew due to an AE (Table 43). In BLAZE, 5% of indacaterol + glycopyrronium patients, 6% of tiotropium patients, and 4% of placebo patients withdrew due to an AE. In BRIGHT, no indacaterol + glycopyrronium patients, 6% of tiotropium patients, and 1% of placebo patients withdrew due to an AE (Table 44). In ARISE, 9% of indacaterol + glycopyrronium patients and no tiotropium patients withdrew due to an AE (Table 45).

Notable Harms

Pneumonia occurred in 2% or less of patients in most studies except SPARK, in which 5% of patients in each group — indacaterol + glycopyrronium, glycopyrronium, and tiotropium — reported pneumonia as an AE, and after 52 weeks in ENLIGHTEN, in which 4% of indacaterol + glycopyrronium and no placebo patients had pneumonia as an AE. In the open-label RCT ARISE, after 52 weeks, 8% of indacaterol + glycopyrronium patients and 3% of tiotropium patients had pneumonia as an AE. Dry mouth occurred in 1% or less of patients across studies. Cerebrovascular or cardiovascular (CCV) AEs occurred in 6% of indacaterol + glycopyrronium patients and 7% of glycopyrronium and tiotropium patients in SPARK. This study had the highest proportion of patients with CCV AEs among those reporting, and it also had the patients with the most severe COPD. There was no clear difference in the proportion of patients with CCV AEs between groups within studies, and the proportions of patients ranged between 1% and 3%.

Pharmacoeconomic Summary

The manufacturer is seeking reimbursement for Ultibro Breezhaler (indacaterol + glycopyrronium) for patients with COPD, including chronic bronchitis and emphysema, who remain symptomatic despite use of monotherapy with a LABA or LAMA. Indacaterol 110 mcg + glycopyrronium 50 mcg is available as a capsule for inhalation at a price of $2.68 per capsule ($2.68 per day).

The manufacturer submitted a cost minimization analysis[10] comparing indacaterol + glycopyrronium to individually dosed formoterol + tiotropium, the individual components indacaterol and glycopyrronium, and a fluticasone propionate + salmeterol fixed combination product in adult patients with COPD who remain symptomatic despite monotherapy with a LABA or LAMA. Comparable efficacy and safety was assumed between treatments based on head-to-head clinical trials. CADTH Common Drug Review calculations confirmed that indacaterol + glycopyrronium is less expensive than formoterol + tiotropium ($3.66 per day), indacaterol and glycopyrronium ($3.32 per day), and fluticasone propionate + salmeterol ($3.25 to $4.61 per day); as well, it is less expensive than all currently available LABA + LAMA combinations (range: $3.26 to $4.04 per day) and ICS + LABA combination products (range: $2.76 to $4.61 per day). Indacaterol + glycopyrronium is, however, more expensive than monotherapy with a LABA (range: $1.49 to $1.87 per day) or a LAMA ($1.77 to $2.17 per day).

Conclusions

Eight double-blind RCTs met the inclusion criteria for this review: two included an open-label tiotropium group, and one study each included tiotropium + formoterol, fluticasone propionate + salmeterol, and placebo. Of three other studies, two were crossover designs and one compared the Ultibro Breezhaler device with its components given in combination. One open-label RCT comparing indacaterol + glycopyrronium with tiotropium also met the inclusion criteria for the review.

When compared with tiotropium + formoterol, indacaterol + glycopyrronium did not statistically significantly reduce the risk of exacerbations or improve dyspnea scores. However, indacaterol + glycopyrronium was non-inferior with respect to health-related quality of life as measured by the SGRQ, and it did elicit a statistically significantly greater improvement in FEV_1 versus tiotropium + formoterol.

When compared with tiotropium monotherapy, indacaterol + glycopyrronium improved SGRQ-C total scores, symptom scores, and trough FEV_1, and these differences were statistically significant. However, indacaterol + glycopyrronium did not reduce the rate of exacerbations compared with tiotropium monotherapy.

When compared with fluticasone propionate + salmeterol, indacaterol + glycopyrronium improved FEV_1 and dyspnea scores, and these differences were statistically significant. However, it did not improve symptom scores or quality of life by SGRQ-C.

The most common AE with indacaterol + glycopyrronium was COPD, and COPD and pneumonia were the most common SAEs across studies.

TABLE 1: SUMMARY OF RESULTS: LAMA/LABA-CONTROLLED

	QUANTIFY	
	IG (N = 476)	TF (N = 458)
Moderate/Severe Exacerbations		
Patients (after 26 weeks), N (%)	62 (13)	70 (15)
RR (CI)	0.852 (0.622 to 1.169)	
P value	*P* = 0.323	
Mortality		
Deaths, N (%)	3 (1)	3 (1)
SGRQ-C total score		
Mean (SD) baseline[a]	44.70 (17.718)	45.68 (17.720)
Mean (SD) change, EOS (26 weeks)	–3.14 (12.059)	–2.19 (12.301)
LS MD (95% CI)	–0.69 (–2.31 to 0.92)	
P value	*P* = 0.399	
Mean (SD) baseline, PP	44.84 (17.93)	44.59 (17.37)
Mean (SD) change, EOS	–3.89 (11.84)	–2.55 (12.14)
LS MD (95% CI)	–0.77 (–2.48 to 0.93)	
P value	*P* = 0.373	
Dyspnea: BDI/TDI		
Mean (SD) baseline	6.53 (2.00)	6.37 (2.08)
LS Mean change, EOS (26 weeks)	1.13	0.75
LS MD (95% CI)	0.38 (–0.06 to 0.82)	
P value	*P* = 0.087	
FEV_1, pre-dose, L		
Mean (SD) baseline	1.33 (0.48)	1.31 (0.45)
LS Mean change, EOS (26 weeks)	0.17	0.10
LS MD (95% CI)	0.07 (0.04 to 0.10)	
P value	*P* < 0.001	
AEs		
Patients with > 0, N (%)	208 (44)	195 (43)
Serious adverse events		
Patients with > 0, N (%)	30 (6)	24 (5)
WDAEs		
WDAEs, N (%)	[redacted]	[redacted]
Notable AEs		
Pneumonia	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

AE = adverse event; ANCOVA = analysis of covariance; BDI = Baseline Dyspnea Index; CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; LS = least squares; MD = mean difference; RR = relative risk; SD = standard deviation; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TDI = Transition Dyspnea Index; TF = tiotropium + formoterol; WDAE = withdrawals due to adverse events.

[a] The primary outcome of QUANTIFY was the non-inferiority of indacaterol + glycopyrronium versus tiotropium + formoterol for change in SGRQ-C total score. The criterion for non-inferiority was that the upper boundary of the confidence interval was lower than the predefined margin for non-inferiority of 4 points.

Note: ANCOVA model: Variable = baseline, centre, treatment.

Source: Clinical study report for QUANTIFY.[11]

TABLE 2: SUMMARY OF RESULTS: VERSUS LAMA (TIOTROPIUM)

	SHINE (EOS = 26 Weeks)				SPARK (EOS = 64 to 76 Weeks)			
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232	IG N = 729	G N = 739	TIO N = 737
Moderate/Severe Exacerbations								
Patients with ≥ 1, N (%)	85 (18)	103 (22)	89 (19)	85 (18)	60 (26)	202 (28)	192 (26)	186 (25)
Exacerbation rate per year	NR	NR	NR	NR	NR	0.94	1.07	1.06
Model-based rate estimate (95% CI)	NR	NR	NR	NR	NR	0.84 (0.75 to 0.94)	0.95 (0.85 to 1.06)	0.93 (0.83 to 1.04)
Ratio of rates (95% CI), IG versus	–	–	–	–	–	–	0.88 (0.77 to 0.99)	0.90 (0.79 to 1.02)
HR, time to first event, versus PLA (95% CI)	–	–	–	–	0.56 (0.40 to 0.78)	–	–	–
P value	–	–	–	–	*P* < 0.001	–	*P* = 0.038	*P* = 0.096
Mortality								
Deaths, N (%)	1 (< 1)	2 (< 1)	1 (< 1)	3 (1)	0	23 (3)	22 (3)	25 (3)
SGRQ-C total score								
Mean (SE) baseline	46.8 (0.9)	46.8 (0.8)	47.8 (0.9)	46.5 (0.9)	46.1 (1.2)	52.1	50.5	51.3
LS Mean (SE) at EOS	37.0 (0.68)	38.1 (0.68)	38.2 (0.69)	39.1 (0.68)	40.0 (0.94)	43.4 (0.78) N = 600	45.5 (0.78) N = 564	46.1 (0.78) N = 579
LS MD (95% CI) EOS, IG versus		–1.09 (–2.68 to 0.50)	–1.18 (–2.78 to 0.42)	–2.13 (–3.72 to –0.54)	–3.01 (–5.05 to –0.97)		–2.07 (–3.57 to –0.58)	–2.69 (–4.17 to –1.21)
P value		*P* = 0.179	*P* = 0.149	*P* = 0.009	*P* = 0.002		*P* = 0.007	*P* < 0.001
Symptom scores, 24 hours								
Mean baseline (SE)	6.94 (0.14)	6.78 (0.14)	6.89 (0.13)	6.83 (0.14)	6.76 (0.20)	7.31 N = 708	7.07 N = 724	7.24 N = 709
LS Mean (SE) over treatment period	–1.65 (0.09)	–1.53 (0.09)	–1.39 (0.09)	–1.42 (0.09)	–0.98 (0.13)	–1.67 (0.09)	–1.30 (0.09)	–1.23 (0.09)
LS MD (95% CI) at EOS, IG versus		–0.13 (–0.36 to 0.10)	–0.26 (–0.49 to –0.03)	–0.24 (–0.46 to –0.01)	–0.67 (–0.96 to –0.39)		–0.37 (–0.55 to –0.19)	–0.44 (–0.62 to –0.26)
P value		*P* = 0.272	*P* = 0.025	*P* = 0.043	*P* < 0.001		*P* < 0.001	*P* < 0.001
Hospital admissions								
Patients, n (%)	NE	NE	NE	NE	NE	106 (15)	110 (15)	84 (11)

	SHINE (EOS = 26 Weeks)				SPARK (EOS = 64 to 76 Weeks)			
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232	IG N = 729	G N = 739	TIO N = 737
Mean (SD)	NE	NE	NE	NE	NE	1.4 (0.69)	1.4 (0.69)	1.4 (0.83)
Emergency visits								
Patients, n (%)	NE	NE	NE	NE	NE	34 (5)	37 (5)	31 (4)
Mean (SD)	NE	NE	NE	NE	NE	1.3 (0.57)	1.5 (0.99)	1.5 (1.31)
Doctor visits (unscheduled)								
Patients with 0, n (%)	NE	NE	NE	NE	NE	553 (76)	544 (74)	554 (75)
Trough FEV_1, L								
Mean (SE) baseline	1.28 (0.02)	1.29 (0.02)	1.28 (0.02)	1.27 (0.02)	1.29 (0.04)	0.90	0.90	0.91
LS Mean (SE) Week 26	1.45 (0.01)	1.38 (0.01)	1.36 (0.01)	1.37 (0.01)	1.25 (0.02)	1.08 (0.01)	0.99 (0.01)	1.00 (0.01)
LS MD (95% CI), IG versus		0.07 (0.05 to 0.10)	0.09 (0.06 to 0.11)	0.08 (0.05 to 0.10)	0.21 (0.17 to 0.24)		0.08 (0.07 to 0.10)	0.07 (0.06 to 0.09)
		P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001		*P* < 0.001	*P* < 0.001
Adverse events								
Patients, N (%)	261 (55)	291 (61)	290 (61)	275 (57)	134 (58)	678 (93)	694 (94)	686 (93)
Serious adverse events								
Patients, N (%)	22 (5)	26 (6)	29 (6)	19 (4)	13 (6)	167 (23)	179 (24)	165 (22)
WDAEs								
WDAEs, N (%)	6 (1)	24 (5)	14 (3)	10 (2)	10 (4)	79 (11)	86 (12)	67 (9)
Notable adverse events								
Pneumonia	4 (1)	3 (1)	4 (1)	6 (1)	3 (1)	33 (5)	36 (5)	34 (5)
Dry mouth	4 (1)	2 (< 1)	4 (1)	5 (1)	1 (< 1)	NR	NR	NR
Any CCV event	7 (2)	12 (3)	14 (3)	9 (2)	6 (3)	44 (6)	50 (7)	50 (7)

CCV = cerebrovascular or cardiovascular; CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; G = glycopyrronium; HR = hazard ratio; I = indacaterol; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; LS = least square; MD = mean difference; NE = not evaluated; PLA = placebo; SD = standard deviation; SE = standard error; TIO = tiotropium; WDAE = withdrawals due to adverse event.

Note: FEV_1: Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + centre (region) + error. Centre was included as a random effect nested within region.

Source: Clinical study report (CSR) SPARK[12]; CSR SHINE.[13]

TABLE 3: SUMMARY OF RESULTS: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG (N = 258)	FP/S (N = 264)
Moderate/Severe Exacerbations		
Patients with ≥ 1, N (%)	NE	NE
Exacerbation rate/year	NE	NE
Mortality		
Deaths, N (%)	0	1 (< 1)
SGRQ-C total score		
Mean (SD) baseline	42.01	42.72
LS Mean (SE) at 26 weeks	35.45 (1.44)	36.68 (1.39)
LS MD (95% CI)	–1.24 (–3.33 to 0.85)	
P value	*P* = 0.245	
Symptom scores, 24 hour		
Mean baseline	6.43	6.24
LS Mean (SE) over treatment period	–1.28 (0.14)	–1.24 (0.14)
LS MD (95% CI) at EOS (26 weeks)	–0.05 (–0.29 to 0.20)	
P value	*P* = 0.715	
Dyspnea, TDI focal score		
Mean (SE) baseline	6.80	6.65
LS Mean (SE) Week 26	2.36 (0.39)	1.60 (0.38)
LS MD (95% CI)	0.76 (0.26 to 1.26)	
P value	*P* = 0.003	
FEV_1 AUC 0 hours to 12 hours, L		
Mean (SE) baseline	1.45	1.40
LS Mean (SE) Week 26	1.69 (0.03)	1.56 (0.03)
LS MD (95% CI)	0.14 (0.10 to 0.18)	
P value	*P* < 0.001	
Adverse events		
Patients, N (%)	143 (55)	159 (60)
Serious adverse events		
Patients, N (%)	13 (5)	14 (5)
WDAEs		
WDAEs, N (%)	22 (9)	27 (10)
Notable adverse events		
Pneumonia	0	4 (2)
Hypertension	6 (2)	4 (2)
Dry mouth	NR	NR
CCV serious adverse event	3 (1)	3 (1)

AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EOS = end of study; FEV_1 = forced expiratory volume in one second; FP/S = fluticasone propionate + salmeterol; IG = indacaterol + glycopyrronium; ICS = inhaled corticosteroid; LABA = long-acting beta-2 adrenergic agonist; LS = least squares; MD = mean difference; NE = not evaluated; NR = not reported; SD = standard deviation; SE = standard error; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TDI = Transition Dyspnea Index; WDAE = withdrawals due to adverse event.
Note: MIXED model: FEV_1 AUC (0 hours to 12 hours) = treatment + baseline FEV_1 + baseline ICS + FEV_1 reversibility components + smoking status + region + centre (region). Centre is included as a random effect nested within region.
Baseline is defined as the average of the –45 minute and –15 minute FEV_1 values taken on Day 1 prior to first dose.
LOCF (last observation carried forward): If the AUC (0 hours to 12 hours) is missing at Week 26, then the non-missing AUC (0 hours to 12 hours) at Week 12 was carried forward for the analysis.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 4: SUMMARY OF RESULTS: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG (N = 225)	**PLA (N = 113)**
Moderate/Severe Exacerbation		
Patients, n (%)	57 (25)	25 (22)
Time to first exacerbation, HR (95% CI)	1.04 (0.64 to 1.70) *P* = 0.878	
Mortality		
Deaths, N (%)	4 (2)	1 (1)
Symptom scores, total (daily diary)		
Mean baseline	7.48	7.41
LS mean (SE) over 52 weeks	–2.34 (0.21)	–1.77 (0.24)
LS MD (95% CI)	–0.57 (–1.01 to –0.13)	
P value	*P* = 0.011	
FEV_1, Pre-dose, L		
Mean baseline	1.43	1.49
Treatment LS mean (SE) Week 52	1.61 (0.02)	1.42 (0.03)
LS MD (95% CI)	0.189 (0.126 to 0.252)	
P value	*P* < 0.001	
Adverse events		
Patients, N (%)	130 (58)	64 (57)
Serious adverse events		
Patients, N (%)	37 (16)	12 (11)
WDAEs		
WDAEs, N (%)	13 (6)	7 (6)
Notable adverse events		
Pneumonia	8 (4)	0
Non-fatal stroke	1 (< 1)	0
Heart failure requiring hospitalization	1 (< 1)	0
Dry mouth	0	1 (1)
Urinary retention	3 (1)	0
Glaucoma	1 (< 1)	0

CI = confidence interval; FEV_1 = forced expiratory volume in one second; HR = hazard ratio; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; PLA = placebo; SE = standard error; WDAE = withdrawals due to adverse event.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 5: SUMMARY OF RESULTS: COMPONENT-CONTROLLED

	BEACON	
	IG N = 90	I and G (Individual Components) N = 103
Moderate/Severe Exacerbation		
Patients, n (%)	NR	NR
Time to first exacerbation, HR (95% CI)	NR	
Mortality		
Deaths, N (%)	0	0
Symptom scores, total (daily diary)		
Mean (SE) baseline	5.25 (0.28)	5.74 (0.30)
LS Mean (SE) over 4 weeks	–0.42 (0.14)	–0.49 (0.13)
LS MD (95% CI)	0.07 (–0.24 to 0.39)	
P value	NR	
Trough FEV_1, L		
Mean (SE) baseline, PPS[a]	1.46 (0.06), N = 81	1.43 (0.05), N = 96
Treatment LS mean (SE) Week 4	1.46 (0.02)	1.47 (0.02)
LS MD (95% CI), PPS	–0.005 (–0.051 to 0.040)	
LS MD (95% CI), FAS	–0.024 (–0.073 to 0.026)	
Adverse events		
Patients, N (%)	23 (26)	26 (25)
Serious adverse events		
Patients, N (%)	4 (4)	6 (6)
WDAE		
WDAEs, N (%)	1 (1)	1 (1)
Notable adverse events		
Pneumonia	2 (2)	0
Dry mouth	NR	NR
CCV adverse event	0	1 (1)

CCV = cerebrovascular and cardiovascular; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; G = glycopyrronium; HR = hazard ratio; I = indacaterol; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; NR = not reported; PPS = per-protocol set; SE = standard error; WDAE = withdrawals due to adverse event.

[a] Per-protocol set used for non-inferiority analysis. Non-inferiority of indacaterol 110 mcg + glycopyrronium 50 mcg daily to the concurrent administration of indacaterol 150 mcg daily plus glycopyrronium 50 mcg daily is demonstrated if the two-sided 95% confidence interval lies entirely to the right of (higher than) –0.1 L.

Source: Clinical study report for BEACON.[16]

TABLE 6: SUMMARY OF RESULTS: CROSSOVER

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
Mortality						
Deaths, N (%)	1 (< 1)	0	0	0	0	0
Symptom scores, 24 hour						
Mean baseline	5.57 (0.20)	5.72 (0.19)	5.48 (0.19)	NE	NE	NE
LS Mean (SE), treatment period	–0.61 (0.10)	–0.58 (0.09)	0.11 (0.10)	NE	NE	NE
LS MD (95% CI) at EOS, IG versus		–0.03 (–0.26 to 0.19)	–0.72 (–0.94 to –0.49)			
P value		*P* = 0.759	*P* < 0.001			
Dyspnea, TDI focal score						
Mean (SE) baseline	7.34 (0.14)	7.31 (0.15)	7.33 (0.15)	NE	NE	NE
LS Mean (SE) Week 6	0.88 (0.18)	0.39 (0.18)	–0.49 (0.18)	NE	NE	NE
LS MD (95% CI), IG versus		0.49 (0.07 to 0.91)	1.37 (0.95 to 1.79)			
P value		*P* = 0.021	*P* < 0.001			
FEV_1 AUC (5 minutes to 4 hours)						
Mean (SE) baseline	1.330 (0.032)	1.339 (0.032)	1.353 (0.033)	NE	NE	NE
LS Mean (SE) Week 6	1.636 (0.012)	1.529 (0.012)	1.302 (0.012)	NE	NE	NE
LS MD (95% CI), IG versus		0.106 (0.079 to 0.133)	0.333 (0.306 to 0.360)			
P value		*P* < 0.001	*P* < 0.001			
Exercise endurance, seconds						
Mean (SE) baseline	NR	NR	NR	435.1 (23.4)	438.5 (24.1)	438.8 (24.1)
LS Mean (SE) Week 3	NR	NR	NR	507.8 (19.3)	514.6 (19.0)	448.3 (19.5)
LS MD (95% CI), IG versus					–6.7 (–47.5 to 34.0)	59.5 (17.7 to 101.3)
P value					*P* = 0.744	*P* = 0.006
IC, Pre-exercise, L						
Mean (SE) baseline	NE	NE	NE	2.01 (0.07)	2.07 (0.07)	2.08 (0.07)
LS Mean (SE) Week 3	NE	NE	NE	2.34 (0.03)	2.19 (0.03)	2.01 (0.03)
LS MD (95% CI), IG versus					0.15	0.34

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
					(0.07 to 0.23)	(0.25 to 0.42)
P value					*P* < 0.001	*P* < 0.001
FEV_1, trough, L						
Mean (SE) baseline	NE	NE	NE	1.35 (0.06)	1.38 (0.06)	1.34 (0.05)
LS Mean (SE) Week 3	NE	NE	NE	1.53 (0.02)	1.43 (0.02)	1.33 (0.02)
LS MD (95% CI), IG versus					0.10 (0.05 to 0.15)	0.20 (0.15 to 0.26)
P value					*P* < 0.001	*P* < 0.001
Dyspnea, Borg CR10 at peak						
Mean (SE) baseline	NE	NE	NE	6.95 (0.28)	7.18 (0.28)	7.29 (0.32)
LS Mean (SE) Week 3	NE	NE	NE	7.01 (0.27)	6.84 (0.26)	7.05 (0.27)
LS MD (95% CI), IG versus					0.17 (–0.36 to 0.71)	–0.04 (–0.59 to 0.51)
P value					*P* = 0.523	*P* = 0.893
Adverse events						
Patients, N (%)	78 (35)	78 (36)	86 (39)	29 (38)	23 (28)	28 (36)
Serious adverse events						
Patients, N (%)	6 (3)	6 (3)	5 (2)	1 (1)	1 (1)	1 (1)
WDAE						
WDAEs, N (%)	11 (5)	12 (6)	9 (4)	0	5 (6)	1 (1)
Notable adverse events						
Pneumonia	–	–	–	0	1 (1)	1 (1)
Hypertension	3 (1)	3 (1)	4 (2)	1 (1)	0	0
Dry mouth	1 (< 1)	0	2 (1)	0	1 (1)	0
Myocardial infarction	–	–	–	0	1 (1)	0

AUC = area under the curve; CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; IC = inspiratory capacity; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; NE = not evaluated; PLA = placebo; SE = standard error; TDI = Transition Dyspnea Index; TIO = tiotropium; WDAE = withdrawals due to adverse event.
Source: Clinical study report (CSR) BLAZE[17]; CSR BRIGHT.[18]

TABLE 7: SUMMARY OF RESULTS: OPEN LABEL

	ARISE	
Moderate/Severe Exacerbations	**IG N = 119**	**TIO N = 39**
Patients with ≥ 1, N (%)	26 (22)	8 (21)
Mean (SD) number	0.4 (0.9)	0.4 (1.1)
Number per year	0.39	0.45
P value	NR	
Mortality		
Deaths, N (%)	1	0
SGRQ-C total		
Mean (SD) baseline	29.5 (14.9) N = 106	34.0 (17.9) N = 38
Mean (SD) change from baseline to Week 52	–2.9 (11.0)	–0.6 (9.9)
P value	NR	
Symptom scores, 24 hours		
Mean baseline	NE	NE
LS Mean (SE) over treatment period (52 weeks)	NE	NE
Inspiratory capacity, L		
Mean (SD) baseline	1.948 (0.514)	1.938 (0.448)
Mean (SD) change at Week 52	0.093 (0.340)	0.081 (0.482)
P value	NR	
FEV_1, pre-dose, L		
Mean (SD) baseline	1.316 (0.469)	1.385 (1.437)
Mean (SD) change, Week 52	0.189 (0.176)	0.052 (0.169)
P value	NR	
Adverse events		
Patients, N (%)	101 (85)	28 (72)
Serious adverse events		
Patients, N (%)	19 (16)	2 (5)
WDAEs		
WDAEs, N (%)	11 (9)	0
Notable adverse events		
Pneumonia	9 (8)	1 (3)
Upper respiratory tract infection	9 (8)	6 (15)

CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; NE = not evaluated; NR = not reported; SD = standard deviation; SE = standard error; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TIO = tiotropium; WDAE = withdrawals due to adverse event.
Source: Clinical study report for ARISE.[19]

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.[1,2] 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.[2] COPD is largely caused by smoking and is associated with multiple comorbid conditions (i.e., diabetes, ischemic heart disease, muscle wasting, bone loss, anemia, cancer, anxiety, and depression).[2]

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.[3] Among COPD patients in Canada aged 35 to 79 years, 7% had stage II (moderate) or higher COPD.[22] 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), which is the amount of air that one can expel in one second, and forced vital capacity (FVC), which is 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 < 0.7 indicates airway obstruction. The Canadian Thoracic Society classification of COPD severity is summarized in Table 8.

TABLE 8: CANADIAN THORACIC SOCIETY CLASSIFICATION OF COPD 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	N/A

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; N/A = not available.
Source: O'Donnell et al., 2007.[1]

COPD is associated with an increased risk of mortality and was ranked the fourth leading cause of death in Canada in 2004.[1] 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 (e.g., of all COPD patients hospitalized in 2006–2007, 18% of COPD patients were readmitted once and 14% were readmitted

twice).[23] Length of stay for hospital admissions for COPD exacerbations averaged 10 days at a cost of $10,000 per stay. The total cost of COPD hospitalizations in Canada is estimated at $1.5 billion per year.[24]

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.[1] Management decisions are guided by disease severity (i.e., symptoms/disability and spirometry measurements) 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.[2] 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[2] and include short-acting beta-2 adrenergic agonists (SABAs), such as salbutamol, and short-acting antimuscarinic agents (SAMAs), such as ipratropium. Long-acting beta-2 adrenergic agonists (LABAs), such as salmeterol, formoterol, and indacaterol, long-acting antimuscarinic agents (LAMA), such as tiotropium and glycopyrronium, as well as combinations of fixed-dose LABAs and inhaled corticosteroids (ICS), such as fluticasone + salmeterol or budesonide + formoterol, are the most commonly used treatments for COPD in Canada. Antimuscarinic and beta agonist drugs are often used in combination for maximal improvement in dyspnea and function. Inhaled steroids may not be useful for mild disease; however, they may have a greater role in the management of moderate to severe COPD, or in patients with persistent symptoms.[4-6] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, in which ICS use may be beneficial.[7-9]

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 with the use of 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.[2]

1.3 Drug

Indacaterol is a LABA, and glycopyrronium is a LAMA, also referred to as a long-acting anticholinergic (LAAC) drug. Stimulation of beta-2 receptors has a bronchodilatory effect on the lungs, as does blockade of muscarinic M3 receptors; thus, the combination of these two drugs exerts a dual bronchodilatory effect. The drugs are administered via inhalation, using the Breezhaler dry powder inhalation device. The recommended dose is indacaterol 110 mcg + glycopyrronium 50 mcg once daily.

Indication under review
For the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema
Listing criteria requested by sponsor
For the once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD (including chronic bronchitis and emphysema) who remain symptomatic despite use of monotherapy with a LABA or LAAC

TABLE 9: KEY CHARACTERISTICS OF OTHER LABA/LAMA COMBINATIONS

	Tiotropium + Formoterol	Umeclidinium + Vilanterol
Mechanism of Action	Tiotropium blocks muscarinic M3 receptors. M3 receptors in lungs mediate bronchoconstriction, so blockade of these receptors leads to bronchodilation Formoterol stimulates beta-2 receptors in the lungs. Beta-2 receptors mediate bronchodilation; stimulation of these receptors also leads to bronchodilation	Umeclidinium blocks muscarinic M3 receptors. M3 receptors in lungs mediate bronchoconstriction, so blockade of these receptors leads to bronchodilation Vilanterol stimulates beta-2 receptors in the lungs. Beta-2 receptors mediate bronchodilation; stimulation of these receptors leads to bronchodilation
Indication[a]	COPD	COPD
Route of administration	Inhalation HandiHaler device for tiotropium	Inhalation Fixed combination, Ellipta device
Recommended dose	Tiotropium 18 mcg once daily Formoterol fumarate 12 mcg to 24 mcg twice daily Formoterol fumarate dihydrate 6 mcg to 12 mcg twice daily	Umeclidinium 62.5 mcg + vilanterol 25 mcg once daily
Serious side effects/safety issues	Anticholinergic adverse effects (dry mouth, urinary retention, aggravation of glaucoma, etc.)	Anticholinergic adverse effects (dry mouth, urinary retention, aggravation of glaucoma, etc.)
Other	Dry powder inhaler	Dry powder inhaler

COPD = chronic obstructive pulmonary disease; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of indacaterol maleate and glycopyrronium bromide (Ultibro Breezhaler) for the treatment of patients with COPD, including chronic bronchitis and/or emphysema.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 10.

TABLE 10: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients diagnosed with COPD, including chronic bronchitis and/or emphysema **Subgroups:** Age, sex, BMI, COPD severity, chronic bronchitis, emphysema, smoking status, bronchodilator reversibility, concomitant COPD medication use, indicators of asthma
Intervention	Indacaterol maleate 110 mcg and glycopyrronium bromide 50 mcg once daily, alone or in combination with conventional therapies
Comparators	The following comparators used alone or in combination (as appropriate): LABA (e.g., salmeterol, formoterol, indacaterol, vilanterol) SABA (e.g., salbutamol) LAMA (e.g., tiotropium, glycopyrronium, aclidinium) SAMA (e.g., ipratropium) ICS (e.g., fluticasone propionate, fluticasone furoate, budesonide) Roflumilast Theophylline Placebo
Outcomes	**Key efficacy outcomes:** • Mortality (all-cause) • Mortality due to COPD • Health care resource utilization (e.g., hospitalization, emergency room visits) • Exacerbations, and time to first exacerbation • Quality of life • Spirometry measurements (e.g., FEV_1, expiratory capacity) • Symptoms (including dyspnea) • Exercise tolerance **Other efficacy outcomes:** • Use of rescue medication, patient adherence and satisfaction, days of missed work or school **Harms outcomes:** • SAEs • WDAEs • AEs • AEs of interest: cardiovascular-related, pneumonia, anticholinergic
Study Design	Published and unpublished RCTs

AE = adverse events; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; RCT = randomized controlled trial; SABA = short-acting beta-2 adrenergic agonist; SAE = serious adverse events; SAMA = short-acting antimuscarinic agent; WDAE = withdrawals due to adverse event.

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 & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were glycopyrronium and indacaterol, or Ultibro Breezhaler.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 4, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 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 Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessments, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases, and an Internet search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

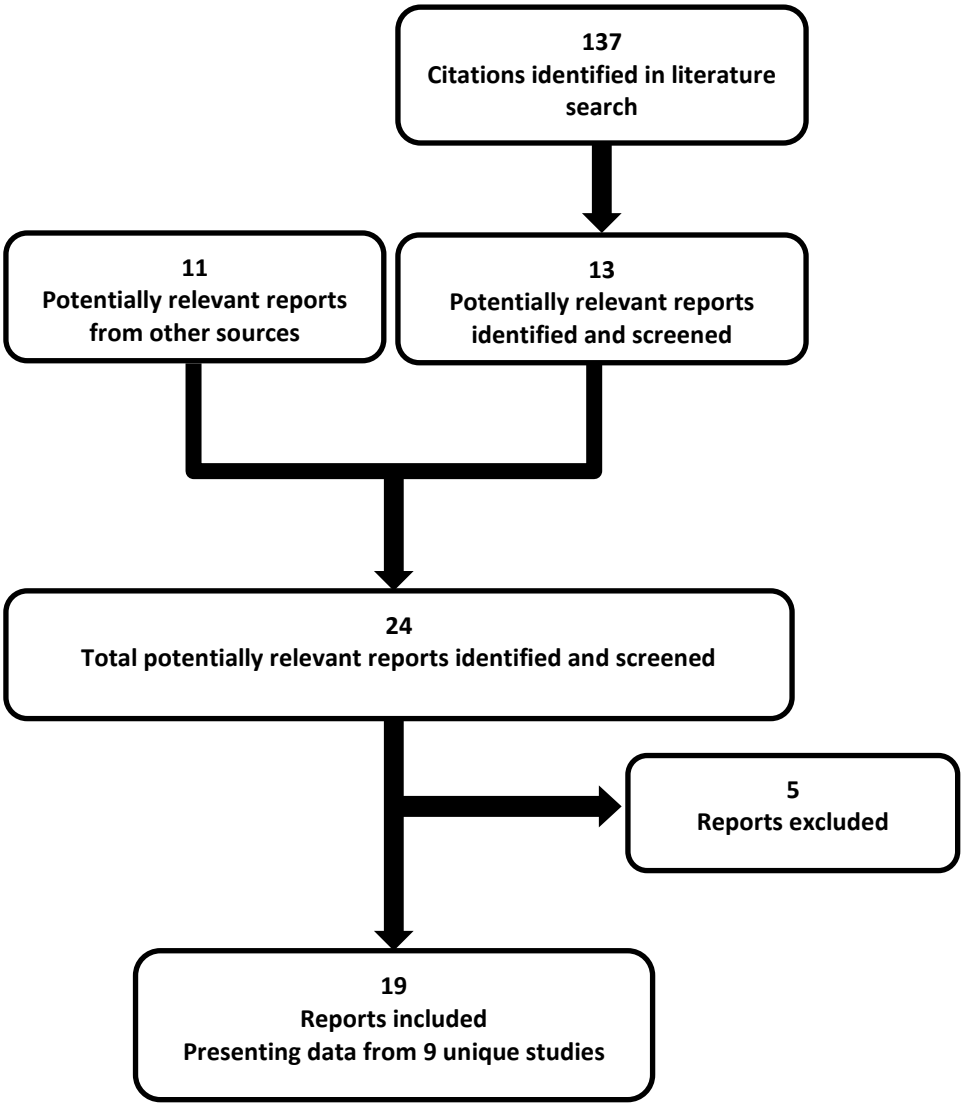
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 12; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of nine studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized beginning in Table 11 and described 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



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 11: DETAILS OF INCLUDED STUDIES: LAMA/LABA-CONTROLLED

		QUANTIFY
DESIGNS AND POPULATIONS	**Study design**	DB RCT
	Locations	164 centres: Germany
	Study period	May 4, 2012, to April 2, 2013
	Randomized (N)	N = 934
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) Current or former smokers, ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 30% to < 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70
	Exclusion criteria	Long QT Significant ECG abnormality COPD exacerbation that required treatment with antibiotics, SCS, or hospitalization in the 6 weeks prior to pre-screening Patients who developed a COPD exacerbation between the pre-screening and randomization visits (Visits 1 and 3) were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation Any history of asthma/COPD indicated by or onset of symptoms prior to 40 years
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Ultibro Breezhaler)
	comparator(s)	Tiotropium 18 mcg once daily + formoterol 12 mcg twice daily
DURATION	**Phase**	
	Run-in	2 weeks
	Double-blind	26 weeks
	Follow-up	NR
OUTCOMES	**Primary end point**	SGRQ-C at end of therapy (non-inferiority)
	Other end points	SGRQ-C at end of therapy (superiority) Dyspnea by BDI/TDI Moderate exacerbations requiring SCS and/or antibiotics Severe exacerbations requiring hospitalization Time to first moderate/severe exacerbation Trough FEV_1 FEV_1 30 minutes after morning dose Symptoms scores from SGRQ-C
NOTES	**Publications**	None

BDI = Baseline Dyspnea Index; COPD = chronic obstructive pulmonary disease; DB = double-blind; ECG = electrocardiogram; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; NR = not reported; PN = predicted normal; RCT = randomized controlled trial; SCS = systemic corticosteroids; SGRQ = St. George's Respiratory Questionnaire-COPD; TDI = Transition Dyspnea Index.
Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).
Source: Clinical study report for QUANTIFY.[11]

TABLE 12: DETAILS OF INCLUDED STUDIES: LAMA-CONTROLLED (TIOTROPIUM)

		SHINE	SPARK
DESIGNS & POPULATIONS	**Study design**	DB/OL RCT	DB/OL RCT
	Locations	301 centres: EU, Canada, Asia, South Africa	362 centres: Canada, EU, Asia, N/S America, South Africa
	Study period	September 21, 2010, to February 10, 2012	April 27, 2010, to July 11, 2012
	Randomized (N)	2,135	2,224
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 30% to < 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70	≥ 40 years of age Severe to very severe COPD (GOLD III or IV) Current or former smokers with ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 < 50% PN Post-bronchodilator FEV./FVC ratio < 0.70 At least one exacerbation in previous 12 months requiring SCS or antibiotics or both
	Exclusion criteria	COPD exacerbation that required SCS, antibiotics, or hospitalization in the 6 weeks before pre-screening or during screening	COPD exacerbation that required SCS, antibiotics, or hospitalization in the 6 weeks before pre-screening or during screening
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Breezhaler)	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Breezhaler)
	Comparator(s)	Indacaterol 150 mcg once daily Glycopyrronium 50 mcg once daily Tiotropium 18 mcg once daily Placebo once daily	Glycopyrronium 50 mcg once daily Tiotropium 18 mcg once daily (OL)
DURATION	**Phase**		
	Run-in	2 weeks	2 weeks
	Double-blind	26 weeks	64 to 76 weeks
	Follow-up	30 days	30 days
OUTCOMES	**Primary end point**	FEV_1 at 26 weeks (superiority versus indacaterol and glycopyrronium)	Rate of moderate to severe exacerbations during treatment period (superiority versus glycopyrronium)
	Other end points	TDI (breathlessness) SGRQ Use of rescue therapy Trough FEV_1 Symptoms (diary) COPD exacerbations	Rate of moderate to severe exacerbations during treatment period (superiority versus tiotropium) Time to first moderate/severe exacerbation Exacerbations requiring SCS, antibiotics, and hospitalizations Rate of mild exacerbations Time to study withdrawal Total exacerbation days Time to multiple exacerbations FEV_1, FVC Use of rescue therapy SGRQ-C scores Safety/tolerability

		SHINE	SPARK
NOTES	**Publications**	Bateman 2013[27]	Wedzicha 2013[28]

DB = double-blind; COPD = chronic obstructive pulmonary disease; EU = European Union; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAMA = long-acting antimuscarinic agent; N = North; OL = open label; PN = predicted normal; RCT = randomized controlled trial; S = South; SCS = systemic corticosteroids; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.
Source: Clinical study reports for SHINE,[13] SPARK.[12]
Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).

TABLE 13: DETAILS OF INCLUDED STUDIES: ICS/LABA-CONTROLLED

		ILLUMINATE
DESIGNS & POPULATIONS	**Study design**	DB RCT
	Locations	93 centres
	Study period	March 25, 2011, to March 12, 2012
	Randomized (N)	523
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) Current or former smokers, ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility between 40% and 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70
	Exclusion criteria	COPD exacerbation needing treatment with antibiotics, SCS, or hospitalization in the year leading up to and including randomization
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Breezhaler)
	Comparator(s)	Fluticasone propionate 500 mcg + salmeterol 50 mcg twice daily (Accuhaler)
DURATION	**Phase**	
	Run-in	2 weeks (ipratropium/salbutamol)
	Double-blind	26 weeks
	Follow-up	30 days
OUTCOMES	**Primary end point**	FEV_1 AUC 0 hours to 12 hours
	Other end points	Pre-dose trough FEV_1 Peak FEV_1 FVC AUC 0 hours to 12 hours Peak FVC Pre-dose trough FVC Serial spirometry Transition Dyspnea Index focal scores, SGRQ-C total scores Rescue medication use Daily patient-reported clinical symptoms
NOTES	**Publications**	Vogelmeier 2013[29]

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting beta-2 adrenergic agonist; PN = predicted normal; RCT = randomized controlled trial; SCS = systemic corticosteroids; SGRQ-C = St. George's Respiratory Questionnaire-COPD.
Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).
Source: Clinical study report for ILLUMINATE.[14]

TABLE 14: DETAILS OF INCLUDED STUDIES: COMPONENT-CONTROLLED

		BEACON
DESIGNS & POPULATIONS	**Study design**	DB RCT
	Locations	26 centres: Europe
	Study period	May 15, 2012, to December 19, 2012
	Randomized (N)	193
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) Current or former smokers, ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 30% to < 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70
	Exclusion criteria	COPD exacerbation that required SCS, antibiotics, or hospitalization in the 6 weeks prior to Visit 1
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Breezhaler)
	Comparator(s)	Indacaterol 150 mcg once daily + glycopyrronium 50 mcg once daily (as separate inhalers)
DURATION	**Phase**	
	Run-in	2 weeks
	Double-blind	4 weeks
	Follow-up	30 days
OUTCOMES	**Primary end point**	Trough FEV_1 (non-inferiority)
	Other end points	FEV_1 AUC 5 minutes to 4 hours at Day 1 FEV_1 AUC 5 minutes to 4 hours at Day 28 Peak FEV_1 on Days 1 and 28 post dose Time course of FEV_1 (pre dose to 4 hours post dose) on Day 28 Use of rescue medication over 28 days of blinded treatment Symptoms reported over 28 days of blinded treatment using eDiary
NOTES	**Publications**	Dahl 2013[30] Dahl 2014[31]

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; OL = open label; PN = predicted normal; SCS = systemic corticosteroids.
Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).
Source: Clinical study report for BEACON.[16]

TABLE 15: DETAILS OF INCLUDED STUDIES: PLACEBO-CONTROLLED

		ENLIGHTEN
DESIGNS & POPULATIONS	**Study design**	DB RCT
	Locations	European Union, Canada, Asia, South Africa
	Study period	April 22, 2010, to December 14, 2011
	Randomized (N)	339
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 30% to < 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70
	Exclusion criteria	COPD exacerbations requiring treatment with SCS, antibiotics, or hospitalization within the 6 weeks prior to screening or between screening and randomization History of asthma Abnormal ECG
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Breezhaler)
	Comparator(s)	Placebo once daily
DURATION	**Phase**	
	Run-in	2 weeks
	Double-blind	52 weeks
	Follow-up	30 days
OUTCOMES	**Primary end point**	Safety and tolerability
	Other end points	FEV_1 and FVC
NOTES	**Publications**	Dahl 2013[32]

COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; OL = open label; PN = predicted normal; RCT = randomized controlled trial; SCS = systemic corticosteroids.
Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 16: DETAILS OF INCLUDED STUDIES: CROSSOVER STUDIES

		BLAZE	BRIGHT
DESIGNS & POPULATIONS	**Study design**	DB RCT (crossover)	DB RCT (crossover)
	Locations	43 centres: Canada, Europe	14 centres: Europe
	Study period	October 26, 2011, to August 29, 2012	March 16, 2011, to November 30, 2011
	Randomized (N)	247	85
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) Current or former smokers, ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 30% to < 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70	≥ 40 years of age Moderate to severe COPD (GOLD II or III) Current or former smokers, ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 40% to < 70% PN Post-bronchodilator FEV_1:FVC ratio < 0.70
	Exclusion criteria	Patients who have had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous), or hospitalization in the 6 weeks prior to screening (Visit 1 or between Visit 1 and Visit 3). Patients who develop a COPD exacerbation between the pre-screening and the randomization visit (Visits 1 and 3) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.	COPD exacerbation that required treatment with antibiotics, SCS, or hospitalization in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 4. Patients who developed a COPD exacerbation between Visits 1 and 4 were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily	3 periods: 1. Indacaterol 110 mcg + glycopyrronium 50 mcg once daily followed by tiotropium 18 mcg once daily 2. Placebo once daily followed by tiotropium once daily 3. Tiotropium 18 mcg once daily followed by indacaterol 110 mcg + glycopyrronium 50 mcg once daily
	Comparator(s)	Tiotropium once daily Placebo once daily	
DURATION	**Phase**		
	Run-in	1-week washout, 2 weeks screening	3 weeks screening
	Double-blind	3 periods, 6 weeks each, 2-week washout	3 periods: 3 weeks each, 3-week washout
	Follow-up	30 days	30 days
OUTCOMES	**Primary end point**	Patient-reported dyspnea by self-administered computerized BDI/TDI (superiority versus placebo)	Exercise tolerance as measured by exercise endurance time during SMETT after 3 weeks

		BLAZE	BRIGHT
	Other end points	Patient-reported dyspnea by self-administered computerized BDI/TDI (superiority versus tiotropium) Post-dose FEV_1 AUC 0 hours to 4 hours for FEV_1 and FVC Use of rescue medications	Isotime IC during SMETT Trough (i.e., 24 hours post dose) IC Trough (i.e., 24 hours post dose) FEV_1 Spirometry after 3 weeks of treatment (1) during exercise and (2) sedentary Exertional dyspnea (Borg CR10 Scale) during exercise Leg discomfort (Borg CR10 Scale) during SMETT Exercise endurance time during SMETT
NOTES	**Publications**	Mahler 2014[33]	Beeh 2014[34]

AUC = area under the curve; BDI = Baseline Dyspnea Index; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IC = inspiratory capacity; RCT = randomized controlled trial; SCS = systemic corticosteroids; SMETT = sub-maximal constant load cycle ergometry test; TDI = Transition Dyspnea Index.
Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).
Source: Clinical study reports for BLAZE,[17] BRIGHT.[18]

TABLE 17: DETAILS OF INCLUDED STUDIES: OPEN LABEL

		ARISE
DESIGNS & POPULATIONS	**Study design**	OL RCT
	Locations	35 centres: Japan
	Study period	January 28, 2011, to September 7, 2012
	Randomized (N)	N = 160
	Inclusion criteria	≥ 40 years of age Moderate to severe COPD (GOLD II or III) Current of former smokers, ≥ 10 pack-years smoking history Post-bronchodilator FEV_1 reversibility of ≥ 30% to < 80% PN Post-bronchodilator FEV_1:FVC ratio < 0.70
	Exclusion criteria	Long QT Significant ECG abnormality COPD exacerbation that required treatment with antibiotics, SCS, or hospitalization in the 6 weeks prior to pre-screening Patients who developed a COPD exacerbation between the pre-screening and randomization visits (Visits 1 and 3) were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation Any history of asthma
DRUGS	**Intervention**	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (Breezhaler)
	Comparator(s)	Tiotropium 18 mcg once daily
DURATION	**Phase**	
	Run-in	2 weeks
	Double-blind	52 weeks
	Follow-up	30 days
OUTCOMES	**Primary end point**	Safety
	Other end points	FEV_1 and FVC measured after 3, 6, 12, 24, 36, and 52 weeks' treatment IC measured after 12, 24, and 52 weeks' treatment Total SGRQ-C score after 12, 24, 36, and 52 weeks' treatment Use of rescue medication (number of puffs) reported by the patients during 52 weeks' treatment Time to first moderate to severe COPD exacerbation during 52 weeks' treatment Proportion of moderate to severe COPD exacerbations during 52 weeks' treatment
NOTES	**Publications**	None

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; ECG = electrocardiogram; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IC = inspiratory capacity; OL = open-label; PN = predicted normal; RCT = randomized controlled trial: SCS = systemic corticosteroids; SGRQ = St. George's Respiratory Questionnaire.

Note: Two additional reports were included (manufacturer's submission[25]; Health Canada Reviewers Report[26]).

Source: Clinical study report for ARISE.[19]

3.2 Included Studies

3.2.1 Description of Studies

Eight double-blind (DB) randomized controlled trials (RCTs) and one open-label RCT met the inclusion criteria for this review. All studies were multi-centre and manufacturer sponsored. One of the studies (QUANTIFY, N = 934) compared once daily indacaterol 110 mcg + glycopyrronium 50 mcg once daily with another LAMA/LABA combination, tiotropium 18 mcg daily + formoterol 12 mcg twice daily, over 26 weeks. QUANTIFY tested the non-inferiority of indacaterol + glycopyrronium versus tiotropium + formoterol for the primary outcome of change in St. George's Respiratory Questionnaire-COPD (SGRQ-C) at end of study. SHINE (N = 2,135) tested the superiority of indacaterol + glycopyrronium versus the individual components of indacaterol (150 mcg once daily) and glycopyrronium (50 mcg once daily) for the primary outcome of FEV_1 at 26 weeks. SPARK (N = 2,224) tested the superiority of indacaterol + glycopyrronium versus the component of glycopyrronium (50 mcg once daily) for the primary outcome of the rate of moderate to severe exacerbations over the course of the 64- to 76-week study. Both SHINE and SPARK included an open-label tiotropium group as a secondary comparator. One study (ILLUMINATE, N = 523) compared indacaterol 110 mcg + glycopyrronium 50 mcg once daily with an ICS + LABA combination, fluticasone propionate 500 mcg + salmeterol 50 mcg twice daily over 26 weeks. One study (ENLIGHTEN, N = 339) compared indacaterol + glycopyrronium with placebo over 52 weeks. ENLIGHTEN identified safety and tolerability as its primary outcome. BEACON (N = 193) compared indacaterol 110 mcg + glycopyrronium 50 mcg once daily administered in the Ultibro Breezhaler device to a combination of the components of the Breezhaler, indacaterol 150 mcg once daily and glycopyrronium 50 mcg once daily, over four weeks. BEACON tested the non-inferiority of indacaterol + glycopyrronium versus these components administered simultaneously, for the primary outcome of trough FEV_1 at four weeks. Two crossover studies, BLAZE (six weeks of treatment in each period, N = 247) and BRIGHT (three weeks' treatment, N = 85), each evaluated indacaterol 110 mcg + glycopyrronium 50 mcg once daily, tiotropium 18 mcg once daily, and placebo. The primary outcome of BLAZE was the superiority of indacaterol + glycopyrronium versus placebo for dyspnea scores, and in BRIGHT the primary outcome was exercise tolerance after 3 weeks' treatment. Finally, ARISE (N = 160) examined the safety of indacaterol 110 mcg + glycopyrronium 50 mcg once daily versus tiotropium 18 mcg once daily using an open-label design.

All studies were multi-centre studies, and were sponsored by the manufacturer of indacaterol + glycopyrronium.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

In all studies, patients had to be a minimum of 40 years of age to be enrolled. All studies included current or former smokers with a smoking history of at least 10 pack-years. Patients in SPARK had severe to very severe COPD by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (Table 12), while the rest of the studies enrolled patients with moderate to severe COPD. All studies specified a cut-off for FEV_1 reversibility, and the thresholds varied between studies. SPARK, which enrolled patients with severe to very severe COPD, required that patients have a FEV_1 reversibility of < 50% of predicted normal (Table 12). In SHINE, QUANTIFY, BEACON, ENLIGHTEN, ARISE, and BLAZE, patients had to have a post-bronchodilator reversibility of between 30% and 80% predicted normal (Table 12, Table 15, Table 16, Table 17). In ILLUMINATE, patients had to have a post-bronchodilator FEV_1 reversibility of between 40% and 80% (Table 13), and in BRIGHT, between 40% and 70% (Table 16). All studies required a post-bronchodilator FEV_1/FVC of 0.70. SPARK required that all patients have had at least one exacerbation that required systemic corticosteroids, antibiotics, or hospitalization in the previous 12 months (Table 12), while other studies did not specify a minimum exacerbation history. All studies

excluded patients who had a recent exacerbation, typically in the six weeks before pre-screening or during screening. ILLUMINATE excluded patients who had an exacerbation needing treatment with antibiotics, systemic corticosteroids, or requiring hospitalization within the year leading up to randomization (Table 13).

b) Baseline Characteristics

Across the DB RCTs, the mean age of patients ranged from 62 to 66 years, and the majority of patients (63% to 77%) were male. In most studies, patients had either moderate or severe COPD; however, in SPARK patients had either severe or very severe COPD (Table 19). With respect to smoking history, approximately half of patients in QUANTIFY and ILLUMINATE were former smokers, while the others were current smokers. In SHINE, a smaller proportion of patients were current smokers (~40%) versus former smokers (Table 19). In other studies, the majority were former smokers (ranging from 55% to 60%). In all studies, there were patients using ICS at baseline. SPARK had the highest proportion of ICS users at baseline (~75%), and this was the study that enrolled patients with severe to very severe COPD (Table 19). BRIGHT had the lowest proportion of ICS users at baseline, at 31% (Table 23). The mean post-bronchodilator reversibility across studies was typically around 20%. The proportion of patients having reported an exacerbation in the past year was highest in SPARK (Table 19), in which all but 1% had reported an exacerbation, and lowest in ILLUMINATE, in which one patient out of 522 had reported an exacerbation in the past year (Table 20). The population in ARISE was older (69 years of age), almost all male (96%), with a small proportion of current smokers (28%)(Table 24).

Baseline characteristics were reasonably similar between groups within studies. One of the exceptions was ENLIGHTEN, in which the proportion of patients with severe COPD was higher in the indacaterol + glycopyrronium group than in the placebo group (31% versus 19%) (Table 21).

TABLE 18: SUMMARY OF BASELINE CHARACTERISTICS: LAMA/LABA-CONTROLLED

	QUANTIFY	
	IG N = 476	TF N = 458
Mean (SD) age, years	62.6 (8.4)	63.1 (8.2)
Male gender, n (%)	317 (67)	298 (65)
Ethnicity, n (%)		
White	472 (99)	454 (99)
Other	4 (1)	4 (1)
Mean (SD) duration of COPD, years	6.5 (5.3)	6.8 (5.2)
COPD severity, n (%)		
Moderate, Stage II	267 (58)	253 (56)
Severe, Stage III	193 (42)	195 (43)
Very severe, Stage IV	2 (< 1)	4 (1)
COPD exacerbation, prior year, n (%)		
0	411 (86)	396 (87)
1	60 (13)	57 (12)
≥ 2	5 (1)	5 (1)
Smoking status, n (%)		
Former smoker	242 (51)	234 (51)
Current smoker	234 (49)	224 (49)
Spirometry		
Mean (SD) post-bronchodilator reversibility, %	19.3 (18.4)	19.6 (18.2)
ICS use		
ICS use at baseline, n (%)	201 (42)	184 (40)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; SD = standard deviation; TF = tiotropium + formoterol.
Source: Clinical study report for QUANTIFY.[11]

TABLE 19: SUMMARY OF BASELINE CHARACTERISTICS: LAMA-CONTROLLED

	SHINE					SPARK		
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232	IG N = 729	G N = 740	TIO N = 737
Mean (SD) age, years	64.0 (8.9)	63.6 (8.8)	64.3 (9.0)	63.5 (8.7)	64.4 (8.6)	63.1 (8.1)	63.1 (8.0)	63.6 (7.8)
Male gender, n (%)	362 (76)	354 (74)	365 (77)	360 (75)	169 (73)	556 (76)	542 (73)	553 (75)
Ethnicity, n (%)								
White	321 (68)	332 (70)	315 (67)	322 (67)	155 (67)	594 (82)	605 (82)	613 (83)
Asian	140 (30)	131 (28)	137 (29)	135 (28)	71 (31)	89 (12)	92 (12)	79 (11)
Black						4 (1)	5 (1)	7 (1)
Other	13 (3)	13 (3)	21 (4)	23 (5)	6 (3)	42 (6)	38 (5)	38 (5)
COPD duration								
Mean (SD) duration of COPD, years	6.0 (5.5)	6.3 (5.6)	6.5 (5.8)	6.1 (56)	6.4 (5.7)	7.2 (5.8)	7.1 (5.3)	7.2 (5.5)
COPD severity, n (%)								
Moderate	313 (66)	294 (62)	298 (63)	296 (62)	157 (68)	1 (< 1)	1 (< 1)	0
Severe	161 (34)	182 (38)	173 (37)	184 (38)	75 (32)	578 (79)	584 (79)	581 (79)
Very severe	NR	NR	NR	NR	NR	150 (21)	155 (21)	156 (21)
COPD exacerbation, prior year, n (%)								
0	352 (74)	348 (73)	346 (73)	363 (76)	184 (79)	8 (1)	13 (2)	11 (2)
1	94 (20)	106 (22)	91 (19)	93 (19)	37 (16)	557 (76)	572 (77)	552 (75)
≥ 2	28 (6)	22 (5)	36 (8)	24 (5)	11 (5)	164 (23)	155 (21)	174 (24)
Smoking status, n (%)								
Former smoker	282 (60)	292 (61)	284 (60)	291 (61)	139 (60)	452 (62)	457 (62)	467 (63)
Current smoker	192 (41)	184 (39)	189 (40)	189 (39)	93 (40)	277 (38)	283 (38)	270 (37)
Spirometry								
Mean (SD) post-bronchodilator reversibility %	20.4(16.8)	20.5(16.8)	20.0(17.6)	20.6 (17.5)	19.3 (15.9)	17.2 (19.6)	18.8 (19.1)	18.9 (19.3)
ICS use								
ICS use at baseline, n (%)	268 (57)	269 (57)	274 (58)	282 (59)	134 (58)	546 (75)	557 (75)	559 (76)

COPD = chronic obstructive pulmonary disease; G = glycopyrronium; I = indacaterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; NR = not reported; PLA = placebo; SD = standard deviation; TIO = tiotropium.
Source: Clinical study report (CSR) SPARK[12]; CSR SHINE.[13]

TABLE 20: SUMMARY OF BASELINE CHARACTERISTICS: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG (N = 258)	FP/S (N = 264)
Mean (SD) age, years	63.2 (8.2)	63.4 (7.7)
Male gender, n (%)	181 (70)	189 (72)
Ethnicity		
White	231 (90)	235 (89)
Asian	27 (11)	29 (11)
COPD duration		
Mean (SD) duration of COPD, years	6.4 (5.2)	7.5 (6.0)
COPD severity, n (%)		
Moderate	207 (80)	212 (80)
Severe	51 (20)	52 (20)
Very severe	0	0
COPD exacerbation, prior year, n (%)		
0	258 (100)	263 (100)
1	0	1 (< 1)
≥ 2	0	0
Smoking status, n (%)		
Former smoker	135 (52)	137 (52)
Current smoker	123 (48)	127 (48)
Spirometry		
Mean (SD) post-bronchodilator reversibility, %	20.5 (15.4)	20.3 (13.0)
ICS use		
ICS use at baseline, n (%)	85 (33)	98 (37)

COPD = chronic obstructive pulmonary disease; LABA = long-acting beta-2 adrenergic agonist; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; SD = standard deviation.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 21: SUMMARY OF BASELINE CHARACTERISTICS: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG (N = 225)	PLA (N = 113)
Mean (SD) age, years	62.5 (8.8)	62.9 (8.1)
Male gender, n (%)	174 (77)	86 (76)
Ethnicity		
Caucasian	178 (79)	94 (83)
Asian[a]	47 (21)	19 (17)
Mean (SD) duration of COPD, years	5.8 (5.7)	5.5 (5.1)
COPD severity, n (%)		
Moderate	154 (68)	91 (81)
Severe	70 (31)	21 (19)
Very severe	0	1 (1)
COPD exacerbation history, n (%)		
0	154 (68)	72 (64)
1	56 (25)	32 (28)
≥ 2	15 (7)	9 (8)
Smoking status, n (%)		
Former smoker	123 (55)	62 (55)
Current smoker	102 (45)	51 (45)
Spirometry		
Mean (SD) post-bronchodilator reversibility, %	15.74 (14.84)	15.59 (14.53)
ICS use		
ICS use at baseline, n (%)	103 (46)	44 (39)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; PLA = placebo; SD = standard deviation.
[a] The majority of Asian patients were from the Indian subcontinent and constituted 12.7% of total patients.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 22: SUMMARY OF BASELINE CHARACTERISTICS: COMPONENT-CONTROLLED

	BEACON	
	IG N = 90	I and G (Individual Components) N = 103
Mean (SD) age, years	65.6 (7.3)	64.2 (7.4)
Male gender, n (%)	58 (64)	59 (57)
Ethnicity		
White	90 (100)	103 (100)
Mean (SD) duration of COPD, years	7.3 (5.0)	6.8 (4.8)
COPD severity, n (%)		
Moderate	55 (61)	60 (58)
Severe	35 (39)	43 (42)
Very severe	0	0
COPD exacerbation, prior year, n (%)		
0	NR	NR
1	NR	NR
≥ 2	NR	NR
Smoking status, n (%)		
Former smoker	53 (59)	62 (60)
Current smoker	37 (41)	41 (40)
Spirometry		
Mean (SD) post-bronchodilator reversibility, %	22.7 (16.8)	24.4 (19.5)
ICS use		
ICS use at baseline, n (%)	61 (68)	64 (62)

COPD = chronic obstructive pulmonary disease; G = glycopyrronium; I = indacaterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; NR = not reported; SD = standard deviation.
Source: Clinical study report for BEACON.[16]

TABLE 23: SUMMARY OF BASELINE CHARACTERISTICS: CROSSOVER STUDIES

	BRIGHT N = 84	BLAZE N = 246
Mean (SD) age, years	62.1 (8.1)	62.8 (8.2)
Male gender, n (%)	53 (63)	173 (70)
Ethnicity		
White	81 (96)	246 (100)
Other	3 (4)	0
COPD duration		
Mean (SD) duration of COPD, years	8.9 (6.8)	7.6 (5.9)
COPD severity, n (%)		
Moderate	61 (73)	168 (68)
Severe	23 (27)	78 (32)
Very severe	0	-
COPD exacerbation, prior year, n (%)		
0	70 (83)	172 (70)
1	12 (14)	57 (23)
≥ 2	2 (2)	17 (7)
Smoking status, n (%)		
Former smoker	39 (46)	134 (54)
Current smoker	45 (54)	112 (46)
Spirometry		
Mean (SD) post-bronchodilator reversibility, %	22.6 (15.6)	21 (15.0)
ICS use		
ICS use at baseline, n (%)	26 (31)	135 (55)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; SD = standard deviation.
Source: Clinical study report BLAZE[17]; CSR BRIGHT.[18]

TABLE 24: SUMMARY OF BASELINE CHARACTERISTICS: OPEN LABEL

	ARISE	
	IG N = 119	TIO N = 39
Mean (SD) age, years	69.3 (6.8)	69.4 (6.9)
Male gender, n (%)	114 (96)	37 (95)
Ethnicity		
Caucasian	0	0
Asian	119 (100)	39 (100)
Mean (SD) duration of COPD, years	3.3 (4.2)	2.9 (3.3)
COPD severity, n (%)		
Moderate	71 (60)	28 (72)
Severe	48 (40)	10 (26)
Very severe	0	1 (3)
COPD exacerbation history, n (%)		
0	100 (84)	31 (80)
1	15 (13)	7 (18)
≥ 2	4 (3)	1 (3)
Smoking status, n (%)		
Former smoker	86 (72)	29 (74)
Current smoker	33 (28)	10 (26)
Spirometry		
Mean (SD) post-bronchodilator reversibility, %	16.0 (13.7)	15.8 (15.7)
ICS use		
ICS use at baseline, n (%)	31 (26)	11 (28)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; SD = standard deviation; TIO = tiotropium.
Source: Clinical study report for ARISE.[19]

3.2.3 Interventions

According to the manufacturer, the selection of the indacaterol 110 mcg + glycopyrronium 50 mcg dose was based on the appropriate doses of the constituent mono-components, selected from the phase II and phase III clinical trials, respectively (glycopyrronium 50 mcg and indacaterol 150 mcg). The dose of the indacaterol component takes into account technical findings relating to the fine particle dose (FPD) of indacaterol in the combination product compared with the indacaterol monotherapy product (i.e., in indacaterol + glycopyrronium, the indacaterol dose has been adjusted to match the FPD of the indacaterol monotherapy [150 mcg], which results in a combination of 110 mcg of indacaterol and 50 mcg of glycopyrronium).

In QUANTIFY, at the pre-screening visit (Visit 1), patients taking a fixed-dose combination treatment of an inhaled corticosteroid plus a LABA discontinued these medications and were prescribed an inhalable corticosteroid monotherapy at an equivalent dose and dosing regimen for the duration of the study. In addition, patients were provided with a short-acting bronchodilator (salbutamol) as rescue therapy for use throughout the study.

In ILLUMINATE, at Visit 1 all patients were provided with a salbutamol inhaler, which they were instructed to use throughout the study as rescue medication. Nebulized salbutamol was not allowed as rescue medication. Patients were instructed to abstain from taking rescue salbutamol within six hours of the start of each visit unless absolutely necessary. If rescue medication was taken within six hours before spirometry at Visit 2 or before administering medication at any of the scheduled visits, the visit was rescheduled to the next possible day. The investigators used their judgment when deciding how many times a visit for an individual patient was rescheduled for Visit 2 and 3. If a patient used a dose of rescue medication after taking study medication at that visit or during any other visits, then the visit continued as planned but the approximate time taken was captured through the central spirometer if taken during a study visit and the number of puffs collected in the eDiary. Rescue medication usage was collected twice daily in the eDiary between study visits.

In SPARK, patients taking an FDC treatment of an ICS plus LABA discontinued the combined medication at least 48 hours before Visit 2 and were instead prescribed an ICS monotherapy at an equivalent dose and dosing regimen (e.g., patients on 500 mcg fluticasone propionate + 50 mcg salmeterol twice a day were switched to fluticasone propionate monotherapy 500 mcg twice daily or equivalent dose for the duration of the study, plus a SABA, e.g., salbutamol, as needed). The daily dose of ICS monotherapy remained stable throughout the study. Salbutamol was available for rescue use throughout the study. Patients were asked to abstain whenever possible from using rescue medication during study visits, and in the six hours prior to attending a study visit. If rescue medication was taken within six hours, the visit was rescheduled and the number of puffs of rescue medication taken recorded in the patient eDiary. Any rescue taken within the study visit was recorded on the spirometer and the number of puffs was recorded in the patient eDiary.

In SHINE, patients taking an FDC treatment of an ICS + LABA discontinued the combined medication at least 48 hours before Visit 2 and were instead prescribed an ICS monotherapy at an equivalent dose and dosing regimen; e.g., patients on 500 mcg fluticasone propionate + 50 mcg salmeterol twice a day were switched to fluticasone propionate monotherapy 500 mcg twice daily or equivalent dose for the duration of the study, plus an inhaled SABA; e.g., salbutamol as needed. The daily dose of ICS monotherapy remained stable throughout the study. Salbutamol was available for rescue use throughout the study.

In ENLIGHTEN, at Visit 2, further screening assessments were performed including screening spirometry and reversibility testing. Between Visit 2 and 3 (Day 1) there was a 14 day run-in period used to assess eligibility of patients for the study and to collect baseline patient eDiary data. At Visit 3 (Day 1) patients remained on allowed background COPD therapy consisting of ICS (if appropriate) and SABAs.

In BEACON, at the start of Visit 1, all patients were provided with a SABA (salbutamol), which they were instructed to use throughout the study as rescue medication. Nebulized salbutamol/albuterol was not allowed as rescue medication. Once eligibility was confirmed, the patient was dispensed two bronchodilators; these were open-label indacaterol 150 mcg once daily and open-label glycopyrronium 50 mcg once daily, administered concurrently during the 14-day run-in period between Visit 2 and Visit 3. The open-label treatment period was used to stabilize patients and baseline lung function before randomization to DB treatment and to provide compliance training with the dosing regimen of two capsules with the use of two inhalers each morning. Patient symptoms were monitored and baseline data collected to confirm eligibility by ensuring patients were symptomatic during the run-in period. Patients had to be at least 80% compliant with run-in medication in order to be randomized.

In BLAZE, at Visit 1 (pre-screening), all patients were provided with a salbutamol inhaler, which they were instructed to use throughout the study as rescue medication. Nebulized salbutamol was not allowed as rescue medication. Patients were instructed to abstain from taking their rescue medication within six hours of the start of each visit unless absolutely necessary. If rescue medication was taken within six hours before spirometry at Visit 2 or before administering study medication at any of the scheduled visits, the visit was to be rescheduled to the next possible day. The study consisted of a screening period (depending on washout required for prior medications), baseline visit, and three six-week treatment periods followed by a study completion evaluation (to be completed 30 days after the last treatment visit). Each treatment period was separated by a 14-day washout period, and patients had a maximum of 11 visits.

In BRIGHT, at Visit 1 all patients were provided with a SABA (salbutamol), which they were instructed to use throughout the study as rescue medication on an "as needed" basis. Nebulized salbutamol was not allowed as rescue medication. Patients were instructed to abstain from taking their rescue medication within six hours of the start of each visit unless absolutely necessary. If rescue medication was taken within six hours of a spirometry visit, the visit was to be rescheduled and the number of puffs of rescue medication taken recorded in the patient eDiary. A washout period of three weeks between treatment periods was selected in order to minimize any carry-over training effects. Both placebo and active comparator were used in this study. A placebo control was used at this current stage of development, as it was unknown whether indacaterol + glycopyrronium would show a statistically significant difference for the outcome of exercise endurance time. It is important to note that the term "placebo" used in the context of this study refers to a placebo control that was added to the patient's already well-established and allowed background COPD therapy.

In ARISE, salbutamol was used as rescue medication. If rescue medication was taken within six hours before spirometry at Visit 2 or before administration of medication at any of the scheduled visits, the visit was rescheduled to the next possible day. The investigators were required to use their judgment when deciding how many times a visit for an individual patient was rescheduled for Visits 2 and 3.

3.2.4 Outcomes

In the studies reporting, COPD exacerbation was defined as:

- A worsening of the following two or more major symptoms for at least two consecutive days:
  - dyspnea
  - sputum volume
  - sputum purulence

OR

- A worsening of any one major symptom together with an increase any one of the following minor symptoms for at least two consecutive days:
  - sore throat
  - colds (nasal discharge and/or nasal congestion)
  - fever without other cause
  - increased coughing
  - increased wheezing

AND

- Requiring treatment with corticosteroids and/or antibiotic, emergency room visit, or hospitalization.

A COPD exacerbation was considered of moderate severity if treatment with systemic corticosteroids (also intramuscular depot corticosteroids) or antibiotics or both was required and severe if

hospitalization was required. An emergency room visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not counted as an exacerbation. A worsening of symptoms that did not meet the above symptom definition but was treated by the investigator with systemic corticosteroids or antibiotics, or met the symptom definition but was not treated by the investigator was not considered a moderate or severe COPD exacerbation for the study.

If a patient experienced a COPD exacerbation matching the above definition at any time after signing the informed consent, the patient was treated for the exacerbation as the investigator deemed appropriate.

In patients with multiple exacerbations, if the start date of an exacerbation was less than seven days after the end date of a previous episode, then this was assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes was taken as the severity of the entire exacerbation.

The study personnel had to record a moderate or severe COPD exacerbation in the Electronic Clinical Research Forms (eCRFs) and, if serious, on the Serious Adverse Event Form as well. Any reported adverse events (AEs) or serious adverse events (SAEs) of pneumonia were confirmed by chest imaging. Following treatment for the exacerbation, the patient was expected to continue in the study provided the investigator considered that the patient could safely return to his or her pre-exacerbation medications. No spirometry assessments were taken until after the exacerbation had resolved. If systemic corticosteroids were taken within seven days before any study visit, the visit was rescheduled to allow a washout of seven days.

For assessment of symptoms, all patients were provided with an electronic patient diary at Visit 2 to record morning and evening daily clinical symptoms: cough, wheezing, shortness of breath, sputum volume, sputum purulence, night time awakenings, and rescue medication (salbutamol) use. Patients were instructed to routinely complete the eDiary twice daily, before taking the study drug at the same time each morning and again (approximately 12 hours later) each evening, considering events over the previous 12 hours.

The SGRQ-C contains 40 items divided into two parts covering three aspects of health related to COPD:

- Part I — “Symptoms”: concerned with respiratory symptoms, their frequency and severity
- Part II — “Activity”: concerned with activities that cause or are limited by breathlessness
- Part III — “Impacts”: concerned with social functioning and psychological disturbances resulting from airway disease.

Most studies did not report details on how the instrument was administered; however, those that did described patients as filling out the instrument at the investigator site. A score was calculated for each of these three subscales, and a total score was also calculated. In each case, the lowest possible value was 0 and the highest 100. Higher values corresponded to greater impairment of health status, and a difference of 4 is considered the minimal clinically important difference (MCID).

All spirometry measurements followed the American Thoracic Society/European Respiratory Society criteria. At screening, spirometry measurements were taken to assess the patient’s eligibility for the study and to assess the post-bronchodilation FEV_1. The reversibility test was to be performed as follows.

A baseline spirometry assessment was to be performed after a washout period of at least:

- six hours for a SABA

- eight hours for a SAMA
- 48 hours for a LABA
- seven days for LAMA
- seven days for indacaterol.

Following the completion of the baseline assessment, 84 mcg of ipratropium bromide and 400 mcg of salbutamol were administered. Pre-dose FEV_1 was derived as the average of those taken 45 minutes and 15 minutes pre-dose. Standardized area under the curve (AUC) 0 hours to 12 hours for FEV_1 was calculated using the trapezoidal rule and standardized with respect to time from the first (five minutes) to the last measurement (12 hours).

The Baseline Transition Index (BDI) and the Transition Dyspnea Index (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. A TDI focal score of 1 is considered a clinically significant improvement from baseline. The accepted MCID for TDI is 1.[35] If TDI had missing values, only the total score from measurements for which all components were populated were carried forward. Values were not carried forward by more than 14 weeks, and scores within four weeks of the baseline visit were not carried forward.

Patients were interviewed by a trained assessor (in accordance with training materials provided by Novartis) who graded the degree of impairment due to dyspnea at Visit 3 (BDI) and at Visits 5 and 7 (TDI). If possible, the same assessor completed both the BDI and TDI assessments for an individual patient, which was undertaken before dosing at these visits. The BDI was administered at the beginning of the treatment period (Visits 3) before any spirometry assessment and administration of study medication. The TDI, filled out at Visits 5 and 7, was completed before any spirometry assessment and administration of study medication.

3.2.5 Statistical Analysis

In QUANTIFY, the non-inferiority of indacaterol + glycopyrronium over tiotropium + formoterol (primary objective) was evaluated by testing the one-sided null hypothesis that the mean change in SGRQ-C score under indacaterol + glycopyrronium was at least 4 points less than the mean change under tiotropium plus formoterol after 26 weeks of treatment. The corresponding alternative hypothesis was that the difference between treatments was less than 4 points to the disadvantage of indacaterol + glycopyrronium. The non-inferiority of indacaterol + glycopyrronium over tiotropium plus formoterol was claimed if the shifted, one-sided *P* value was less than 2.5%, or, equivalently, if the two-sided 95% confidence interval (CI) lay entirely to the left (smaller than) of the non-inferiority margin of 4 points. The manufacturer chose this margin because it was often quoted in the literature as demonstrating a clinically relevant effect for this instrument. Superiority of indacaterol + glycopyrronium over tiotropium + formoterol was claimed if the (unshifted) two-sided *P* value was less than 5% (in favour of indacaterol + glycopyrronium) or, equivalently, if the two-sided 95% CI lay entirely to the left (smaller than) of 0 points. The primary analysis was performed using an analysis of covariance (ANCOVA) model. The model contained treatment, SGRQ-C at baseline, and centre as fixed effects. The estimated adjusted treatment difference for indacaterol + glycopyrronium minus tiotropium + formoterol was displayed along with the associated 95% CI and *P* value (two-sided). Additionally, a (one-sided) *P* value for the

shifted null hypothesis of inferiority was given. No power analysis was performed for the key secondary outcomes.

SPARK was designed to demonstrate that indacaterol + glycopyrronium is superior to glycopyrronium with regard to the rate of moderate to severe COPD exacerbations during the treatment period, in patients with severe to very severe COPD. The key secondary objective was to determine whether indacaterol + glycopyrronium was superior to tiotropium for rate of moderate to severe exacerbations. The primary efficacy analysis was performed using a two-sided test at alpha = 0.05, to compare the (time-adjusted) rates of moderate or severe COPD exacerbations of indacaterol + glycopyrronium versus glycopyrronium treatment groups over the treatment period. The number of moderate or severe COPD exacerbations was analyzed using the negative binomial model. The negative binomial model accounts for most over-dispersion that may result from assuming a Poisson distribution by allowing a different Poisson rate for each patient and assuming that these rates, as a set, are distributed across patients according to a gamma distribution. The model included terms for treatment, smoking status at baseline, medication history of ICS use, and country as fixed effects. The model also contained the baseline daily total symptom score, baseline COPD exacerbation history (the number of COPD exacerbations in the year before screening), FEV_1 before inhalation, and FEV_1 60 minutes after inhalation of two short-acting bronchodilators (components of reversibility at Visit 2) as covariates. The baseline daily total symptom score was calculated as the sum of the worst (i.e., worst of the morning or evening) score of the day of the following symptoms: respiratory symptoms, breathless feeling, sputum production, sputum colour, cough, and wheeze averaged over the 14-day run-in period. For some patients, additional symptoms (sore throat, fever, and cold) were collected but did not contribute to the total symptom score. All reversibility components of FEV_1 measured at Visit 2, regardless of the particular symptoms recorded, were used as covariates for the analysis model. For the purpose of this analysis, countries that randomized 15 patients or fewer were pooled with countries of similar medical practice.

In SHINE, trough FEV_1 after 26 weeks of treatment imputed with last observation carried forward (LOCF) was summarized by treatment for the full analysis set (FAS). The superiority contrasts (indacaterol + glycopyrronium versus indacaterol, and indacaterol + glycopyrronium versus glycopyrronium) were evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

- H_0: There is no difference in trough FEV_1 following 26 weeks' treatment for COPD patients being compared.
- H_a: There is a difference in trough FEV_1 following 26 weeks' treatment for COPD patients being compared using a mixed model for the FAS. The model contained treatment as a fixed effect with the baseline FEV_1 measurement, FEV_1 before inhalation of two short-acting bronchodilators, and FEV_1 1 hour after inhalation of two short-acting bronchodilators (components of reversibility at Visit 2) as covariates. The model also included baseline smoking status (current/ex-smoker), baseline ICS use (Yes/No), and region as fixed effects, and centre nested within region as a random effect. A statistical gate-keeping procedure was applied to control for multiplicity. Superiority of indacaterol + glycopyrronium to indacaterol or glycopyrronium was demonstrated if the adjusted one-sided *P* value was less than the multiplicity-adjusted significance level. To demonstrate the superiority of indacaterol 110 mcg + glycopyrronium 50 mcg compared with placebo following 26 weeks of treatment, the following measures were used for outcomes:
  - Level of breathlessness experienced by the patients, evaluated using the TDI
  - Health-related quality of life (HRQoL) as reported by the patients, evaluated using the SGRQ-C
  - Rescue medication used (number of puffs) reported by the patients, evaluated using the patient diary.

Important secondary objectives included:

- To evaluate the superiority of indacaterol 110 mcg + glycopyrronium 50 mcg, glycopyrronium 50 mcg, and indacaterol 150 mcg compared with placebo in terms of lung function at trough FEV_1 following 26 weeks of treatment
- To evaluate whether indacaterol 110 mcg + glycopyrronium 50 mcg is at least as effective as open-label tiotropium 18 mcg in terms of lung function at trough FEV_1 following 26 weeks of treatment.

In ILLUMINATE, the superiority of indacaterol + glycopyrronium over fluticasone 500 mcg + salmeterol 50 mcg was evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

- H_0: There is no difference in standardized AUC 0 hours to 12 hours for FEV_1 following 26 weeks of treatment in patients with moderate to severe COPD treated with indacaterol + glycopyrronium compared with fluticasone + salmeterol
- H_a: There is a difference in standardized AUC 0 hours to 12 hours for FEV_1 following 26 weeks of treatment in patients with moderate to severe COPD treated with indacaterol + glycopyrronium compared with fluticasone + salmeterol.

The primary analysis was performed on the FAS population using a mixed model, which contained treatment as a fixed effect with the baseline FEV_1, FEV_1 before inhalation of short-acting bronchodilator, and FEV_1 after inhalation of short-acting bronchodilator as covariates. The model also included smoking status at baseline (current/ex-smoker), history of ICS use, and region as fixed effects, and centre nested within region as a random effect. In this study, each country is considered a region. The estimated adjusted treatment difference for indacaterol + glycopyrronium minus fluticasone + salmeterol was displayed along with the associated 95% CI and *P* value (two-sided). Superiority of indacaterol + glycopyrronium to fluticasone + salmeterol was demonstrated if the *P* value was less than the 5% significance level and the 95% CI lay entirely to the right of 0 L.

Through previous Phase 2 and 3 inhaled bronchodilatory projects, standard deviations of FEV_1 AUC 0 hours to 12 hours appeared to be 0.2 L. To detect statistical significance in the primary end point (at alpha = 0.05, with 80% power) for a treatment group differential of 0.6 L in FEV_1 AUC 0 hours to 12 hours at Week 26 (with conservatively assumed standard deviation of 0.225 L), and assuming a 15% dropout rate, an estimated total sample size of 522 patients (261 per group) was needed to be randomized (444 completers). With a subgroup of 200 randomized patients (100 patients per treatment group) in pre-selected centres, the precision of the 95% CI for treatment difference should be within 0.103 L, assuming a standard deviation of 0.370 L.

In ENLIGHTEN, the primary objective of the study was to evaluate the overall safety of indacaterol + glycopyrronium versus placebo. Multiplicity-unadjusted hypotheses of no difference between the two treatment groups were tested for certain safety variables for this class of drug; namely, serum potassium, serum glucose, increased heart rate, systolic and diastolic blood pressure, and QTcF. For these safety parameters, a mixed model was used to analyze the post-baseline visit measurements. The model contained treatment as a fixed effect, with the baseline measurements as covariates. The model also included smoking status at baseline (current or ex-smoker), history of ICS use, and country as fixed effects, and centre nested within country as a random effect. For the treatment contrasts with placebo, 95% CIs were provided together with the associated *P* values. No adjustment was made for multiplicity.

In BEACON, the non-inferiority of indacaterol + glycopyrronium to the concurrent administration of indacaterol 150 mcg daily and glycopyrronium 50 mcg daily was evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

- H_0: indacaterol + glycopyrronium is inferior to indacaterol 150 mcg daily and glycopyrronium 50 mcg daily with respect to mean trough FEV_1 after 28 days of blinded treatment in patients with moderate to severe COPD.
- H_a: indacaterol + glycopyrronium is non-inferior to indacaterol 150 mcg daily and glycopyrronium 50 mcg daily with respect to mean trough FEV_1 after 28 days of blinded treatment in patients with moderate to severe COPD.

The primary analysis was performed on the per-protocol set (PPS), to be aligned with the principle of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 Guideline, with a mixed model. The FAS was also used for supportive analysis of the primary variable. The mixed model contained treatment as a fixed effect with the baseline measurement of trough FEV_1, FEV_1 before inhalation of short-acting bronchodilator, and FEV_1 after inhalation of short-acting bronchodilator as covariates. This model also included smoking status at baseline (current/ex-smoker) and history of ICS use as fixed effects, and centre as a random effect. The estimated adjusted treatment difference for indacaterol + glycopyrronium minus indacaterol 150 mcg and glycopyrronium 50 mcg was displayed along with the associated 95% CI. The non-inferiority of indacaterol + glycopyrronium to the concurrent administration of indacaterol 150 mcg and glycopyrronium 50 mcg was claimed if the lower bound of the two-sided 95% CI was greater than –0.1 L.

The treatment difference (indacaterol + glycopyrronium minus indacaterol 150 mcg and glycopyrronium 50 mcg) with respect to trough FEV_1 after 28 days of treatment was expected and assumed to be 0 L. A common standard deviation estimate of 0.190 L was assumed based on previous relevant studies. A total of 154 evaluable patients (77 per treatment group) would achieve a power of no less than 90% with a one-sided non-inferiority test at a significance level of 2.5%. Approximately 184 patients were randomized to adjust for an estimated combined attrition rate of 17%, an estimated exclusion rate from PPS of 12% (based on three previous Novartis trials), and an estimated dropout rate of 5%.

In ARISE, the primary objective was to assess safety of indacaterol + glycopyrronium. The Japanese health authority required a minimum of one year of safety data for 100 patients in Japan treated with indacaterol + glycopyrronium. Considering a dropout rate of approximately 15%, it was planned to randomize 120 patients to the indacaterol + glycopyrronium group. When patients were randomized to treatment with indacaterol + glycopyrronium group or tiotropium group in a ratio of 3:1, 40 patients were allocated to tiotropium. It was anticipated that approximately 300 patients needed to be screened in order to randomize 160 patients (indacaterol + glycopyrronium: 120 patients, tiotropium: 40 patients) to the study so that at least 100 patients who were randomized to indacaterol + glycopyrronium would be expected to complete the study.

In BLAZE, the superiority of indacaterol + glycopyrronium over placebo (primary objective) was evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

- H_0: There is no difference in TDI following 6 weeks of treatment in patients with moderate to severe COPD treated with indacaterol + glycopyrronium compared with placebo.
- H_a: There is a difference in TDI following 6 weeks of treatment in patients with moderate to severe COPD treated with indacaterol + glycopyrronium compared with placebo.

The primary analysis was performed on the FAS using a mixed model. The model contained treatment, BDI assessment at period baseline, reversibility components at screening visit (FEV_1 before and after inhalation of bronchodilator), country, sequence, and period as fixed effects, and patient (sequence) as a random effect. The estimated adjusted treatment difference for indacaterol + glycopyrronium minus placebo was displayed along with the associated 95% CI and *P* value (two-sided). The superiority of indacaterol + glycopyrronium over placebo was claimed if the difference in TDI total score was statistically significant at the 5% level and the 95% CI lay entirely to the right of (higher than) 0 unit. No testing for carry-over was performed as it was assumed that the two-week washout would be adequate.

In BRIGHT, the effect of indacaterol 110 mcg + glycopyrronium 50 mcg compared with placebo was evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a) using a type I error of 5%:

- H_0: There is no difference in exercise duration time (in seconds) for patients with COPD treated with indacaterol + glycopyrronium compared with placebo.
- H_a: There is a difference in exercise duration time (in seconds) for patients with COPD treated with indacaterol + glycopyrronium compared with placebo.

The primary variable was analyzed using a mixed model for the FAS. The model contained patient (sequence) as a random effect, and treatment, pre-treatment exercise period baseline (measured at Visit 3 for period 1, Visit 6 for period 2, and Visit 9 for period 3), sequence, and period as fixed effects. The least squares means and the estimated treatment difference (indacaterol + glycopyrronium versus placebo), together with the associated 95% CI and two-sided *P* value, were displayed. Superiority of indacaterol 110 mcg + glycopyrronium 50 mcg over placebo was demonstrated if the *P* value was less than the 5% significance level and the 95% CI lay entirely to the right of 0 seconds. Missing values were not imputed for the primary efficacy variable, and no adjustments for multiplicity were made for analysis of the secondary efficacy outcomes.

a) Accounting for Missing Data

In QUANTIFY, missing items of the SGRQ-C were handled as described in the SGRQ-C manual. If the number of missing values exceeded the acceptable number of items given in the manual, the SGRQ-C total score was set to "missing." For patients who completed the study but with missing SGRQ-C items during treatment, the missing SGRQ-C items were replaced by the LOCF. Symptom scores were expected to improve during treatment; therefore, the replacement of missing values with earlier measurements did not result in over-optimistic imputation, and this procedure could be regarded as conservative. Alternative strategies (i.e., multiple imputations) could be considered in case of substantial dropout. Missing SGRQ-C values at baseline were not replaced, and these patients did not contribute to the respective analyses.

In SPARK, since the negative binomial model includes the length of time the patient was in the study as an offset variable that automatically accounts for patients who discontinued prematurely, the primary analysis was done without imputation. Patients who discontinued prematurely were followed up until the end of the study (i.e., a 64-week period). During the post-treatment follow-up, adverse events including COPD exacerbations were collected. For these patients, moderate or severe COPD exacerbations that occurred within 14 days of the last treatment date were added to the number of COPD exacerbations (adjudicated events) that occurred before discontinuation from the study. As a sensitivity analysis, this augmented count of exacerbations was reanalyzed using a generalized linear model the same way as the primary analysis.

In SHINE, FEV_1, FVC, and inspiratory capacity measurements within six hours of rescue medication use or within seven days of systemic corticosteroid use were set to "missing." Systemic corticosteroid use was identified by looking at the start and end dates of exacerbations requiring treatment with systemic glucocorticosteroids recorded on the COPD exacerbation page of the eCRF. If the end date of an exacerbation requiring treatment with systemic corticosteroids was missing, then the start date of the exacerbation plus 14 days was considered the end date of the exacerbation. For trough FEV_1 and trough FVC, if the actual measurement times of the scheduled 23 hour 15 minute and 23 hour 45 minute measurements were outside of a 22 hour 45 minute to 24 hour 15 minute post-dose time window, then the individual FEV_1 (FVC) value was set to "missing." If trough FEV_1 was missing, then either the trough FEV_1 (the mean of 23 hour 15 minute and the 23 hour 45 minute FEV_1 measurements) or the pre-dose trough FEV_1 (the mean of 45 minute and 15 minute pre-dose values) was carried forward from the last non-missing visit, as long as the visit was not before Day 29, more than 11 weeks behind schedule, or a premature discontinuation visit, or an unscheduled visit.

In ILLUMINATE, if any of the values contributing to the AUC 0 hours to 12 hours were collected within six hours of rescue medication or within seven days of systemic corticosteroid use, then the individual FEV_1 value was set to "missing" before the AUC was calculated. For FEV_1 and FVC measurements, if the scheduled assessment was pre-dose but the measurement was post dose (or at the same time as the dose), or the scheduled assessment was at five minutes post dose but the measurement was taken pre-dose, or the scheduled assessment was at greater than five minutes post dose but the measurement was taken pre-dose (or the same time as the dose), the measurement was set to "missing." If the 12-hour spirometry was started but not completed for any reason, the AUC was calculated only for the portion of the 12 hours up to this point. Specifically, for those patients who had an assessment at only one time point, their AUC 0 hours to 12 hours was approximated by the observed FEV_1. For the primary analysis, if AUC 0 hours to 12 hours was missing at Visit 7 (Week 26), then the non-missing AUC 0 hours to 12 hours at Visit 5 (Week 12) was carried forward. If the Week 12 assessment was still missing, then no imputation was carried out.

In ENLIGHTEN, all available data were used in these evaluations of safety. No imputation was done for missing data.

In BEACON, if any of the values contributing to trough FEV_1 were collected within six hours of rescue medication or within seven days of systemic corticosteroid use, then the individual FEV_1 value was set to "missing" before calculation. If trough FEV_1 after 28 days of blinded treatment was missing, then the trough FEV_1 at Day 2 was carried forward. The primary analyses for trough FEV_1 were repeated for the FAS imputed with LOCF and for the PPS and FAS without LOCF.

In BLAZE, for patients who completed the study but with missing TDI in a specific treatment period, the missing TDI was kept as "missing." No cross-period imputation was performed, and the model chosen provided a valid analysis under a "missing at random" assumption. For patients who prematurely discontinued from the study, a final TDI test was collected and carried forward for the missing TDI in the same period, as appropriate.

b) Multiplicity

In SPARK, to maintain the overall type I error rate at the 5% level, the primary and key secondary efficacy analyses were performed using the following hierarchical steps:

Step 1: A two-sided superiority test of indacaterol + glycopyrronium versus glycopyrronium in terms of rate of moderate or severe COPD exacerbations during the treatment period was conducted at the type I error rate of 5% (the primary objective). If the result of this test was non-significant, then planned key secondary efficacy tests were reported as exploratory analyses.

Step 2: If the primary efficacy test was found to be significant, then a two-sided superiority test of indacaterol + glycopyrronium versus tiotropium on the rate of moderate or severe COPD exacerbations during the treatment period (the key secondary objective) was performed at alpha = 0.05. All other secondary variables were not adjusted for multiplicity.

In SHINE, to handle the issue of multiplicity, a statistical gate-keeping procedure was applied to hierarchical families of hypotheses for the primary, key, and important secondary comparisons. To ensure a familywise false-positive error rate at an overall level of less than 5%, a flexible gate-keeping procedure was employed, allowing type I error rate associated with a rejected hypothesis to be reallocated according to a set of pre-specified rules. Family 1 consisted of hypotheses to demonstrate assay sensitivity of indacaterol + glycopyrronium, indacaterol, and glycopyrronium for trough FEV_1 at Week 26 and was tested first, since these were considered the low-risk hypotheses. The primary set of end points, defined as superior improvement between indacaterol + glycopyrronium and the single components indacaterol and glycopyrronium for trough FEV_1 at Week 26, were contained in Family 2 in the hierarchical structure using the combination rule. The third end point formally tested concerned showing non-inferiority of indacaterol + glycopyrronium versus open-label tiotropium in 26-week trough FEV_1 (Family 3-A). Family 3-B consisted of three hypothesis tests (i.e., the set of key secondary end points), and at this stage a Hochberg adjustment was used to control the type I error rate (Family 3-B). Other secondary efficacy variables were analyzed for the FAS only, and treatment comparisons were displayed without an adjustment for multiplicity.

In ENLIGHTEN and ILLUMINATE, no adjustment was made for multiplicity. QUANTIFY and ARISE did not describe any adjustment for multiplicity.

In BEACON, the primary objective was tested in a confirmatory sense. All other variables were tested in an exploratory sense (significance level of 5%), and no adjustment for multiplicity was made.

In BLAZE, the key secondary objective was analyzed in the same way as the primary objective. To control the multiplicity, the primary analysis (indacaterol + glycopyrronium versus placebo) and key secondary analysis (indacaterol + glycopyrronium versus tiotropium) were tested sequentially using a hierarchical procedure: to proceed to the key secondary test in the hierarchy, the primary test must be statistically significant at $P < 0.05$.

In BRIGHT, treatment comparisons between tiotropium versus placebo and indacaterol + glycopyrronium versus tiotropium were not controlled for multiplicity. No adjustment for multiplicity was made when analyzing secondary outcomes.

c) Subgroups

In QUANTIFY, subgroups were defined by gender, age group, use of inhaled corticosteroids, and disease stage (according to GOLD). The variable defining the subgroup was assessed by adding the interaction between treatment and subgroup variable to the ANCOVA model. A statistically significant influence of the variable defining the subgroups was not seen in any of the subgroup analyses.

In SHINE, the following exploratory subgroup analyses for the positive expiratory pressure (PEP) (trough FEV_1 at Week 26 [imputed with LOCF]) were performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the FAS to explore the treatment effect by age (< 65 years, 65 to < 75 years, ≥ 75 years), sex (male, female), race (White, Black, Asian, other), severity of disease (moderate or less, severe or worse, based on the classification of severity of COPD defined in GOLD 2009), baseline smoking status (current smoker, ex-smoker), baseline ICS use (Yes/No), body mass index (BMI; males with BMI > 30 kg/m^2, males with BMI ≤ 30 kg/m^2, females with BMI > 30 kg/m^2, females with BMI ≤ 30 kg/m^2), and patient's larger value of FEV_1 reversibility after bronchodilator (reversibility ≤ 5% increase, reversibility > 5% and ≤ 12% increase, reversibility > 12% increase).

In SPARK, the following subgroup analyses were performed for the rate of moderate or severe COPD exacerbation and to the time to first moderate or severe COPD exacerbation variables. The same analysis model as the primary analysis was used, except that subgroup and treatment by subgroup interaction were added to the model:

- with and without ICS use
- smoking status at baseline (current/ex-smoker)
- gender
- age category (< 65, 65 to < 75, and ≥ 75)
- race (white, Asian, and others)
- COPD severity (severe or very severe)
- BMI (> 30 and ≤ 30)

The following subgroup analyses were performed for the primary analyses (rate of moderate or severe COPD exacerbation) only:

- region (North America, South America, Western Europe, Eastern Europe, and Asia)
- reversibility at screening (≤ 5%, > 5% and ≤ 12%, > 12%)
- history of exacerbation (< 2, ≥ 2 in the previous year)
- completers and non-completers
- northern and southern hemisphere
- for the winter season and summer season.

No information on subgroups was provided in ENLIGHTEN.

In ILLUMINATE, in order to characterize the consistency of treatment response for the primary analysis within the study population, exploratory post hoc analyses of the primary efficacy variable of AUC 0 hours to 12 hours imputed with LOCF were performed for the following demographic and disease characteristic subgroups: age (< 65, 65 to < 75, ≥ 75 years), gender, smoking status (ex-smokers, current smokers), COPD disease severity (moderate, severe), FEV_1 reversibility (reversibility ≤ 5% increase, reversibility > 5% and ≤ 12% increase, reversibility > 12% increase) and by quartiles of reversibility (FEV_1 reversibility < 10%; ≥ 10% to < 18%; ≥ 18% to < 27%; and ≥ 27%).

In BEACON, the following subgroup analyses shown below were performed for the primary efficacy end point on the PPS and modified PPS. In the subgroup analysis, the appropriate interaction term of subgroup with treatment was included as a fixed effect in the model:

- age (< 65 years, ≥ 65 years)
- gender (male, female)
- smoking status at baseline (current smoker, ex-smoker)

- ICS use at baseline (Yes/No).

In BRIGHT, the following exploratory subgroup analyses for exercise endurance time (in seconds) were performed (using the appropriate interaction term in the model and the additional covariate as a fixed effect if necessary) for the FAS to explore the treatment effect by baseline smoking status (current, ex-smokers), severity of disease (moderate or less, severe or worse based on the classification of severity of COPD defined in GOLD 2009) and baseline ICS use (Yes/No).

d) Analysis Populations

For all studies:

- FAS: all randomized patients who received at least one dose of randomized study drug. Following the intention-to-treat principle, patients were analyzed according to the treatment they were assigned to. The FAS was used for all efficacy variables unless otherwise stated.
- PPS: all patients in the FAS without any major protocol deviations. Major protocol deviations were defined in the validation analysis plan (general) and in the protocol of the blind review meeting (details) before database lock and the unblinding of the study. PPS was used for the supportive analysis to assess robustness of the primary variable.
- Safety set: all patients who received at least one dose of study drug, whether they had been randomized. Patients were analyzed according to the treatment they received. The safety set was used in the analysis of all safety variables.

In SPARK, there was also:

- Modified FAS: included all patients in the FAS except patients from site 820, which had major issues with compliance with good clinical practice. All efficacy end points, unless otherwise stated, were analyzed using the modified FAS.

3.3 Patient Disposition

SPARK had the highest proportion of patients discontinuing from the study: approximately 25% of the randomized population (Table 26). In SHINE, 10% of patients discontinued, and this [redacted] (Table 25, Table 26), while ILLUMINATE and ENLIGHTEN had discontinuations of about 17% (Table 27, Table 28). In the crossover studies, the discontinuation rate was 23% in BLAZE and 14% in BRIGHT (Table 30). BEACON had the lowest proportion of discontinuations, at 3%, and was also the shortest study (Table 29). ARISE was an open-label study, and withdrawals were 14% with indacaterol + glycopyrronium and 3% with tiotropium (Table 31). The proportion of patients who discontinued from the DB RCTs was generally similar between groups within studies; however, the placebo groups in SHINE (19% versus 10%, Table 26) and in ENLIGHTEN (21% versus 14%, Table 28) had higher proportions of discontinuations than the active comparator groups in those studies. An adverse event was the most common reason for discontinuing in most studies.

TABLE 25: PATIENT DISPOSITION: LAMA/LABA-CONTROLLED

	QUANTIFY	
	IG (N = [redacted])	**TF (N = [redacted])**
Screened, N	[redacted]	
Randomized, N	[redacted]	[redacted]
Treated, n	[redacted]	[redacted]
Completed, N (%)	[redacted]	[redacted]
Discontinued, N (%)	[redacted]	[redacted]
Adverse event	[redacted][a]	[redacted][a]
Lack of efficacy	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]
Abnormal laboratory values	[redacted]	[redacted]
Abnormal test procedure results	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Administrative problems	[redacted]	[redacted]
Subject withdrew consent	[redacted]	[redacted]
Death	[redacted]	[redacted]
Unable to use device	[redacted]	[redacted]
FAS, N	[redacted]	[redacted]
Per-protocol, N (%)	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]

FAS = full analysis set; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; TF = tiotropium + formoterol.

[a] One patient was randomized to tiotropium + formoterol at Visit 3, but inadvertently received QVA149 at Visit 4 and discontinued from treatment with QVA149 due to a serious adverse event (suspected pulmonary embolism).

Source: CSR[11]

TABLE 26: PATIENT DISPOSITION: LAMA-CONTROLLED (TIOTROPIUM)

	SHINE				SPARK			
	IG	I	G	TIO	PLA	IG	G	TIO
Screened, N	3,625				3,865			
Randomized, N	475	477	475	483	234	741	741	742
Randomized and treated						736	739	739
Completed, n (%)	437 (92)	421 (88)	422 (89)	441 (91)	189 (81)			
Discontinued, N (%)	38 (8)	56 (12)	53 (11)	42 (9)	45 (19)	171 (23)	203 (27)	183 (25)
Protocol deviation	14 (3)	8 (2)	12 (3)	10 (2)	11 (5)	13 (2)	12 (2)	12 (2)
Withdrew consent	12 (3)	13 (3)	22 (5)	11 (2)	13 (6)	33 (5)	50 (7)	44 (6)
Adverse event	5 (1)	23 (5)	13 (3)	10 (2)	10 (4)	59 (8)	67 (9)	47 (6)
Administrative problems	3 (1)	2 (< 1)	1 (< 1)	1 (< 1)	2 (1)	15 (2)	8 (1)	9 (1)
Lack of efficacy	2 (< 1)	8 (2)	2 (< 1)	5 (1)	8 (3)	18 (2)	32 (4)	38 (5)
Lost to follow-up	1 (< 1)	1 (< 1)	0	4 (1)	1 (< 1)	5 (1)	6 (1)	4 (1)
Death	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0	21 (3)	22 (3)	24 (3)
Abnormal test results	0	0	2 (< 1)	0	0	3 (< 1)	2 (< 1)	1 (< 1)
Unable to use device						3 (< 1)	1 (< 1)	0
Abnormal laboratory value						1 (< 1)	3 (< 1)	4 (1)
FAS, N (%)	474 (100)	476 (100)	473 (100)	480 (99)	232 (99)	736 (99)	739 (100)	739 (100)
Modified FAS						729 (98)	739 (100)	737 (99)
Per-protocol, N	412 (87)	428 (90)	403 (85)	405 (84)	191 (82)	666 (90)	688 (93)	685 (92)
Safety, N	474 (100)	476 (100)	473 (100)	480 (99)	232 (99)	736 (99)	740 (100)	739 (100)

FAS = full analysis set; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; PLA = placebo; TIO = tiotropium.
Source: Clinical study report (CSR) SPARK[12]; CSR SHINE.[13]

TABLE 27: PATIENT DISPOSITION: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG N = 259	FP/S N = 264
Screened, N	832	
Randomized, N (%)	259	264
Randomized and treated		
Completed, n (%)	215 (83)	217 (82)
Discontinued, N (%)	44 (17)	47 (18)
Protocol deviation	8 (3)	5 (2)
Withdrew consent	11 (4)	10 (4)
Adverse event	22 (9)	26 (10)
Administrative problems	1 (< 1)	0
Lack of efficacy	0	1 (< 1)
Lost to follow-up	0	2 (1)
Death	0	1 (< 1)
Abnormal test results	1 (< 1)	2 (1)
Unable to use device	1 (< 1)	0
Abnormal laboratory value	–	–
FAS, N (%)	258 (100)	264 (100)
Per-protocol, N (%)	237 (92)	248 (94)
Safety, N (%)	258 (100)	264 (100)

FAS = full analysis set; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 28: PATIENT DISPOSITION: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG N = 226	PLA N = 113
Screened, N	498	
Randomized, N	226	113
Randomized and treated		
Completed, n (%)	194 (86)	89 (79)
Discontinued, N (%)	32 (14)	24 (21)
Protocol deviation	2 (1)	5 (4)
Withdrew consent	11 (5)	6 (5)
Adverse event	10 (4)	6 (5)
Administrative problems	–	–
Lack of efficacy	3 (1)	3 (3)
Lost to follow-up	2 (1)	3 (3)
Death	3 (1)	1 (1)
Abnormal test results	1 (< 1)	0
Unable to use device	–	–

	ENLIGHTEN	
	IG N = 226	PLA N = 113
Abnormal laboratory value	–	–
FAS, N (%)	225 (100)	113 (100)
Per-protocol, N (%)	174 (77)	89 (79)
Safety, N (%)	225 (100)	113 (100)

FAS = full analysis set; IG = indacaterol + glycopyrronium; PLA = placebo.
Source: CSR for ENLIGHTEN.[15]

TABLE 29: PATIENT DISPOSITION: COMPONENT-CONTROLLED

	BEACON	
	IG N = 90	I AND G (Individual Components) N = 103
Screened, N	320	
Randomized, N	90	103
Randomized and treated		
Completed, n (%)	87 (97)	100 (97)
Discontinued, N (%)	3 (3)	3 (3)
Protocol deviation	0	1 (1)
Withdrew consent	–	–
Adverse event	1 (1)	1 (1)
Administrative problems	2 (2)	1 (1)
FAS, N (%)	90 (100)	103 (100)
Per-protocol, N (%)	84 (93)	97 (94)
Safety, N (%)	90 (100)	103 (100)

FAS = full analysis set; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium.
Source: Clinical study report for BEACON.[16]

TABLE 30: PATIENT DISPOSITION: CROSSOVER

	BLAZE			BRIGHT		
Screened, N	411			126		
Randomized, N (%)	247 (100)			85 (100)		
Randomized and treated						
Completed, n (%)	191 (77)			73 (86)		
Discontinued, N (%)	56 (23)			12 (14)		
Protocol deviation	13 (5)					
Withdrew consent	5 (2)			3 (4)		
Adverse event	35 (14)			6 (7)		
Administrative problems	–			2 (2)		
Lack of efficacy	1 (< 1)			–		
Lost to follow-up	1 (< 1)			–		
Death	1 (< 1)			–		
No longer requires drug				1 (1)		
Treatment at discontinuation						
IG	20 (8)			0		
TIO	19 (8)			9 (11)		
PLA	16 (7)			2 (2)		
	IG	**TIO**	**PLA**	**IG**	**TIO**	**PLA**
FAS, N (%)	223 (90)	220 (89)	218 (88)	77 (91)	83 (98)	77 (91)
Per-protocol, N (%)	194 (79)	194 (79)	195 (79)	74 (87)	80 (94)	75 (88)
Safety, N (%)	223 (90)	220 (89)	218 (88)	77 (91)	83 (98)	77 (91)

FAS = full analysis set; IG = indacaterol + glycopyrronium; PLA = placebo; TIO = tiotropium.
Source: Clinical study report (CSR) BLAZE[17]; CSR BRIGHT.[18]

TABLE 31: PATIENT DISPOSITION: OPEN LABEL

	ARISE	
	IG	**TIO**
Screened, N	230	
Randomized, N	121	39
Randomized and treated		
Completed, n (%)	104 (86)	38 (97)
Discontinued, N (%)	17 (14)	1 (3)
Protocol deviation	3 (3)	0
Withdrew consent	2 (2)	1 (3)
Adverse event	11 (9)	0
Death	1 (1)	0
FAS, N (%)	119 (98)	39 (100)
Per-protocol, N (%)	89 (74)	30 (77)
Safety, N (%)	119 (98)	39 (100)

FAS = full analysis set; IG = indacaterol + glycopyrronium; TIO = tiotropium.
Source: Clinical study report for ARISE.[19]

3.4 Exposure to Study Treatments

The longest duration of exposure was in SPARK: 434 days for indacaterol + glycopyrronium and 415 days for glycopyrronium and tiotropium (Table 47). The shortest duration of exposure was in BRIGHT, at 21 days, although this was a crossover study (Table 51). The largest difference in exposure between groups within a study was in ENLIGHTEN, in which the indacaterol + glycopyrronium group was on treatment for 337 days, and the placebo group was on treatment for 313 days (Table 49).

3.5 Critical Appraisal

3.5.1 Internal Validity

Most of the studies described patients as having received some type of training on use of the inhaler devices. Although they received training, it was not clear whether patients actually demonstrated that they knew how to use the devices before initiating therapy. Although compliance was high in the included studies, this simply reflects the number of doses actuated rather than whether the dose was delivered optimally.

Most of the studies were double-blinded; however, ARISE was an open-label RCT, and the tiotropium groups in both SHINE and SPARK were open-label. The lack of blinding of the tiotropium groups in SHINE and SPARK could introduce significant bias into the results, particularly for patient-reported outcomes such as QoL and symptoms. Withdrawals might also be affected, as patients may be influenced in their decision to stay in the trial by the fact that they are taking an established therapy such as tiotropium. Reporting of adverse events may also be biased, as patients may anticipate certain adverse effects associated with use of anticholinergics (e.g., dry mouth). This bias is further complicated by the fact that only the tiotropium group was open label in SHINE and SPARK; therefore, comparisons such as those for QoL must take this into account.

Steps appear to have been taken to ensure allocation concealment throughout the randomization process. Treatment assignment appears to have been accomplished through an automated interactive voice response system that produced randomization numbers. Randomization was stratified by smoking status in most studies. QUANTIFY did not describe stratification.

Both BLAZE and BRIGHT employed crossover designs, with a two-week washout between treatment periods in BLAZE and 3 weeks in BRIGHT. In both studies, patients received indacaterol + glycopyrronium, tiotropium, and placebo, and it is not clear what the optimal washout period is for bronchodilators, nor why the washout period differed between these two studies.

Across the studies, adjustments appear to have been made to account for missing data, with the exception of ENLIGHTEN, which was a safety study in which all available data were used in the analysis.

QUANTIFY was a non-inferiority study that appeared to use an appropriate threshold of 4 for change from baseline in the SGRQ. The MCID for the SGRQ is 4 points (APPENDIX 5: VALIDITY OF OUTCOME MEASURES). The BEACON study tested the non-inferiority of a fixed-dose combination of indacaterol + glycopyrronium versus a combination of indacaterol and glycopyrronium administered as separate inhalers. The non-inferiority threshold for trough FEV_1 was a difference of 100 mL, and this also appears to fall within the accepted MCID (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).

There was a high rate of withdrawals from SPARK — approximately 25% across groups. Once the proportion of withdrawals becomes this high, there is concern that the original allocation of randomized patients has been compromised. A key purpose of randomization is to ensure that the groups being

compared are as balanced as possible with respect to baseline characteristics, but if a larger proportion of one population (males, for instance) withdraws from a given group than from the other groups, this might affect results. There was no clear difference in rate of withdrawals between groups, and this makes determination of potential direction of bias a significant challenge.

3.5.2 External Validity

Most of the included studies were 26 weeks in duration or less, the exceptions being SPARK (64 to 76 weeks), ENLIGHTEN (52 weeks), and the open-label RCT ARISE (52 weeks). This is not likely a sufficient duration to assess key clinical outcomes such as mortality and mortality due to COPD. Even among the longer-term studies, ENLIGHTEN was a placebo-controlled study, SPARK enrolled only severe to very severe COPD patients, and ARISE was an open-label study. Therefore, even the longer-term studies were limited in their ability to assess the impact on key clinical outcomes of a combination of indacaterol + glycopyrronium versus another LAMA/LABA combination in a population that included patients with moderate COPD, with a DB RCT design.

ARISE was conducted entirely in Japan; therefore, the findings of this study may have limited generalizability to the Canadian population. QUANTIFY was conducted in Germany, and this might also limit generalizability to the Canadian population. The population was 99% white, and this may not reflect the multicultural population of Canada. QUANTIFY is a particularly important study, as it is the only study that compared indacaterol + glycopyrronium with another LAMA/LABA combination.

The included studies enrolled patients as young as 40 years, and this would be considered young for a disease that typically begins in the later 50s and early 60s. However, despite this relatively young minimum age for inclusion, the average age of patients was typically in the early to mid-60s, which is more consistent with the COPD population in Canada.[36]

In many of the included studies, the mean post-bronchodilator reversibility was around 20%, suggesting that a number of patients may have had asthma along with COPD. This might be considered a high proportion compared with what one would expect to see in the general COPD population. The implication is that these patients with underlying asthma may be more responsive to bronchodilators than to ICS. Subgroup data from SHINE suggests that baseline reversibility may affect spirometry results during the study, as patients with less reversibility (5% or less) appeared to derive less benefit from indacaterol + glycopyrronium than patients with baseline reversibility greater than 12%. These data are limited somewhat by a lack of statistical power and by the multiple comparisons being made; however, they generate the hypothesis that baseline bronchodilator reversibility may have a significant impact on patients' response to indacaterol + glycopyrronium.

The majority of patients across the studies were male, and this reflects the current COPD population. However, with the majority of current smokers being female, it is anticipated that in the near future there may be more females than males with COPD.

Many of the included studies assessed dyspnea using a scoring system; however, most used BDI/TDI scores rather than Borg dyspnea scores. According to the clinical expert, the Borg scoring system is the one more commonly used in practice. Therefore, this might affect the generalizability of the dyspnea data from the included studies.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 10), according to the type of study. See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Deaths

a) LAMA/LABA-Controlled Study

In QUANTIFY, there were three deaths in each of the indacaterol + glycopyrronium (myocardial infarction, pulmonary embolism, and not specified) and tiotropium + formoterol (acute heart failure, coronary artery disease, and acute dyspnea/brain injury) groups (Table 32).

b) LAMA-Controlled Studies (Tiotropium)

In SHINE, there was one death in each of the indacaterol + glycopyrronium and glycopyrronium groups and two deaths in the indacaterol group (Table 33). In SPARK, 3% of patients died in each group. The most common reason for death was COPD, followed by cardiorespiratory arrest (Table 33).

c) ICS/LABA-Controlled Study

In ILLUMINATE, there was one death with fluticasone propionate + salmeterol (sudden cardiac death) and none in the indacaterol + glycopyrronium group.

d) Placebo-Controlled Study

In ENLIGHTEN, there were four deaths in the indacaterol + glycopyrronium group and one death in the placebo group. Of the four deaths in the indacaterol + glycopyrronium group, three were due to a COPD exacerbation.

e) Component Study

There were no deaths in BEACON.

f) Crossover Studies

There was one death across both crossover studies. In the BLAZE study, a patient being treated with indacaterol + glycopyrronium died of acute heart failure.

g) Open-Label Study

In ARISE, there was one death of an indacaterol + glycopyrronium patient.

3.6.2 Exacerbations

a) LAMA/LABA-Controlled Study

In QUANTIFY, the proportion of patients with a moderate or severe exacerbation did not differ between indacaterol + glycopyrronium (13%) and tiotropium + formoterol (15%) groups by the end of the 26-week treatment period (Table 32).

b) LAMA-Controlled Studies (Tiotropium)

As the primary outcome of SPARK, the superiority of indacaterol + glycopyrronium was tested versus glycopyrronium in reducing the rate of moderate to severe exacerbations. The exacerbation rate was statistically significantly lower with indacaterol + glycopyrronium versus glycopyrronium (ratio of rates 0.88; 95% CI, 0.77 to 0.99; *P* = 0.038) at the end of 64 to 76 weeks. There was no statistically significant difference in event rate between indacaterol + glycopyrronium and tiotropium (ratio of rates 0.90; 95% CI, 0.79 to 1.02; *P* = 0.096) (Table 33).

In SPARK, subgroup analyses were provided for the primary outcome of moderate to severe exacerbations (Table 65). With respect to subgroup by COPD severity, there was a statistically significant reduction in exacerbation rate for indacaterol + glycopyrronium versus tiotropium in patients with severe COPD (ratio of rates 0.85; 95% CI, 0.74 to 0.98; *P* = 0.023) but not in those with very severe COPD. In subgroups based on smoking status, there was no statistically significant difference between indacaterol + glycopyrronium and tiotropium in subgroups of either current smokers or former smokers.

In SHINE, the proportions were similar between the indacaterol + glycopyrronium and tiotropium groups: 18% in each group after 26 weeks. In SHINE, 26% of placebo patients experienced a moderate or severe exacerbation compared with 22% of indacaterol and 19% of glycopyrronium patients (Table 33).

c) ICS/LABA-Controlled Study (Fluticasone Propionate + Salmeterol)

Exacerbations were not reported as an efficacy outcome.

d) Crossover Studies

Exacerbations were not reported as an efficacy outcome in either of the crossover studies.

e) Open-Label Study

The proportion of patients experiencing a moderate or severe exacerbation was 22% with indacaterol + glycopyrronium and 21% with tiotropium (Table 38).

3.6.3 Health-Related Quality of Life

a) LAMA/LABA-Controlled Study

In QUANTIFY, at end of study (26 weeks), non-inferiority was shown between indacaterol + glycopyrronium and tiotropium + formoterol in change from baseline in total score on the SGRQ-C (Table 32). The least squares mean difference (LS MD) between groups of –0.69 (95% CI, –2.31 to 0.92) in the FAS and –0.77 (95% CI, –2.48 to 0.93; *P* = 0.373) in the PPS met the criteria for non-inferiority, as the upper boundary of the confidence interval was lower than the predefined margin for non-inferiority of four points. A four-point change in total score is considered to be the MCID for this instrument. The difference between groups did not meet the pre-specified criteria for superiority.

In QUANTIFY, subgroup analyses were performed for the primary outcome of SGRQ-C total scores (Table 64). No interaction *P* values were reported. [redacted] between indacaterol + glycopyrronium and tiotropium + formoterol in any of the subgroups, by GOLD status or by age.

b) LAMA-Controlled Studies (Tiotropium)

In SHINE, there was a statistically significant decrease (improvement) in SGRQ-C total scores at end of study (26 weeks) when comparing indacaterol + glycopyrronium with tiotropium (LS MD –2.13; 95% CI, –3.72 to –0.54; *P* = 0.009) and with placebo (LS MD –3.01; 95% CI, –5.05 to –0.97; *P* = 0.002) (Table 33).

In SPARK, there was a statistically significant decrease (improvement) in SGRQ-C total scores at end of study (64 to 76 weeks) when comparing indacaterol + glycopyrronium with tiotropium (LS MD –2.69; 95% CI, –4.17 to –1.21; *P* < 0.001) and with glycopyrronium (LS MD –2.07; 95% CI, –3.57 to –0.58; *P* = 0.007) (Table 33).

c) ICS/LABA-Controlled Study

There was no statistically significant difference between indacaterol + glycopyrronium and fluticasone propionate + salmeterol for change from baseline to end of study (26 weeks) in SGRQ-C total scores (Table 34).

d) Open-Label Study

The SGRQ was assessed in ARISE; however, no statistical analyses were provided (Table 38).

HRQoL was not reported in ENLIGHTEN, BEACON, BLAZE, or BRIGHT.

3.6.4 Dyspnea Scores

a) LAMA/LABA-Controlled Study

There was no statistically significant difference between indacaterol + glycopyrronium and tiotropium + formoterol in dyspnea scores measured by BDI/TDI at end of study (26 weeks) (Table 32).

b) ICS/LABA-Controlled Study

There were statistically significantly greater (improved) dyspnea scores with indacaterol + glycopyrronium than with fluticasone propionate + salmeterol at Week 26 (LS MD 0.76; 95% CI, 0.26 to 1.26; $P = 0.003$) (Table 34). The MCID is 1 for this instrument; thus, the difference versus tiotropium is unlikely to be clinically significant.

c) Crossover Studies

In BLAZE, there was a statistically significant improvement in TDI focal scores for indacaterol + glycopyrronium versus placebo (LS MD 1.37; 95% CI, 0.95 to 1.79; $P < 0.001$) and versus tiotropium (LS MD 0.49; 95% CI, 0.07 to 0.91; $P = 0.021$) after six weeks of treatment (Table 37). The MCID is 1 for this instrument; thus, the difference versus tiotropium is unlikely to be clinically significant.

In BRIGHT, there was no difference in change in Borg dyspnea scores between indacaterol + glycopyrronium versus placebo or versus tiotropium after three weeks of treatment (Table 37).

Dyspnea scores were not reported in the other studies.

3.6.5 Symptoms

a) LAMA-Controlled Studies

In SPARK, there was a statistically significant improvement in symptom scores at end of study (64 to 76 weeks) for indacaterol + glycopyrronium versus tiotropium (LS MD –0.44; 95% CI, –0.62 to –0.26; $P < 0.001$) (Table 33).

In SHINE, there was a statistically significant improvement in symptoms scores at end of study (26 weeks) for indacaterol + glycopyrronium versus tiotropium (LS MD –0.24; 95% CI, –0.46 to –0.01; $P = 0.043$) (Table 33). The clinical significance of these differences is unknown.

b) ICS/LABA-Controlled Study

There was no statistically significant difference in symptom scores between indacaterol + glycopyrronium and fluticasone propionate + salmeterol over 26 weeks (Table 34).

c) Placebo-Controlled Study

There was a statistically significant improvement in symptom scores for indacaterol + glycopyrronium versus placebo over 52 weeks (LS MD –0.57; 95% CI, –1.01 to –0.13; *P* = 0.011) (Table 35).

d) Component-Controlled Study

There was no statistically significant difference in symptom scores between indacaterol + glycopyrronium administered in the combination device and the separate components of indacaterol and glycopyrronium administered simultaneously with separate devices at Week 4 (Table 36).

e) Crossover Studies

End of study symptom scores were improved for indacaterol + glycopyrronium versus placebo in BLAZE (after six weeks), and this difference was statistically significant (LS MD –0.72; 95% CI, –0.94 to –0.49; *P* < 0.001). There was no statistically significant difference in symptom scores between indacaterol + glycopyrronium and tiotropium at end of study (LS MD –0.03; 95% CI, –0.26 to 0.19; *P* = 0.759) (Table 37). Symptom scores were not reported in BRIGHT.

3.6.6 Forced Expiratory Volume in One Second

a) LAMA/LABA-Controlled Study

Pre-dose FEV_1 at end of study (26 weeks) was improved to a statistically significantly greater extent with indacaterol + glycopyrronium than with tiotropium + formoterol in QUANTIFY (LS MD 0.07 L; 95% CI, 0.04 to 0.10; *P* < 0.001) (Table 32). However, this difference was less than what is typically accepted as the MCID for change in FEV_1 of 0.1 L.

b) LAMA-Controlled Studies (Tiotropium)

In SHINE, trough FEV_1 was improved to a greater extent with indacaterol + glycopyrronium than with either indacaterol (LS MD 0.07 L; 95% CI, 0.05 to 0.10; *P* < 0.001) or with glycopyrronium (LS MD 0.09 L; 95% CI, 0.06 to 0.11; *P* < 0.001) after 26 weeks. Superiority of indacaterol + glycopyrronium over these two components was the primary outcome of this study, and indacaterol + glycopyrronium did demonstrate superiority. Trough FEV_1 was also improved to a greater extent with indacaterol + glycopyrronium than with tiotropium in SHINE, and this difference was statistically significant (LS MD 0.08 L; 95% CI, 0.05 to 0.10; *P* < 0.001). There was also a statistically significant improvement in trough FEV_1 versus placebo (LS MD 0.020 L; 95% CI, 0.17 to 0.24; *P* < 0.001) (Table 33). However, these between-group differences were all less than the MCID of 0.1 L.

In SPARK, trough FEV_1 was also statistically significantly improved for indacaterol + glycopyrronium versus tiotropium (LS MD 0.07 L; 95% CI, 0.06 to 0.09; *P* < 0.001), and versus glycopyrronium (LS MD 0.08 L; 95% CI, 0.07 to 0.10; *P* < 0.001); however, this difference is unlikely to be clinically significant.

In SHINE, subgroup analyses were performed for trough FEV_1 (Table 66). With respect to COPD severity, there was a statistically significant difference between indacaterol + glycopyrronium and indacaterol, glycopyrronium, tiotropium, and placebo in both patients who had moderate or better COPD, and in those who had severe COPD. These differences were only clinically significant for the comparison with placebo. The same was true for smoking status, with statistically significant differences for indacaterol + glycopyrronium versus all groups in both current smokers and former smokers, and for age (patients < 65 years, 65 to < 75 years, and ≥ 75 years of age), but with clinically significant differences limited to placebo. Trough FEV_1 results were also analyzed by bronchodilator reversibility. In patients with greater reversibility (> 12%), there were statistically significant differences between indacaterol + glycopyrronium and all other comparator groups, but in patients with less reversibility (≤ 5%), there was

no statistically significant difference in trough FEV_1 results for indacaterol + glycopyrronium versus any of its comparators. Of the statistically significant differences, clinical significance was only consistently seen versus placebo.

c) ICS/LABA-Controlled Study

There was a statistically and clinically significant improvement in FEV_1 AUC (0 hours to 12 hours) for indacaterol + glycopyrronium versus fluticasone propionate + salmeterol in ILLUMINATE after 26 weeks (LS MD 0.14 L; 95% CI, 0.10 to 0.18; $P < 0.001$) (Table 34). The demonstration of superiority of indacaterol + glycopyrronium over fluticasone propionate + salmeterol was the primary outcome of this study; therefore, the study achieved its primary outcome.

In ILLUMINATE, subgroup analyses were performed on the primary outcome of FEV_1 AUC (0 hours to 12 hours) (Table 67). There were statistically significant differences between indacaterol + glycopyrronium and fluticasone propionate + salmeterol across all age subgroups (< 65, 65 to < 75 and ≥ 75 years of age), in both current and former smokers, and in patients with moderate and with severe COPD. Patients with higher baseline reversibility (> 5% to ≤ 12% and > 12%) had statistically significant differences in favour of indacaterol + glycopyrronium, but not at the lowest level of reversibility (≤ 5%).

d) Component-Controlled Study

The primary outcome of BEACON was to assess the non-inferiority of the fixed-dose combination versus the components administered simultaneously. Non-inferiority of indacaterol 110 mcg + glycopyrronium 50 mcg once daily to the concurrent administration of indacaterol 150 mcg daily and glycopyrronium 50 mcg daily was demonstrated if the two-sided 95% CI lay entirely to the right of (higher than) –0.100 L, in the PPS. Non-inferiority was demonstrated if the 95% CI of the LS MD –0.005 (95% CI, –0.051 to 0.040, PP analysis set) was above –0.100 L (Table 36). The same analysis was also carried out on the FAS, and non-inferiority was also demonstrated in the population with an LS MD of –0.024 L; 95% CI, –0.073 to 0.026).

In BEACON, there were no statistically significant differences between groups for trough FEV_1 in either of the subgroups based on age or on smoking status (Table 69).

e) Placebo-Controlled Study

There was a statistically and clinically significant improvement in pre-dose FEV_1 for indacaterol + glycopyrronium versus placebo in ENLIGHTEN (LS MD 0.189 L; 95% CI, 0.126 to 0.252; $P < 0.001$) (Table 35).

f) Crossover Studies

In BLAZE, there was a statistically significant improvement in FEV_1 AUC (5 minutes to 4 hours) for indacaterol + glycopyrronium versus placebo (LS MD 0.333 L; 95% CI, 0.306 to 0.360; $P < 0.001$) and versus tiotropium (LS MD 0.106 L; 95% CI, 0.079 to 0.133; $P < 0.001$) after 6 weeks' treatment (Table 37).

In BRIGHT, there was a statistically significant improvement in trough FEV_1 for indacaterol + glycopyrronium versus placebo (LS MD 0.20 L; 95% CI, 0.15 to 0.26; $P < 0.001$) and versus tiotropium (LS MD 0.10 L; 95% CI, 0.05 to 0.15; $P < 0.001$) after 3 weeks' treatment (Table 37).

g) Open-Label Study

Change in pre-dose FEV_1 was assessed in ARISE, but no statistical analysis was provided (Table 38).

3.6.7 Health Care Resource Utilization

a) LAMA-Controlled Study

In SPARK, after 64 to 76 weeks, 15% of indacaterol + glycopyrronium and 15% of glycopyrronium patients had been hospitalized versus 11% of patients treated with tiotropium. The mean number of hospital admissions was 1.4 per person hospitalized in each group. In SPARK, 5% of indacaterol + glycopyrronium patients and glycopyrronium patients had an emergency room admission, while 4% of patients treated with tiotropium had an emergency room admission. In SPARK, 76% of patients treated with indacaterol + glycopyrronium did not have an unscheduled doctor visit, versus 75% of patients treated with tiotropium and 74% of patients treated with glycopyrronium (Table 33).

Health care resource utilization was not reported as an efficacy outcome in the other studies.

3.6.8 Exercise Tolerance

a) Crossover Study

In BRIGHT, there was a statistically significant increase in exercise endurance for indacaterol + glycopyrronium versus placebo after 3 weeks (LS MD 59.5 seconds; 95% CI, 17.7 to 101.3; $P = 0.006$). There was no statistically significant difference in exercise endurance between indacaterol + glycopyrronium and tiotropium groups (Table 37).

3.6.9 Other Efficacy Outcomes

Compliance was high (> 97%) in all groups in all studies reporting (Table 53, Table 54, Table 55, Table 56, Table 57, Table 58, Table 59).

The use of rescue medications decreased in all groups in all studies reporting. These reductions were statistically significantly greater for indacaterol + glycopyrronium versus indacaterol and glycopyrronium, as well as tiotropium and placebo in SHINE (Table 54). There were also statistically significant reductions in use of rescue medications in SPARK, when indacaterol + glycopyrronium was compared with indacaterol (LS MD –0.30; 95% CI, –0.57 to –0.03; $P = 0.027$), glycopyrronium (LS MD –0.66; 95% CI, –0.93 to –0.39; $P < 0.001$), and tiotropium (LS MD –0.54; 95% CI, –0.81 to –0.27; $P < 0.001$), as well as versus placebo (LS MD –0.96; 95% CI, –1.29 to –0.62; $P < 0.001$) (Table 54). There was a statistically significant reduction in mean puffs used for indacaterol + glycopyrronium versus fluticasone propionate + salmeterol (LS MD –0.39; 95% CI, –0.71 to –0.06; $P = 0.09$) (Table 55).

TABLE 32: KEY EFFICACY OUTCOMES: LAMA/LABA-CONTROLLED

	QUANTIFY	
Moderate/Severe Exacerbations	**IG N = 476**	**TF N = 458**
Patients, N (%)	62 (13)	70 (15)
RR (95% CI)	0.852 (0.622 to 1.169)	
P value	*P* = 0.323	
Deaths		
Number of deaths, N (%)	3 (1)	3 (1)
SGRQ-C total score		
Mean (SD) baseline, FAS	44.70 (17.718)	45.68 (17.720)
Mean (SD) change, EOS (26 weeks)	–3.14 (12.059)	–2.19 (12.301)
LS MD (95% CI)[a]	–0.69 (–2.31 0.92)	
P value	*P* = 0.399	
Mean (SD) baseline, PP	44.84 (17.93)	44.59 (17.37)
Mean (SD) change, EOS	–3.89 (11.84)	–2.55 (12.14)
LS MD (95% CI)[a]	–0.77 (–2.48 to 0.93)	
P value	*P* = 0.373	
Dyspnea: BDI/TDI		
Mean (SD) baseline	6.53 (2.00)	6.37 (2.08)
LS Mean change, EOS (26 weeks)	1.13	0.75
LS MD (95% CI)[a]	0.38 (–0.06 to 0.82)	
P value	*P* = 0.087	
FEV_1 (L), pre-dose		
Mean (SD) baseline	1.33 (0.48)	1.31 (0.45)
LS Mean change, EOS (26 weeks)	0.17	0.10
LS MD (95% CI)[a]	0.07 (0.04 to 0.10)	
P value	*P* < 0.001	

BDI = Baseline Dyspnea Index; CI = confidence interval; EOS = end of study; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; LS = least squares; MD = mean difference; PP = per-protocol; RR = relative risk; SD = standard deviation; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TDI = Transition Dyspnea Index; TF = tiotropium + formoterol.
[a] Analysis of covariance (ANCOVA) model: Variable = baseline, centre, treatment.
Source: Clinical study report for QUANTIFY.[11]

TABLE 33: KEY EFFICACY OUTCOMES: VERSUS LAMA (TIOTROPIUM)

	SHINE (EOS = 26 Weeks)					SPARK (EOS = 64 to 76 Weeks)		
Moderate/ Severe Exacerbations	**IG N = 474**	**I N = 476**	**G N = 473**	**TIO N = 480**	**PLA N = 232**	**IG N = 729**	**G N = 739**	**TIO N = 737**
Patients with ≥ 1, N (%)	85 (18)	103 (22)	89 (19)	85 (18)	60 (26)	202 (28)	192 (26)	186 (25)
Exacerbation rate per year	NR	NR	NR	NR	NR	0.94	1.07	1.06
Model-based rate estimate (95% CI)	NR	NR	NR	NR	NR	0.84 (0.75 to 0.94)	0.95 (0.85 to 1.06)	0.93 (0.83 to 1.04)
Ratio of rates (95% CI), IG versus	–	–	–	–	–	–	0.88 (0.77 to 0.99)	0.90 (0.79 to 1.02)
HR, time to first event, (95% CI) versus PLA	–	–	–	–	0.56 (0.40 to 0.78)	–	–	–
P value	–	–	–	–	*P* < 0.001	–	*P* = 0.038	*P* = 0.096
Mortality								
Deaths, N (%)	1 (< 1)	2 (< 1)	1 (< 1)	3 (1)	0	23 (3)	22 (3)	25 (3)
SGRQ-C total								
Mean (SE) baseline	46.8 (0.9)	46.8 (0.8)	47.8 (0.9)	46.5 (0.9)	46.1 (1.2)	52.1	50.5	51.3
LS Mean (SE) at EOS	37.0 (0.68)	38.1 (0.68)	38.2 (0.69)	39.1 (0.68)	40.0 (0.94)	43.4 (0.78) N = 600	45.5 (0.78) N = 564	46.1 (0.78) N = 579
LS MD (95% CI) EOS, IG versus		–1.09 (–2.68 to 0.50)	–1.18 (–2.78 to 0.42)	–2.13 (–3.72 to –0.54)	–3.01 (–5.05 to –0.97)		–2.07 (–3.57 to –0.58)	–2.69 (–4.17 to –1.21)
P value		*P* = 0.179	*P* = 0.149	*P* = 0.009	*P* = 0.002		*P* = 0.007	*P* < 0.001
Symptom scores, 24 hours								
Mean baseline	6.94 (0.14)	6.78 (0.14)	6.89 (0.13)	6.83 (0.14)	6.76 (0.20)	7.31 N = 708	7.07 N = 724	7.24 N = 709
LS Mean (SE) over treatment period	–1.65 (0.09)	–1.53 (0.09)	–1.39 (0.09)	–1.42 (0.09)	–0.98 (0.13)	–1.67 (0.09)	–1.30 (0.09)	–1.23 (0.09)
LS MD (95% CI) at EOS, IG versus		–0.13 (–0.36 to	–0.26 (–0.49 to	–0.24 (–0.46 to	–0.67 (–0.96 to		–0.37 (–0.55 to	–0.44 (–0.62 to

	SHINE (EOS = 26 Weeks)					SPARK (EOS = 64 to 76 Weeks)		
Moderate/ Severe Exacerbations	**IG N = 474**	**I N = 476**	**G N = 473**	**TIO N = 480**	**PLA N = 232**	**IG N = 729**	**G N = 739**	**TIO N = 737**
		0.10)	–0.03)	–0.01)	–0.39)		–0.19)	–0.26)
P value		*P* = 0.272	*P* = 0.025	*P* = 0.043	*P* < 0.001		*P* < 0.001	*P* < 0.001
Hospital admissions								
Patients, n (%)	NE	NE	NE	NE	NE	106 (15)	110 (15)	84 (11)
Mean (SD)	NE	NE	NE	NE	NE	1.4 (0.69)	1.4 (0.69)	1.4 (0.83)
Emergency visits								
Patients, n (%)	NE	NE	NE	NE	NE	34 (5)	37 (5)	31 (4)
Mean (SD)	NE	NE	NE	NE	NE	1.3 (0.57)	1.5 (0.99)	1.5 (1.31)
Doctor visits (unscheduled)								
Patients with 0, n (%)	NE	NE	NE	NE	NE	553 (76)	544 (74)	554 (75)
1	NE	NE	NE	NE	NE	102 (14)	111 (15)	95 (13)
2	NE	NE	NE	NE	NE	41 (6)	37 (5)	33 (5)
3	NE	NE	NE	NE	NE	15 (2)	21 (3)	22 (3)
≥ 4	NE	NE	NE	NE	NE	18 (3)	26 (4)	33 (5)
Trough FEV_1, L								
Mean (SE) baseline	1.28 (0.02)	1.29 (0.02)	1.28 (0.02)	1.27 (0.02)	1.29 (0.04)	0.90	0.90	0.91
LS Mean (SE) Week 26	1.45 (0.01)	1.38 (0.01)	1.36 (0.01)	1.37 (0.01)	1.25 (0.02)	1.08 (0.01)	0.99 (0.01)	1.00 (0.01)
LS MD (95% CI)[a], IG versus		0.07 (0.05 to 0.10)	0.09 (0.06 to 0.11)	0.08 (0.05 to 0.10)	0.21 (0.17 to 0.24)		0.08 (0.07 to 0.10)	0.07 (0.06 to 0.09)
		P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001		*P* < 0.001	*P* < 0.001

CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; G = glycopyrronium; HR = hazard ratio; I = indacaterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; LS = least squares; MD = mean difference; NE = not evaluated; NR = not reported; PLA = placebo; SD = standard deviation; SE = standard error; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TIO = tiotropium.

[a] Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + centre (region) + error. Centre was included as a random effect nested within region.

Source: Clinical study report (CSR) SPARK[12]; CSR SHINE.[13]

TABLE 34: KEY EFFICACY OUTCOMES: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG (N = 258)	FP/S (N = 264)
Mortality		
Deaths, N (%)	0	1 (< 1)
SGRQ-C total score		
Mean (SD) baseline	42.01	42.72
LS mean (SE)	35.45 (1.44)	36.68 (1.39)
LS mean difference (95% CI)	–1.24 (–3.33 to 0.85)	
P value	*P* = 0.245	
Symptom scores, 24-hour		
Mean baseline	6.43	6.24
LS mean (SE) over treatment period	–1.28 (0.14)	–1.24 (0.14)
LS mean (95% CI) difference at EOS (26 weeks)	–0.05 (–0.29 to 0.20)	
P value	*P* = 0.715	
Dyspnea, TDI focal score		
Mean (SE) baseline	6.80	6.65
LS mean (SE) Week 26	2.36 (0.39)	1.60 (0.38)
LS MD (95% CI)	0.76 (0.26 to 1.26)	
P value	*P* = 0.003	
FEV_1 AUC 0 hours to 12 hours		
Mean (SE) baseline	1.45	1.40
LS mean (SE) Week 26	1.69 (0.03)	1.56 (0.03)
LS MD (95% CI)[a, b]	0.14 (0.10 to 0.18)	
P value	*P* < 0.001	

AUC = area under the curve; CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LS = least squares; MD = mean difference; SE = standard error; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TDI = Transition Dyspnea Index.

[a] MIXED model: FEV_1 AUC (0 hours to 12 hours) = treatment + baseline FEV_1 + baseline ICS + FEV_1 reversibility components + smoking status + region + centre (region). Centre is included as a random effect nested within region.
Baseline is defined as the average of the –45 minute and –15 minute FEV_1 values taken on Day 1 prior to first dose.

[b] LOCF (last observation carried forward): If the AUC (0 hours to 12 hours) is missing at Week 26, then the non-missing AUC (0 hours to 12 hours) at Week 12 was carried forward for the analysis.

Source: Clinical study report for ILLUMINATE.[14]

TABLE 35: KEY EFFICACY OUTCOMES: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG N = 225	PLA N = 113
Moderate/Severe Exacerbation		
Patients, n (%)	57 (25)	25 (22)
Time to first exacerbation, HR (95% CI)	1.04 (0.64 to 1.70)	
P value	*P* = 0.878	
Mortality		
Deaths, N (%)	4 (2)	1 (1)
Symptom scores, total (daily diary)		
Mean baseline	7.48	7.41
LS Mean (SE) over 52 weeks	–2.34 (0.21)	–1.77 (0.24)
LS mean difference (95% CI)	–0.57 (–1.01 to –0.13)	
P value	*P* = 0.011	
FEV_1, Pre-dose, L		
Mean baseline	1.43	1.49
Treatment LS mean (SE) Week 52	1.61 (0.02)	1.42 (0.03)
LS MD (95% CI)	0.189 (0.126 to 0.252)	
P value	*P* < 0.001	

CI = confidence interval; FEV_1 = forced expiratory volume in one second; HR = hazard ratio; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; PLA = placebo; SE = standard error.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 36: KEY EFFICACY OUTCOMES: COMPONENT-CONTROLLED

	BEACON	
	IG N = 90	I and G (Individual Components) N = 103
Symptom scores, total (daily diary)		
Mean (SE) baseline	5.25 (0.28)	5.74 (0.30)
LS Mean (SE) over 4 weeks	–0.42 (0.14)	–0.49 (0.13)
LS MD (95% CI)	0.07 (–0.24 to 0.39)	
P value		
Mortality		
Deaths, N (%)	0	0
Trough FEV_1, L		
Mean (SE) baseline, PPS[a]	1.46 (0.06) N = 81	1.43 (0.05) N = 96
Treatment LS mean (SE) Week 4[b]	1.46 (0.02)	1.47 (0.02)
LS MD (95% CI), PPS	–0.005 (–0.051 to 0.040)	
LS MD (95% CI), FAS	–0.024 (–0.073 to 0.026)	

CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; SE = standard error.
[a] Per-protocol set used for non-inferiority analysis.
[b] Non-inferiority of indacaterol 110 mcg + glycopyrronium 50 mcg daily to the concurrent administration of indacaterol 150 mcg daily and glycopyrronium 50 mcg daily is demonstrated if the two-sided 95% confidence interval lies entirely to the right of (higher than) –100 mL.
Source: Clinical study report for BEACON.[16]

TABLE 37: KEY EFFICACY OUTCOMES: CROSSOVER

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
Moderate/severe exacerbations						
Patients, n (%)	NE	NE	NE	NE	NE	NE
Symptom scores, 24 hour						
Mean baseline	5.57 (0.20)	5.72 (0.19)	5.48 (0.19)	NE	NE	NE
LS Mean (SE) over treatment period	–0.61 (0.10)	–0.58 (0.09)	0.11 (0.10)	NE	NE	NE
LS MD (95% CI) at EOS, IG versus		–0.03 (–0.26 to 0.19)	–0.72 (–0.94 to –0.49)	NE	NE	NE
P value		*P* = 0.759	*P* < 0.001	NE	NE	NE
Deaths						
Number of deaths, N (%)	1 (< 1)	0	0	0	0	0
Dyspnea, TDI focal score						
Mean (SE) baseline	7.34 (0.14)	7.31 (0.15)	7.33 (0.15)	NE	NE	NE
LS Mean (SE) Week 6	0.88 (0.18)	0.39 (0.18)	–0.49 (0.18)	NE	NE	NE
LS MD (95% CI), IG versus		0.49 (0.07 to 0.91)	1.37 (0.95 to 1.79)	NE	NE	NE
P value		*P* = 0.021	*P* < 0.001	NE	NE	NE
FEV_1 AUC (5 minutes to 4 hours)						
Mean (SE) baseline	1.330 (0.032)	1.339 (0.032)	1.353 (0.033)	NE	NE	NE
LS Mean (SE) Week 6	1.636 (0.012)	1.529 (0.012)	1.302 (0.012)	NE	NE	NE
LS MD (95% CI), IG versus		0.106 (0.079 to 0.133)	0.333 (0.306 to 0.360)	NE	NE	NE
P value		*P* < 0.001	*P* < 0.001	NE	NE	NE
Exercise endurance, seconds						
Mean (SE) baseline	NE	NE	NE	435.1 (23.4)	438.5 (24.1)	438.8 (24.1)
LS Mean (SE) Week 3	NE	NE	NE	507.8 (19.3)	514.6 (19.0)	448.3 (19.5)
LS MD (95% CI), IG versus	NE	NE	NE		–6.7 (–47.5 to 34.0)	59.5 (17.7 to 101.3)
P value	NE	NE	NE		*P* = 0.744	*P* = 0.006
IC, pre-exercise, L						
Mean (SE) baseline	NE	NE	NE	2.01 (0.07)	2.07 (0.07)	2.08 (0.07)

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
LS Mean (SE) Week 3	NE	NE	NE	2.34 (0.03)	2.19 (0.03)	2.01 (0.03)
LS MD (95% CI), IG versus	NE	NE	NE		0.15 (0.07 to 0.23)	0.34 (0.25 to 0.42)
P value	NE	NE	NE		*P* < 0.001	*P* < 0.001
FEV_1, trough, L						
Mean (SE) baseline	NE	NE	NE	1.35 (0.06)	1.38 (0.06)	1.34 (0.05)
LS Mean (SE) Week 3	NE	NE	NE	1.53 (0.02)	1.43 (0.02)	1.33 (0.02)
LS MD (95% CI), IG versus	NE	NE	NE		0.10 (0.05 to 0.15)	0.20 (0.15 to 0.26)
P value	NE	NE	NE		*P* < 0.001	*P* < 0.001
Dyspnea, Borg CR10 at peak						
Mean (SE) baseline	NE	NE	NE	6.95 (0.28)	7.18 (0.28)	7.29 (0.32)
LS Mean (SE) Week 3	NE	NE	NE	7.01 (0.27)	6.84 (0.26)	7.05 (0.27)
LS MD (95% CI), IG versus	NE	NE	NE		0.17 (–0.36 to 0.71)	–0.04 (–0.59 to 0.51)
P value	NE	NE	NE		*P* = 0.523	*P* = 0.893

AUC = area under the curve; CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; IC = inspiratory capacity; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; NE = not evaluated; PLA = placebo; SE = standard error; TDI = Transition Dyspnea Index; TIO = tiotropium.
Source: Clinical study report (CSR) BLAZE[17]; CSR BRIGHT.[18]

TABLE 38: KEY EFFICACY OUTCOMES: OPEN LABEL

	ARISE	
Moderate/Severe Exacerbations	**IG (N = 119)**	**TIO (N = 39)**
Patients with ≥ 1, N (%)	26 (22)	8 (21)
Mean (SD) number	0.4 (0.9)	0.4 (1.1)
Number per year	0.39	0.45
P value	NR	
Mortality		
Deaths, N (%)	1	0
SGRQ-C total score		
Mean (SD) baseline	29.5 (14.9) N = 106	34.0 (17.9) N = 38
Mean (SD) change from baseline to Week 52	–2.9 (11.0)	–0.6 (9.9)
P value	NR	

	ARISE	
Moderate/Severe Exacerbations	**IG (N = 119)**	**TIO (N = 39)**
Symptom scores, 24 hours		
Mean baseline	NE	NE
LS Mean (SE) over treatment period (52 weeks)	NE	NE
LS MD (95% CI) at EOS	NE	
Inspiratory capacity, L		
Mean (SD) baseline	1.948 (0.514)	1.938 (0.448)
Mean (SD) change at Week 52	0.093 (0.340)	0.081 (0.482)
P value	NR	
FEV_1, Pre-dose, L		
Mean (SD) baseline	1.316 (0.469)	1.385 (1.437)
Mean (SD) change, Week 52	0.189 (0.176)	0.052 (0.169)
P value	NR	

CI = confidence interval; EOS = end of study; FEV_1 = forced expiratory volume in one second; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; SD = standard deviation; SE = standard error; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TIO = tiotropium.
Source: Clinical source report for ARISE.[19]

3.7 Harms

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

3.7.1 Adverse Events

a) LAMA/LABA-Controlled Study

In QUANTIFY, [redacted]% of indacaterol + glycopyrronium patients and [redacted]% of tiotropium + formoterol patients reported an adverse event (Table 39). According to the manufacturer's analysis, this difference was not statistically significant. Nasopharyngitis was the most commonly reported adverse event. Exacerbations were not included in the adverse events in this study.

b) LAMA-Controlled Studies (Tiotropium)

Adverse events were reported in 55% to 61% of patients in SHINE and 93% to 94% of patients in SHARK (Table 40). COPD was the most common adverse event in both studies.

c) ICS/LABA-Controlled Study

In ILLUMINATE, 55% of indacaterol + glycopyrronium patients and 60% of fluticasone propionate + salmeterol patients reported an adverse event (Table 41). COPD was the most common adverse event, occurring in 17% of indacaterol + glycopyrronium patients and 24% of fluticasone propionate + salmeterol patients.

d) Placebo-Controlled Study

In ENLIGHTEN, 58% of indacaterol + glycopyrronium patients and 57% of placebo patients reported an adverse event (Table 42). The most common adverse event was COPD.

e) Component-Controlled Study

In BEACON, 26% of patients treated with the fixed-dose combination of indacaterol + glycopyrronium and 25% of patients treated with the separate combination of these two components experienced an adverse event (Table 43).

f) Crossover-Controlled Studies

In BLAZE, 35% of indacaterol + glycopyrronium patients, 36% of tiotropium patients, and 39% of placebo patients experienced an adverse event while taking these interventions. In BRIGHT, 38% of indacaterol + glycopyrronium patients, 28% of tiotropium patients, and 36% of placebo patients experienced an adverse event while taking these interventions (Table 44).

g) Open-Label Study

In ARISE, 85% of indacaterol + glycopyrronium-treated patients and 72% of tiotropium-treated patients experienced an adverse event (Table 45).

3.7.2 Serious Adverse Events

a) LAMA/LABA-Controlled Study

In QUANTIFY, [redacted]% of indacaterol + glycopyrronium patients and [redacted]% of tiotropium + formoterol patients reported a serious adverse event (Table 39). According to the manufacturer's analysis, there was no statistically significant difference between groups. The most common serious adverse events were pneumonia (zero patients with indacaterol + glycopyrronium and four patients with tiotropium + formoterol) and myocardial infarction (three indacaterol + glycopyrronium patients and one tiotropium + formoterol patient).

b) LAMA-Controlled Studies (Tiotropium)

The proportion of patients with SAEs ranged from 4% to 6% in SHINE and from 22% to 24% in SPARK (Table 40). The most common SAE in each study was "COPD worsening," which occurred in 2% to 3% of patients in SHINE and 12% to 15% of patients in SPARK. In SHINE, two patients had pneumonia as an SAE with indacaterol + glycopyrronium, and three patients with tiotropium and three with placebo had pneumonia as an SAE.

c) ICS/LABA-Controlled Study

In ILLUMINATE, 5% of patients had at least one serious adverse event in each of the indacaterol + glycopyrronium and fluticasone propionate + salmeterol groups (Table 41). The most common serious adverse event was COPD (one patient in indacaterol + glycopyrronium and three patients in fluticasone propionate + salmeterol).

d) Placebo-Controlled Study

In ENLIGHTEN, 16% of patients treated with indacaterol + glycopyrronium and 11% of patients treated with placebo had a serious adverse event (Table 42). The most common SAEs were COPD (5% with indacaterol + glycopyrronium and 4% with placebo) and pneumonia (4% versus 0%, respectively).

e) Component-Controlled Study

In BEACON, 4% of patients treated with indacaterol + glycopyrronium and 6% of patients treated with indacaterol and glycopyrronium experienced a serious adverse event (Table 43).

f) Crossover Studies

In BLAZE, 3% of patients in each of the indacaterol + glycopyrronium and tiotropium groups had a serious adverse event, and 2% of placebo patients. In BRIGHT, one patient in each of the indacaterol + glycopyrronium, tiotropium, and placebo group had a serious adverse event (Table 44).

g) Open-Label Study

In ARISE, 16% of patients in the indacaterol + glycopyrronium-treated group and 5% of those in the tiotropium-treated group had a serious adverse event. The most common events were colon polyp and COPD (3% in indacaterol + glycopyrronium, and none with tiotropium) (Table 45).

3.7.3 Withdrawals Due to Adverse Events

a) LAMA/LABA-Controlled Study

In QUANTIFY, [redacted]% of indacaterol + glycopyrronium patients and [redacted]% of tiotropium + formoterol patients withdrew due to an adverse event (Table 39). The most common reason in either group was pneumonia ([redacted] with indacaterol + glycopyrronium and [redacted] with tiotropium + formoterol).

b) LAMA-Controlled Studies (Tiotropium)

In SHINE, 1% of patients treated with indacaterol + glycopyrronium, 2% of patients treated with tiotropium, and 4% of patients treated with placebo withdrew due to an adverse event (Table 40).

In SPARK, 11% of patients treated with indacaterol + glycopyrronium and 9% of patients treated with tiotropium withdrew due to an adverse event (Table 40).

c) ICS/LABA-Controlled Study

In ILLUMINATE, 9% of indacaterol + glycopyrronium-treated and 10% of fluticasone propionate + salmeterol–treated patients withdrew due to an adverse event (Table 41). The most common reason was COPD (6% versus 8%, respectively).

d) Placebo-Controlled Study

In ENLIGHTEN, 6% of patients in each of the indacaterol + glycopyrronium-treated and placebo-treated groups withdrew due to an adverse event (Table 42). The most common reason was COPD, in 2% of indacaterol + glycopyrronium- and 1% of placebo-treated patients.

e) Component-Controlled Study

In BEACON, 1% of patients in each group withdrew due to an adverse event (Table 43).

f) Crossover Studies

In BLAZE, 5% of indacaterol + glycopyrronium patients, 6% of tiotropium patients, and 4% of placebo patients withdrew due to an adverse event. In BRIGHT, no indacaterol + glycopyrronium patients, 6% of tiotropium patients, and 1% of placebo patients withdrew due to an adverse event (Table 44).

g) Open-Label Study

In ARISE, 9% of indacaterol + glycopyrronium patients and no tiotropium patients withdrew due to an adverse event (Table 45).

3.7.4 Adverse Events of Interest

a) LAMA/LABA-Controlled Study

In QUANTIFY, there were no cases of pneumonia with indacaterol + glycopyrronium and cases of pneumonia in 1% of patients on tiotropium + formoterol. Myocardial infarction occurred in 1% of indacaterol + glycopyrronium patients and less than 1% of tiotropium + formoterol patients, and hypertension in 2% of indacaterol + glycopyrronium patients and 1% of tiotropium + formoterol patients. Dry mouth was reported by 1% of patients in each group.

b) LAMA-Controlled Studies (Tiotropium)

In SHINE, 1% of patients in each of the indacaterol + glycopyrronium, indacaterol, glycopyrronium, tiotropium, and placebo groups reported pneumonia, as did 5% of patients in each of the indacaterol + glycopyrronium, glycopyrronium, and tiotropium groups in SPARK.

In SHINE, a cerebrovascular or cardiovascular (CCV) AE was reported in 3% of indacaterol, glycopyrronium, and placebo patients, and in 2% of indacaterol + glycopyrronium and tiotropium patients. In SPARK, a CCV AE was reported in 6% of indacaterol + glycopyrronium patients, 7% of glycopyrronium patients, and 7% of patients with tiotropium. Dry mouth was reported in 1% of indacaterol + glycopyrronium and glycopyrronium and tiotropium groups and in less than 1% of indacaterol and placebo patients in SHINE. Dry mouth was not reported in SPARK.

c) ICS/LABA-Controlled Study

In ILLUMINATE, no patients in the indacaterol + glycopyrronium group reported pneumonia, while 2% reported pneumonia with fluticasone propionate + salmeterol after 26 weeks. A CCV SAE was reported in 1% of patients in each group. Dry mouth was not reported.

d) Placebo-Controlled Study

In ENLIGHTEN, 4% of indacaterol + glycopyrronium patients reported pneumonia versus none in the placebo group after 52 weeks. Non-fatal stroke and heart failure requiring hospitalization occurred in less than 1% of indacaterol + glycopyrronium patients and no placebo patients. Urinary retention was the most common anticholinergic AE, occurring in 1% of indacaterol + glycopyrronium patients and no placebo patients.

e) Component-Controlled Study

In BEACON, 2% of indacaterol + glycopyrronium patients had pneumonia after 4 weeks' treatment, and none of those treated with the individual components of indacaterol and glycopyrronium, administered as separate inhalers, had pneumonia. CCV AEs were not reported in any indacaterol + glycopyrronium patients and were reported in 1% of patients receiving the separate inhalers.

f) Crossover-Controlled Studies

No cases of pneumonia as an AE were reported in BLAZE after 6 weeks treatment, although 1% of patients treated with tiotropium and 1% with placebo reported pneumonia as a SAE. Hypertension was reported in 1% of indacaterol + glycopyrronium and tiotropium patients and 2% of placebo patients. Dry mouth was reported in < 1% of indacaterol + glycopyrronium patients, no tiotropium patients, and 1% of placebo.

In BRIGHT, no indacaterol + glycopyrronium patients had pneumonia as an AE, while 1% of tiotropium and 1% of placebo patients had pneumonia after 3 weeks' treatment. Myocardial infarction occurred in

1% of tiotropium patients, but not in indacaterol + glycopyrronium or in placebo patients. Dry mouth occurred in 1% of tiotropium patients and in no indacaterol + glycopyrronium or placebo patients.

g) Open-Label Study

In ARISE, 8% of indacaterol + glycopyrronium patients and 3% of tiotropium patients reported pneumonia after 52 weeks. Dry mouth and CCV AE were not reported.

TABLE 39: HARMS: LAMA/LABA-CONTROLLED

	QUANTIFY	
AEs[a]	IG N = 476	TF N = 458
Subjects with > 0 AEs, N (%)	[redacted]	[redacted]
Most common AEs		
Nasopharyngitis	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
SAEs		
Subjects with > 0 SAEs, N (%)	[redacted]	[redacted]
Most common SAEs		
Pneumonia	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
WDAEs		
WDAEs, N (%)	[redacted]	[redacted]
Most common reasons		
Pneumonia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Mortality		
Deaths, N (%)	[redacted]	[redacted]
Most common reasons		
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Notable AEs	[redacted]	
Pneumonia	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

AE = adverse event; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; SAE = serious adverse events; TF = tiotropium + formoterol; WDAE = withdrawals due to adverse events.
[a] AEs, SAEs, and WDAEs exclude exacerbations.
Source: Clinical study report for QUANTIFY.[11]

TABLE 40: HARMS: LAMA (TIOTROPIUM)-CONTROLLED

	SHINE					SPARK		
Adverse Events	**IG N = 474**	**I N = 476**	**G N = 473**	**TIO N = 480**	**PLA N = 232**	**IG N = 729**	**G N = 740**	**TIO N = 737**
Subjects with > 0 AEs, N (%)	261 (55)	291 (61)	290 (61)	275 (57)	134 (58)	678 (93)	694 (94)	686 (93)
Most common AEs								
COPD	137 (29)	153 (32)	150 (32)	138 (29)	91 (39)	636 (87)	651 (88)	642 (87)
SAEs								
Subjects with > 0 SAEs, N (%)	22 (5)	26 (6)	29 (6)	19 (4)	13 (6)	167 (23)	179 (24)	165 (22)
Most common SAEs								
Pneumonia	2 (< 1)	2 (< 1)	3 (1)	3 (1)	3 (1)	23 (3)	25 (3)	24 (3)
LRTI	0	1 (< 1)	0	0	1 (< 1)	14 (2)	24 (3)	13 (2)
COPD worsening	10 (2)	15 (3)	9 (2)	7 (2)	7 (3)	107 (15)	116 (16)	87 (12)
WDAEs								
WDAEs, N (%)	6 (1)	24 (5)	14 (3)	10 (2)	10 (4)	79 (11)	86 (12)	67 (9)
Most common reasons								
COPD	1 (< 1)	7 (2)	3 (1)	7 (2)	4 (2)	34 (5)	36 (5)	18 (2)
Pneumonia						7 (1)	4 (1)	1 (< 1)
Mortality								
Deaths, N (%)	1 (< 1)	2 (< 1)	1 (< 1)	3 (1)	0	23 (3)	22 (3)	25 (3)
Most common reasons								
COPD	0	0	0	1 (< 1)	0	7 (1)	3 (< 1)	3 (< 1)
Cardiorespiratory arrest	0	0 (< 1)	0	0	0	2 (< 1)	3 (< 1)	3 (< 1)
Pneumonia	0	0	0	1 (< 1)	0	1 (< 1)	1 (< 1)	0
Notable AEs								
LRTI	9 (2)	15 (3)	7 (2)	12 (3)	5 (2)	58 (8)	83 (11)	77 (10)
Pneumonia	4 (1)	3 (1)	4 (1)	6 (1)	3 (1)	33 (5)	36 (5)	34 (5)
Viral URTI	15 (3)	11 (2)	13 (3)	12 (3)	7 (3)	74 (10)	77 (10)	75 (10)
URTI	20 (4)	32 (7)	20 (4)	24 (5)	13 (6)	28 (4)	25 (3)	28 (4)
Bacterial URTI	10 (2)	13 (3)	15 (3)	22 (5)	13 (6)	132 (18)	133 (18)	115 (16)
Hypertension	9 (2)	8 (2)	9 (2)	9 (2)	2 (1)	32 (4)	22 (3)	26 (4)
Dry mouth	4 (1)	2 (< 1)	4 (1)	5 (1)	1 (< 1)	NR	NR	NR
Any CCV event	7 (2)	12 (3)	14 (3)	9 (2)	6 (3)	44 (6)	50 (7)	50 (7)

AE = adverse event; CCV = cerebrovascular and cardiovascular; COPD = chronic obstructive pulmonary disease; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; LRTI = lower respiratory tract infection; NR = not reported; PLA = placebo; SAE = serious adverse events; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawals due to adverse events.
Source: Clinical study report (CSR) SPARK[12]; CSR SHINE.[13]

TABLE 41: HARMS: ICS/LABA-CONTROLLED

	ILLUMINATE	
AEs	**IG (N = 258)**	**FP/S (N = 264)**
Subjects with > 0 AEs, N (%)	143 (55)	159 (60)
Most common AEs		
COPD	44 (17)	62 (24)
Nasopharyngitis	37 (14)	29 (11)
SAEs		
Subjects with > 0 SAEs, N (%)	13 (5)	14 (5)
Most common SAEs		
Pneumonia	0	2 (1)
COPD	1 (< 1)	3 (1)
WDAEs		
WDAEs, N (%)	22 (9)	27 (10)
Most common reasons		
Bacterial URTI	3 (1)	1 (< 1)
COPD	16 (6)	20 (8)
Mortality		
Deaths, N (%)	0	1 (< 1)
Most common reasons		
Sudden cardiovascular death	0	1 (< 1)
Notable AEs		
Pneumonia	0	4 (2)
Viral URTI	1 (< 1)	3 (1)
URTI	3 (1)	3 (1)
Bacterial URTI	7 (3)	2 (1)
Hypertension	6 (2)	4 (2)
Dry mouth	NR	NR
CCV SAE	3 (1)	3 (1)

AE = adverse event; CCV = cerebrovascular and cardiovascular; COPD = chronic obstructive pulmonary disease; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LRTI = lower respiratory tract infection; SAE = serious adverse events; URTI = upper respiratory tract infection; WDAE = withdrawals due to adverse events.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 42: HARMS: PLACEBO-CONTROLLED

	ENLIGHTEN	
AEs	**IG (N = 225)**	**PLA (N = 113)**
Subjects with > 0 AEs, N (%)	130 (58)	64 (57)
Most common AEs		
COPD worsening	63 (28)	29 (26)
Viral URTI	18 (8)	15 (13)
URTI	12 (5)	9 (8)
Bacterial URTI	11 (5)	5 (4)
SAEs		
Subjects with > 0 SAEs, N (%)	37 (16)	12 (11)
Most common SAEs		
Pneumonia	8 (4)	0

	ENLIGHTEN	
AEs	**IG (N = 225)**	**PLA (N = 113)**
COPD	12 (5)	4 (4)
CCV-related	5 (2)	0
WDAEs		
WDAEs, N (%)	13 (6)	7 (6)
Most common reasons		
Pneumonia	4 (2)	0
COPD	5 (2)	1 (1)
Mortality		
Deaths, N (%)	4 (2)	1 (1)
Most common reasons		
Sudden death	1	1
COPD exacerbation with pneumonia	1	0
COPD exacerbation	2	0
Notable AEs		
LRTI	15 (7)	4 (4)
Pneumonia	8 (4)	0
Non-fatal stroke	1 (< 1)	0
HF requiring hospitalization	1 (< 1)	0
Dry mouth	0	1 (1)
Urinary retention	3 (1)	0
Glaucoma	1 (< 1)	0

AE = adverse event; CCV = cerebrovascular and cardiovascular; COPD = chronic obstructive pulmonary disease; HF = heart failure; IG = indacaterol + glycopyrronium; LRTI = lower respiratory tract infection; PLA = placebo; SAE = serious adverse events; URTI = upper respiratory tract infection; WDAE = withdrawals due to adverse events.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 43: HARMS: COMPONENT-CONTROLLED

	BEACON	
AEs	**IG N = 90**	**I and G (Individual Components) N = 103**
Subjects with > 0 AEs, N (%)	23 (26)	26 (25)
Most common AEs		
COPD	4 (4)	2 (2)
Cough	4 (4)	2 (2)
Nasopharyngitis	7 (8)	6 (6)
SAEs		
Subjects with > 0 SAEs, N (%)	4 (4)	6 (6)
Most common SAEs		
Pneumonia	2 (2)	0
Bronchial carcinoma	0	2 (2)
COPD	1 (1)	0
WDAEs		
WDAEs, N (%)	1 (1)	1 (1)
Mortality		
Deaths, N (%)	0	0

	BEACON	
AEs	**IG N = 90**	**I and G (Individual Components) N = 103**
Notable AEs		
Pneumonia	2 (2)	0
Dry mouth	NR	NR
CCV AE	0	1 (1)

AE = adverse event; CCV = cerebrovascular and cardiovascular; COPD = chronic obstructive pulmonary disease; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; SAE = serious adverse events; URTI = upper respiratory tract infection; WDAE = withdrawals due to adverse events.
Source: Clinical study report for BEACON.[16]

TABLE 44: HARMS: CROSSOVER

	BLAZE			BRIGHT		
AEs	**IG (N = 223)**	**TIO (N = 220)**	**PLA (N = 218)**	**IG (N = 77)**	**TIO (N = 83)**	**PLA (N = 77)**
Subjects with > 0 AEs, N (%)	78 (35)	78 (36)	86 (39)	29 (38)	23 (28)	28 (36)
Most common AEs						
COPD	18 (8)	21 (10)	20 (9)	7 (9)	5 (6)	3 (4)
Cough	7 (3)	8 (4)	5 (2)	5 (7)	0	1 (1)
Nasopharyngitis	14 (6)	8 (4)	13 (6)	3 (4)	1 (1)	3 (4)
SAEs						
Subjects with > 0 SAEs, N (%)	6 (3)	6 (3)	5 (2)	1 (1)	1 (1)	1 (1)
Most common SAEs						
Pneumonia	0	1 (1)	1 (1)	0	0	1 (1)
Bronchial carcinoma	0	0	0	0	0	0
COPD	3 (1)	2 (1)	1 (1)	0	0	0
WDAEs						
WDAEs, N (%)	11 (5)	12 (6)	9 (4)	0	5 (6)	1 (1)
Most common reasons						
COPD	10 (5)	7 (3)	5 (2)	0	2 (2)	0
LRTI	2 (1)	2 (1)	1 (1)	0	0	0
Mortality						
Deaths, N (%)	1 (< 1)	0	0	0	0	0
Most common reasons						
Acute heart failure	1	0	0	0	0	0
Notable AEs						
Pneumonia	0	0	0	0	1 (1)	1 (1)
Hypertension	3 (1)	3 (1)	4 (2)	1 (1)	0	0
Dry mouth	1 (< 1)	0	2 (1)	0	1 (1)	0

	BLAZE			BRIGHT		
AEs	IG (N = 223)	TIO (N = 220)	PLA (N = 218)	IG (N = 77)	TIO (N = 83)	PLA (N = 77)
URTI	1 (< 1)	2 (1)	4 (2)	0	0	0
URTI bacterial	2 (1)	0	1 (1)	0	0	0
Myocardial infarction	0	0	0	0	1 (1)	0

AE = adverse event; COPD = chronic obstructive pulmonary disease; IG = indacaterol + glycopyrronium; LRTI = lower respiratory tract infection; PLA = placebo; SAE = serious adverse events; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawals due to adverse events.
Source: Clinical study report (CSR) BLAZE[17]; CSR BRIGHT.[18]

TABLE 45: HARMS: OPEN LABEL

	ARISE	
AEs	IG (N = 119)	TIO (N = 39)
Subjects with > 0 AEs, N (%)	101 (85)	28 (72)
Most common AEs[a]		
COPD worsening	32 (27)	8 (21)
Nasopharyngitis	40 (34)	12 (31)
SAEs		
Subjects with > 0 SAEs, N (%)	19 (16)	2 (5)
Most common SAEs		
Pneumonia	2 (2)	0
Colon polyp	3 (3)	0
COPD	4 (3)	0
WDAEs		
WDAEs, N (%)	11 (9)	0
Most common reasons		
Pneumonia	1 (1)	0
COPD	3 (3)	0
Mortality		
Deaths, N (%)	1	0
Most common reasons		
Arrhythmia	1	0
Notable AEs		
Pneumonia	9 (8)	1 (3)
URTI	9 (8)	6 (15)

AE = adverse event; COPD = chronic obstructive pulmonary disease; IG = indacaterol + glycopyrronium; SAE = serious adverse events; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawals due to adverse events.
Source: Clinical study report for ARISE.[19]

4. DISCUSSION

4.1 Summary of Available Evidence

Of the eight multi-centre, manufacturer-sponsored DB RCTs that met the inclusion criteria for this review, one study (QUANTIFY, 26 weeks) compared once daily indacaterol + glycopyrronium to twice daily tiotropium + formoterol, two studies included groups with tiotropium monotherapy (SHINE, 26 weeks and SPARK, 64 to 76 weeks), one study included a fluticasone propionate + salmeterol group (ILLUMINATE, 26 weeks), one study compared indacaterol + glycopyrronium to placebo (ENLIGHTEN, 52 weeks), and one study compared indacaterol + glycopyrronium in the Breezhaler formulation with separate indacaterol and glycopyrronium inhalers administered at the same time (BEACON, four weeks). Finally, there were two crossover studies, each with indacaterol + glycopyrronium, tiotropium, and placebo as groups (BLAZE, six weeks' treatment per period; BRIGHT, three weeks' treatment per period). Additionally, one open-label RCT (ARISE) was included in this review, also multi-centre and manufacturer sponsored.

The proportion of patients with moderate or severe exacerbations was not statistically significantly different between indacaterol + glycopyrronium and tiotropium + formoterol, or between indacaterol + glycopyrronium and tiotropium. Regarding HRQoL, assessed by the SGRQ-C, indacaterol + glycopyrronium was non-inferior to tiotropium + formoterol, and there was also no statistically significant difference between indacaterol + glycopyrronium versus fluticasone propionate + salmeterol. There was a statistically significant improvement in SGRQ-C for indacaterol + glycopyrronium over tiotropium in SHINE and in SPARK; however, tiotropium was administered open label in these studies, and the difference between groups was less than the accepted MCID of 4. Dyspnea scores were not statistically significantly different between indacaterol + glycopyrronium and tiotropium + formoterol, but were statistically significantly improved for indacaterol + glycopyrronium versus fluticasone propionate + salmeterol. Other studies did not report this outcome. Symptom scores were statistically significantly improved for indacaterol + glycopyrronium versus tiotropium in SPARK, but there was no difference in symptom scores between indacaterol + glycopyrronium and fluticasone propionate + salmeterol. Symptom scores were statistically significantly improved for indacaterol + glycopyrronium versus placebo. These symptom scores were based on daily diaries completed by patients and are considered to have reliability issues, in addition to lacking an established MCID. Pre-dose FEV_1 was statistically significantly improved for indacaterol + glycopyrronium versus tiotropium + formoterol, and statistically significantly improved versus tiotropium alone; as well, FEV_1 AUC (0 hours to 12 hours) was statistically significantly improved for indacaterol + glycopyrronium versus fluticasone propionate + salmeterol. However, of these statistically significant differences, the only comparison that demonstrated a clinically significant improvement was indacaterol + glycopyrronium versus fluticasone propionate + salmeterol. This might not be a surprising finding, considering that bronchodilators would be expected to have a greater impact on FEV_1 than ICS. The most common adverse event was COPD, and this was also the most common serious adverse event and the most common reason for a withdrawal due to an adverse event.

4.2 Interpretation of Results

4.2.1 Efficacy

There was only one study, QUANTIFY, that compared indacaterol + glycopyrronium with another LABA/LAMA combination, tiotropium + formoterol. A potential advantage of indacaterol + glycopyrronium over this and other LABA/LAMA combinations is that it is administered once daily, versus the twice daily dosing required with formoterol. A once-daily dosing regimen might lead to

improved compliance versus a twice-daily regimen. However, compliance with both groups in QUANTIFY was high, 99% or above; therefore, no conclusions can be drawn about whether the once-daily indacaterol + glycopyrronium regimen will lead to improved compliance. Compliance is typically high in clinical trials, as patients are more closely monitored and tend to be a more motivated population.

Although QUANTIFY was a non-inferiority design and indacaterol + glycopyrronium did demonstrate non-inferiority to tiotropium + formoterol, it did not demonstrate superiority. A difference in QoL might have suggested potential improved adherence and persistence with the indacaterol + glycopyrronium regimen. Based on the data from QUANTIFY, the only advantage of indacaterol + glycopyrronium over tiotropium + formoterol was an improved FEV_1. Although this difference was statistically significant, it is of questionable clinical significance. Although QUANTIFY was not powered to be a superiority study, there is no evidence to support a clear difference between the once-daily indacaterol + glycopyrronium regimen and tiotropium + formoterol.

Mortality and morbidity were key outcomes of this review; however, none of the included studies was adequately powered or was of sufficient duration to assess such outcomes. SPARK had the most deaths in any study, as it was also the only study with patients having severe to very severe COPD, and a 64- to 76-week follow-up; however, there was no difference in mortality between groups in this study. There were seven deaths due to COPD with indacaterol + glycopyrronium and three in each of the glycopyrronium and tiotropium groups. There were also three COPD-related deaths in ENLIGHTEN and none in the placebo group. Once again, none of the studies was large enough or of sufficient duration to determine whether a difference in COPD-related deaths exists. Few studies reported outcomes that might be considered indicators of morbidity, such as hospitalizations. In SPARK, the proportion of patients with a hospitalization was numerically higher with indacaterol + glycopyrronium than with tiotropium (14.5% versus 11.4%); however, no statistical analysis was provided, and this study was not powered to detect differences in this outcome. Emergency room visits and unscheduled doctor's visits occurred in similar proportions between groups in SPARK. Given the importance of these events to the patient and as cost drivers in the health care system, it would have been useful to have had a study that was designed to assess these outcomes.

Exacerbations are another key event in COPD, and, according to the patient group submission for this review, are an important consideration for COPD patients. Moderate to severe exacerbations were consistently defined in the studies as those resulting either in treatment with systemic corticosteroids or antibiotics (moderate) or those requiring hospitalization (severe). Of the included studies, SPARK was the only one specifically designed to assess the impact of indacaterol + glycopyrronium on exacerbations. Although there was an open-label tiotropium group in this study, the study was designed to test the superiority of indacaterol + glycopyrronium to one of its components, glycopyrronium, for this outcome. Specifically, the primary outcome of SPARK was to test the superiority of indacaterol + glycopyrronium versus glycopyrronium for the rate of moderate to severe exacerbations, and indacaterol + glycopyrronium was superior to glycopyrronium for this outcome, with a *P* value of 0.038. However, the proportion of patients with a moderate to severe exacerbation was similar between indacaterol + glycopyrronium and glycopyrronium (28% versus 26%), suggesting that indacaterol + glycopyrronium may reduce the number of exacerbations per patient, rather than the number of patients who experience an exacerbation, compared with one of its components. Indacaterol was not included as a comparator in this study, so it is not clear whether indacaterol + glycopyrronium would have demonstrated superiority to its other component or not. SPARK was also the only study that enrolled a population with severe to very severe COPD, while SHINE enrolled a population with moderate to severe COPD. In SHINE, which was not powered to assess exacerbations, the proportion of patients with exacerbations was again

similar between indacaterol + glycopyrronium and glycopyrronium (18% versus 19%, respectively), and with indacaterol was 22%. Taken collectively, the data from these studies at least suggest that, with respect to the key outcome of exacerbations, indacaterol + glycopyrronium may have a greater impact on exacerbation rates rather than on the proportion of patients with an exacerbation.

QoL is another important consideration for COPD patients, as noted in the patient input summary. QUANTIFY was the only study that assessed QoL as a primary outcome. Using the SGRQ-C instrument, indacaterol + glycopyrronium was found to be non-inferior to tiotropium + formoterol with respect to total score. Although not a primary outcome of other studies, indacaterol + glycopyrronium was found to elicit statistically significant improvements in SGRQ-C scores versus both tiotropium and versus fluticasone propionate + salmeterol, as well as versus placebo. As noted elsewhere, however, the tiotropium groups in SHINE and SPARK were open label, and, due to the bias associated with lack of blinding for patient-reported outcomes such as QoL, these data must be considered hypothesis-generating. A DB RCT would need to be conducted with tiotropium as comparator in order to determine whether the combination of indacaterol + glycopyrronium represents a QoL advantage over tiotropium monotherapy. With respect to comparisons to fluticasone propionate + salmeterol, it is not clear whether the population that would be treated with fluticasone propionate + salmeterol is comparable to the population that would be treated with dual bronchodilator therapy in the real-world setting.

The included studies did not address the potential use of indacaterol + glycopyrronium as part of triple therapy with an ICS. Triple therapy is recommended as part of the COPD management guidelines for patients with moderate to severe disease and persistent symptoms.[2] Across the studies included in this review, between 20% and 40% of patients were classified as having severe disease at baseline, and, in SPARK, all patients had severe to very severe disease. It would seem that triple therapy would be appropriate for at least some of these patients, particularly those that did not respond to dual therapy. For example, in SPARK, 28% of patients treated with indacaterol + glycopyrronium had at least one moderate to severe exacerbation during the 64- to 76-week duration of treatment (versus 26% with glycopyrronium and 25% with tiotropium). If these patients are determined to be treatment failures, they might then be switched to triple therapy, with an added cost to the health care system and risk of harm for the patient. However, the role of indacaterol + glycopyrronium in triple-therapy regimens has yet to be established.

4.2.2 Harms

Pneumonia is a key safety issue associated with COPD and COPD management. Patients with COPD are at higher risk of pneumonia, and this risk increases further with use of ICS. As it does not contain a corticosteroid, indacaterol + glycopyrronium might be expected to carry a lower risk of pneumonia than ICS/LABA combinations. In ILLUMINATE, the only study that compared indacaterol + glycopyrronium with an ICS/LABA, there were four cases of pneumonia with patients on fluticasone propionate + salmeterol and none in patients treated with indacaterol + glycopyrronium. Given the small number of events, it cannot be ascertained whether indacaterol + glycopyrronium does have a lower risk of pneumonia than an ICS/LABA. A larger, longer-term study might be able to determine whether such a safety advantage exists for indacaterol + glycopyrronium versus an ICS/LABA. In QUANTIFY, there was one patient with pneumonia as an adverse event in the indacaterol + glycopyrronium group versus eight patients treated with tiotropium + formoterol. Given that neither of these combinations contains an ICS, this may have been a chance finding rather than an indication that indacaterol + glycopyrronium carries a lower risk of pneumonia versus other LABA/LAMA combinations. There is no evidence that indacaterol + glycopyrronium has a protective effect with respect to pneumonia, as in the ENLIGHTEN study, there were four patients with pneumonia in the indacaterol + glycopyrronium group and none in the placebo group.

Another safety issue relevant to the indacaterol + glycopyrronium combination is the increased risk of death observed with LABA treatment. This risk has been associated with use of LABA for asthma, particularly when used as monotherapy, and is noted in the product monograph for indacaterol + glycopyrronium.[25] Although this safety warning has not been extended to COPD, as noted elsewhere in this review, a number of patients with COPD in the included studies exhibited airway reversibility suggestive of underlying asthma. There was no evidence from the included trials of an increased risk of sudden death due to asthma with the use of indacaterol + glycopyrronium; however, given that patients may be at higher risk with longer-term use of a LABA, these studies may not be of sufficient duration or sample size to assess this risk. Additionally, the risk is thought to be mitigated by concomitant use of ICS; however, it is unclear that the risk is affected by combination LABA/LAMA use.[37,38]

5. CONCLUSIONS

Eight DB RCTs met the inclusion criteria for this review: two included an open-label tiotropium group, and one study each included tiotropium + formoterol, fluticasone propionate + salmeterol, and placebo. Of three other studies, two were crossover designs and one compared the Breezhaler device with its components given in combination. One open-label RCT comparing indacaterol + glycopyrronium with tiotropium also met the inclusion criteria for the review.

When compared with tiotropium + formoterol, indacaterol + glycopyrronium did not statistically significantly reduce the risk of exacerbations or improve dyspnea scores. However, indacaterol + glycopyrronium was non-inferior with respect to HRQoL as measured by the SGRQ, and it elicited a statistically significantly greater improvement in FEV_1 than tiotropium + formoterol.

When compared with tiotropium monotherapy, indacaterol + glycopyrronium improved SGRQ-C total scores, symptom scores, and trough FEV_1, and these differences were statistically significant. However, indacaterol + glycopyrronium did not reduce the rate of exacerbations compared with tiotropium monotherapy.

When compared with fluticasone propionate + salmeterol, indacaterol + glycopyrronium improved FEV_1 and dyspnea scores, and these differences were statistically significant. However, it did not improve symptom scores or QoL by SGRQ-C.

The most common adverse event with indacaterol + glycopyrronium was COPD, and COPD and pneumonia were the most common serious adverse events across studies.

APPENDIX 1: PATIENT INPUT SUMMARY

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

Brief Description of Patient Group(s) Supplying Input

COPD Canada is an independent non-profit patient advocacy association, established in 2005, with a mandate to assist Canadians who suffer from chronic obstructive pulmonary disease (COPD). It is a patient advocacy group and an educational association that provides materials and services in a variety of formats to patients and their families and also to Canadian medical professionals, government agencies, non-governmental organizations, and other health care personnel. Membership of COPD Canada is restricted to patients with COPD and their families.

COPD Canada has received unrestricted educational grants from Almirall Canada, AstraZeneca (AZ) Canada, Novartis Pharmaceuticals, and Nycomed/Takeda; educational grants from ProResp Inc.; and a general grant from GlaxoSmithKline (GSK) Canada. It declared no conflict of interest in the preparation of this submission.

The Ontario Lung Association (OLA) is a registered charity that both assists and empowers patients and caregivers of those living with lung disease. The OLA provides programs and services to patients and health care providers, campaigns for lung health improvement, and also invests in lung research. It is also a recognized leader, voice, and primary resource in the control and prevention of respiratory illness.

The OLA has received both sponsorships and grants from the following pharmaceutical companies: Pfizer, GSK, Boehringer Ingelheim, AZ, Merck, Novartis, Takeda, InterMune, Grifols, Actelion, Astellas, Bayer, Johnson & Johnson, Ontario Home Respiratory Services Association (OHRSA), Roche, Valeant Pharmaceuticals, and Eli Lilly. It declared no conflict of interest in preparation of this submission.

Condition and Current Therapy-Related Information

The primary source of information provided by COPD Canada comes from patients, families, and caregivers who have a membership in this organization. Information-gathering was primarily through direct one-on-one consultations.

The OLA gathered information for this submission using an online survey (sent to both patients and their caregivers), one-to-one telephone conversations (with patients), a certified respiratory educator, and previous patient surveys.

COPD is a disease associated with considerable burdens on patients, their families, and the health care system. It is characterized by shortness of breath, difficulty breathing, coughing, fatigue, low energy, mucus, and wheezing. Everyday life is affected, including the patient's ability to breath, talk, sleep, work, and socialize. As the disease progresses, patients with COPD need to adapt their lifestyle in order to cope with their condition. This can include retiring early, 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 such as the loss of appetite, increased risk of infections, chronic bronchitis, increased reliance on supplemental oxygen, and increased risk of hospitalization and mortality are also of concern. Additionally, exacerbations are a source of concern for COPD patients, as they are associated with both short- and long-term consequences on overall health. 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 and families, particularly the children and spouses, of those with COPD are also heavily affected by the burden of disease, including limited time for managing their own health; feelings of isolation, anxiety, stress, depression, and fatigue; unending days, increased need for social support, decrease in ability to travel, and decreased independence. Adult children caring for their parents are often torn between caring for their parent and their own children.

There is no cure for COPD, no medications that reverse the loss of lung function caused by COPD, and no drug that 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 to prevent or minimize the frequency and duration of exacerbations. Non-drug interventions include pulmonary rehabilitation, exercise programs, breathing lessons, and use of supplemental oxygen. The surgical options include lung transplantation and lung reduction surgery — invasive options, only available to a small group of COPD patients who qualify.

Treatments tried by those interviewed included Spiriva, Advair, Symbicort, Daxas, prednisone, Ventolin, Atrovent, Serevent, Onbrez, and Breo Ellipta. Typical maintenance therapy included the use of Spiriva once daily with Advair 250 mg twice daily. While current treatments provide some relief, they do have side effects such as palpitations, dry mouth, voice hoarseness, mouth sores, changes in vision, impacts on mood, and urinary problems. One patient remarked, “I wanted to make you aware that Spiriva was the most horrible medication I have ever taken. I was hospitalized twice with chest pain and had almost every side effect listed.” Also, treatment effectiveness reduces over time. Exacerbations are often managed with prednisone and antibiotics. While prednisone works quickly, it is associated with numerous side effects such as stomach upset, general swelling, and increases in the symptoms of osteoporosis and ophthalmic problems.

There are distinct challenges with accessing the current therapies available for the treatment of COPD. The most notable challenges are for the disadvantaged and those relying on provincial drug formularies (e.g., patients older than 65 years). While some provinces provide good coverage (e.g., Alberta), there remains large variability in COPD medication coverage between the other provinces (i.e., poor coverage in Atlantic Canada and moderate-to-poor in Ontario).

Related Information About the Drug Being Reviewed

No patient experience with Ultibro Breezhaler was available for this submission.

Patients are looking for agents that can improve lung function (including reduced shortness or breath and coughing), quality of life, reduce exacerbations, reduce fatigue, reduce hospital admissions, and delay disease progression and improve survival over the long-term.

Patients with COPD believe that the new Ultibro Breezhaler treatment will lead to an improvement in overall disease management, as it is expected to reduce airflow obstruction, improve breathing, and reduce the need for rescue medication. Patients are happy that evidence shows that this is a long-acting treatment, is easy to use, and has a fast onset of action. This fast-acting element will be of particular benefit in the morning so that patients can experience relief and get on with their day. Patients also expect that the once-daily treatment will help with compliance. In addition, patients are looking for a treatment that will allow them to be independent, and there are hopes that Ultibro Breezhaler will

provide this. Patients are willing to live with some side effects, but nothing that is worse than what they are currently experiencing and nothing that is irreversible.

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:	July 4, 2014
Alerts:	Search updates every other week until November 2014 (date of CDEC meeting).
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied 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 [MEDLINE database]
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.sh	MeSH subject heading [MEDLINE database]
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
	Embase search
1	glycopyrronium bromide plus indacaterol/
2	(Ultibro Breezhaler* or QVA149 or QVA-149 or QVA149A or QVA-149A or Xoterna Breezhaler* or Ulunar Breezhaler*).ti,ab.
3	or/1-2
4	indacaterol/
5	(indacaterol* or QAB149 or QAB-149 or Onbrez or Hirobriz or Oslif).ti,ab.
6	or/4-5
7	glycopyrronium bromide/
8	(glycopyrronium* or glycopyrrolate* or NVA237 or NVA-237 or Seebri or Enurev or Tavanor).ti,ab.
9	or/7-8
10	3 or (6 and 9)
11	10 use oemezd
12	11 not conference abstract.pt.
	MEDLINE search
13	(Ultibro Breezhaler* or QVA149 or QVA-149 or QVA149A or QVA-149A or Xoterna Breezhaler* or Ulunar Breezhaler*).ti,ab,ot,sh,hw,rn,nm.
14	(indacaterol* or QAB149 or QAB-149 or Onbrez or Hirobriz or Oslif).ti,ab,ot,sh,hw,rn,nm.
15	(312753-06-3 or 753498-25-8).rn,nm.
16	or/14-15
17	Glycopyrrolate/
18	(glycopyrronium* or glycopyrrolate* or NVA237 or NVA-237 or Seebri or Enurev or Tavanor).ti,ab,ot,sh,hw,rn,nm.
19	596-51-0.rn,nm.
20	or/17-19
21	13 or (16 and 20)
22	21 use pmez
	Combine MEDLINE and Embase results
23	12 or 22
24	exp animals/
25	exp animal experimentation/ or exp animal experiment/
26	exp models animal/
27	nonhuman/
28	exp vertebrate/ or exp vertebrates/
29	animal.po.
30	or/24-29
31	exp humans/
32	exp human experimentation/ or exp human experiment/
33	human.po.
34	or/31-33

MULTI-DATABASE STRATEGY	
#	**Searches**
35	30 not 34
36	23 not 35
37	remove duplicates from 36

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:	June 24 – 30, 2014
Keywords:	Ultibro Breezhaler, indacaterol and glycopyrronium, COPD
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

Wrong Dose

Vincken W, et al. Int J Chron Obstruct Pulmon Dis [Internet]. 2014 [cited 2014 Jul 9];9:215-28. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3940646/pdf/copd-9-215.pdf

Van de Maele B, et al. COPD. 2010 Dec;7(6):418-27.

van Noord JA, et al. Thorax [Internet]. 2010 Dec [cited 2014 Jul 9];65(12):1086-91. Available from: http://thorax.bmj.com/content/65/12/1086.full.pdf + html

No Outcomes of Interest

Pavkov R, et al. Curr Med Res Opin. 2010 Nov;26(11):2527-33.

Not a Randomized Controlled Trial

European database of suspected adverse drug reaction reports [data tables on the Internet]. London: European Medicines Agency (EMA), EudraVigilance; 2012. Ultibro Breezhaler (up to Jun 2014); 2014 [cited 2014 Jul 29]. Available from: https://bi.ema.europa.eu/analyticsSOAP/saw.dll?PortalPages&PortalPath = %2Fshared%2FDAP%2F_portal%2FDAP&Action = Navigate&P0 = 1&P1 = eq&P2 = %22Line%20Listing%20Objects%22.%22Product%20High%20Level%20Code%22&P3 = 1 + 435471

APPENDIX 4: DETAILED OUTCOME DATA

Exposure

TABLE 46: EXPOSURE: LAMA/LABA-CONTROLLED

	QUANTIFY	
	IG (N = 476)	TF (N = 458)
Mean (SD) duration, days	167.2 (44.6)	169.0 (41.0)

IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; SD = standard deviation; TF = tiotropium + formoterol.
Source: Clinical study report for QUANTIFY.[11]

TABLE 47: EXPOSURE: LAMA (TIOTROPIUM)-CONTROLLED

	SHINE				SPARK			
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232	IG N = 729	G N = 740	TIO N = 737
Mean (SD) duration, days	174.3 (34.8)	171.0 (38.7)	170.6 (41.2)	173.6 (35.8)	160.0 (53.5)	434.4 (136.3)	415.4 (154.6)	415.4 (155.2)

G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; PLA = placebo; SD = standard deviation; TIO = tiotropium.
Source: Clinical study reports for SHINE and SPARK.[12,13]

TABLE 48: EXPOSURE: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG (N = 258)	FP/S (N = 264)
Mean (SD) duration, days	168.8 (39.7)	165.8 (42.5)

FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; SD = standard deviation.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 49: EXPOSURE: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG (N = 225)	PLA (N = 113)
Mean (SD) duration, days	336.6 (82.4)	312.5 (112.7)

IG = indacaterol + glycopyrronium; PLA = placebo; SD = standard deviation.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 50: EXPOSURE: COMPONENT-CONTROLLED

	BEACON	
	IG N = 90	I and G (individual components) N = 103
Mean (SD) duration, days	29.0 (3.1)	28.8 (3.7)

G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; SD = standard deviation.
Source: Clinical study report for BEACON.[16]

TABLE 51: EXPOSURE: CROSSOVER

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
Mean (SD) duration, days	41.6 (5.4)	41.7 (5.2)	42.0 (4.8)	21.4 (1.1)	21.4 (2.2)	20.9 (2.6)

IG = indacaterol + glycopyrronium; PLA = placebo; SD = standard deviation; TIO = tiotropium.
Source: Clinical study reports for BLAZE and BRIGHT.[17,18]

TABLE 52: EXPOSURE: OPEN LABEL

	ARISE	
	IG N = 119	TIO N = 39
Mean (SD) duration, days	340.4 (70.9)	352.8 (54.8)

IG = indacaterol + glycopyrronium; SD = standard deviation; TIO = tiotropium.
Source: Clinical study report for ARISE.[19]

Other Outcomes

TABLE 53: OTHER OUTCOMES: LAMA/LABA-CONTROLLED

	QUANTIFY	
Compliance	IG N = 476	TF N = 458
Mean (SD) % doses taken over study period	99.5 (8.6)	98.9 (11.0)

IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; SD = standard deviation; TF = tiotropium + formoterol.
Source: Clinical study report for QUANTIFY.[11]

TABLE 54: OTHER OUTCOMES: LAMA-CONTROLLED

	SHINE				SPARK			
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232	IG N = 729	G N = 740	TIO N = 737
Compliance, mean (SD) % doses taken over study period	98.7 (4.9)	98.5 (5.9)	98.7 (3.7)	98.6 (5.4)	98.5 (6.4)	98.9 (6.4)	98.6 (7.0)	98.3 (6.2)
Rescue medication, daily puffs								
Mean (SE) baseline	4.21 (0.20) N = 419	3.66 (0.16) N = 416	3.70 (0.18) N = 403	3.83 (0.17) N = 424	3.88 (0.29) N = 199	5.7 N = 708	5.7 N = 724	5.5 N = 709
LS mean (SE) change over treatment period	–1.9 (0.11)	–1.6 (0.11)	–1.2 (0.11)	–1.3 (0.11)	–0.9 (0.15)	–2.3 (0.13)	–1.5 (0.13)	–1.5 (0.13)
LS MD (95% CI), IG versus		–0.30 (–0.57 to –0.03) *P* = 0.027	–0.66 (–0.93 to –0.39) *P* < 0.001	–0.54 (–0.81 to –0.27) *P* < 0.001	–0.96 (–1.29 to –0.62) *P* < 0.001		–0.81 (–1.07 to –0.56) *P* < 0.001	–0.76 (–1.01 to –0.50) *P* < 0.001

CI = confidence interval; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; LS = least squares; MD = mean difference; PLA = placebo; SE = standard error; TIO = tiotropium.
Source: Clinical study reports for SHINE and SPARK.[12,13]

TABLE 55: OTHER OUTCOMES: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG N = 258	FP/S N = 264
Mean (SD) % doses taken over study period	101.1 (17.4)	99.2 (8.4)
Rescue medication		
Mean daily puffs, Weeks 1 to 26	3.95	4.25
LS mean (SE) change over treatment period	–2.32 (0.19)	–1.93 (0.19)
LS MD (95% CI) over treatment period	–0.39 (–0.71 to –0.06)	
P value	*P* = 0.019	

CI = confidence interval; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LS = least squares; MD = mean difference; SD = standard deviation; SE = standard error.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 56: OTHER OUTCOMES: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG N = 225	PLA N = 113
Compliance		
Mean (SD) % doses taken over study period	98.8 (5.7)	97.4 (8.0)
Rescue medication		
Mean daily puffs, weeks 1 to 26	4.14 N = 222	3.90 N = 110
LS mean (SE) change over treatment period	2.04 (0.18)	2.76 (0.22)
LS MD (95% CI) over treatment period	–0.73 (–1.18 to –0.27)	
P value	*P* = 0.002	

CI = confidence interval; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; PLA = placebo; SD = standard deviation; SE = standard error
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 57: OTHER OUTCOMES: COMPONENT-CONTROLLED

	BEACON	
Rescue Medication	IG N = 90	I and G (Individual Components) N = 103
Mean daily puffs, weeks 1 to 4	2.24 (0.27) N = 84	2.04 (0.27) N = 95
LS mean (SE) change over treatment period	–0.45 (0.12)	–0.42 (0.11)
LS MD (95% CI) over treatment period	–0.04 (–0.35 to 0.28)	
P value	NR	NR

CI = confidence interval; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; SE = standard error
Source: Clinical study report for BEACON.[16]

TABLE 58: OTHER OUTCOMES: CROSSOVER

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
Adherence						
Mean (SD) % doses taken over study period						
SDDPI device	99.5 (6.5)	99.3 (3.3)	99.5 (2.5)	99.9 (3.1)	99.9 (2.2)	99.7 (2.1)
HandiHaler	99.1 (5.6)	99.2 (3.3)	99.6 (2.5)	100.0 (2.5)	99.8 (2.5)	99.7 (1.9)
Rescue medication						
Mean (SE) daily puffs	4.1 (0.3) N = 212	4.2 (0.3) N = 215	4.2 (0.3) N = 206	3.5 (0.5)	3.0 (0.4)	3.5 (0.4)
LS mean (SE) change over treatment period	–1.0 (0.2)	–0.6 (0.2)	0.4 (0.2)	–1.6 (0.2)	–0.5 (0.2)	–0.4 (0.2)
LS MD (95% CI) over treatment period		–0.45 (–0.74 to –0.16)	–1.43 (–1.72 to –1.13)		–1.08 (–1.52 to –0.63)	–1.23 (–1.68 to –0.78)
P value		*P* = 0.002	*P* < 0.001		*P* < 0.001	*P* < 0.001

CI = confidence interval; IG = indacaterol + glycopyrronium; LS = least square; MD = mean difference; PLA = placebo; SD = standard deviation; SDDPI = single-dose dry powder inhaler; SE = standard error; TIO = tiotropium.
Source: Clinical study reports for BLAZE and BRIGHT.[17,18]

TABLE 59: OTHER OUTCOMES: OPEN LABEL

	ARISE	
	IG N = 119	TIO N = 39
Compliance		
Mean (SD) % doses taken over study period	98.8 (2.2)	97.2(8.5)
Rescue medication		
Mean (SD) daily puffs, baseline	0.8 (1.4) N = 118	0.9 (1.5) N = 39
Mean (SD) change, treatment period	–0.6 (1.1)	–0.2 (0.8)
P value	NR	

IG = indacaterol + glycopyrronium; SD = standard deviation; TIO = tiotropium.
Source: Clinical study report for ARISE.[19]

TABLE 60: USE OF CONCOMITANT MEDICATIONS: LAMA-CONTROLLED

	SHINE					SPARK		
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232	IG N = 729	G N = 740	TIO N = 737
Other medications, n (%)								
Any COPD-related	307 (65)	307 (65)	305 (65)	311 (65)	158 (68)	650 (89)	652 (88)	664 (90)
Total CS	280 (59)	286 (60)	284 (60)	288 (60)	144 (62)	613 (84)	610 (82)	620 (84)
ICS	265 (56)	264 (56)	263 (56)	274 (57)	129 (56)	551 (76)	557 (75)	560 (76)
Total oral	46 (10)	64 (13)	51 (11)	45 (9)	40 (17)	284 (39)	321 (43)	293 (40)
Prednisone	22 (5)	27 (6)	20 (4)	18 (4)	19 (8)	140 (19)	158 (21)	146 (20)
Prednisolone	13 (3)	17 (4)	14 (3)	12 (3)	13 (6)	87 (12)	84 (11)	92 (13)
Methylprednisolone	NA	NA	NA	NA	NA	43 (6)	59 (8)	50 (7)
Meprednisone	NA	NA	NA	NA	NA	11 (2)	24 (3)	21 (3)
Antibiotics, total	NA	NA	NA	NA	NA	380 (52)	392 (53)	366 (50)

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; G = glycopyrronium; I = indacaterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; NA = not applicable; PLA = placebo; SE = standard error; TIO = tiotropium.
Source: Clinical study report for SHINE and SPARK.[12,13]

TABLE 61: USE OF CONCOMITANT MEDICATIONS: ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG N = 258	FP/S N = 264
Other medications, n (%)		
Any COPD-related	80 (31)	78 (30)
CS	13 (5)	15 (6)
Antibiotic	14 (5)	12 (5)
Other	32 (12)	29 (11)
SABA	29 (11)	35 (13)
Xanthine	2 (1)	4 (2)
LABA	5 (2)	4 (2)
Beta-2 adrenergic agonist plus steroid	2 (1)	4 (2)

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; SABA = short-acting beta-2 adrenergic agonist.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 62: USE OF CONCOMITANT MEDICATIONS: PLACEBO-CONTROLLED

	ENLIGHTEN	
	IG N = 225	PLA N = 113
Other medications, n (%)		
Any COPD-related	136 (60)	58 (51)
CS	116 (52)	49 (43)
Antibiotic	55 (24)	25 (22)
Other	29 (13)	18 (16)
SABA	21 (9)	7 (6)
Xanthine	5 (2)	2 (2)
SAMA	4 (2)	1 (1)
LAMA	3 (1)	1 (1)

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; PLA = placebo; SABA = short-acting beta-2 adrenergic agonist; SAMA = short-acting antimuscarinic agent.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 63: USE OF CONCOMITANT MEDICATIONS: CROSSOVER STUDIES

	BLAZE			BRIGHT		
	IG N = 223	TIO N = 220	PLA N = 218	IG N = 77	TIO N = 83	PLA N = 77
Other medications, n (%)						
Any COPD-related	127 (57)	128 (58)	127 (58)	31 (40)	29 (35)	29 (38)
Total CS	115 (52)	113 (51)	114 (52)	26 (34)	26 (31)	26 (34)
ICS	109 (49)	108 (49)	108 (50)	26 (34)	26 (31)	26 (34)
Total oral	7 (3)	4 (2)	5 (2)	NA	NA	NA
Prednisone	3 (1)	1 (1)	1 (1)	NA	NA	NA

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; NA = not applicable; PLA = placebo; SD = standard deviation; TIO = tiotropium.
Source: Clinical study report for BLAZE and BRIGHT.[17,18]

Subgroups

TABLE 64: SUBGROUP ANALYSIS OF SGRQ-C SCORES: LAMA/LABA-CONTROLLED

	QUANTIFY	
	IG N = [redacted]	TF N = [redacted]
By GOLD ≤ II		
Mean (SD) change from baseline	–3.56 (12.438) N = [redacted]	–3.13 (12.363) N = [redacted]
LS MD (95% CI)		0.05 (–2.34 to 2.43) *P* = 0.969
By GOLD ≥ III		
Mean (SD) change from baseline	–2.55 (11.631) N = [redacted]	–1.14 (12.200) N = [redacted]
LS MD (95% CI)		–1.20 (–3.76 to 1.36) *P* = 0.356
By age		
< 65 years Mean (SD) change from baseline	–3.43 (11.799) N = [redacted]	–2.55 (12.719) N = [redacted]
LS MD (95% CI)		–0.04 (–2.27 to 2.18) *P* = 0.969
≥ 65 years Mean (SD) change from baseline	–2.75 (12.417) N = [redacted]	–1.73 (11.759) N = [redacted]
LS MD (95% CI)		–1.81 (–4.60 to 0.99) *P* = 0.205

GOLD = Global Initiative for Chronic Obstructive Lung Disease; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; SD = standard deviation; SGRQ-C = St. George's Respiratory Questionnaire-COPD; TF = tiotropium + formoterol.

Source: Clinical study report for QUANTIFY.[11]

TABLE 65: SUBGROUP ANALYSIS OF EXACERBATIONS: LAMA-CONTROLLED

	SPARK		
Moderate/Severe Exacerbations, Rate	**IG N = 729**	**G N = 739**	**TIO N = 737**
By COPD severity			
Severe (95% CI)	0.81 (0.72 to 0.92)	0.91 (0.80 to 1.03)	0.96 (0.85 to 1.08)
Ratio of rates		0.89 (0.77 to 1.03) *P* = 0.120	0.85 (0.74 to 0.98) *P* = 0.023
Very severe (95% CI)	0.92 (0.75 to 1.14)	1.11 (0.91 to 1.36)	0.84 (0.68 to 1.03)
Ratio of rates		0.83 (0.64 to 1.07) *P* = 0.145	1.10 (0.84 to 1.43) *P* = 0.489
By smoking status			
Former smoker (95% CI)	0.83 (0.72 to 0.94)	0.97 (0.85 to 1.11)	0.96 (0.84 to 1.09)
Ratio of rates		0.85 (0.73 to 0.99) *P* = 0.042	0.86 (0.74 to 1.01) *P* = 0.065
Current smoker (95% CI)	0.86 (0.73 to 1.01)	0.93 (0.80 to 1.09)	0.89 (0.76 to 1.05)
Ratio of rates		0.92 (0.75 to 1.13) *P* = 0.441	0.97 (0.79 to 1.19) *P* = 0.750

CI = confidence interval; COPD = chronic obstructive pulmonary disease; G = glycopyrronium; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; TIO = tiotropium.

Source: Clinical study report for SPARK.[12]

TABLE 66: SUBGROUP ANALYSIS OF TROUGH FEV_1: LAMA-CONTROLLED

	SHINE				
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232
Trough FEV_1 by COPD severity					
Moderate or less LS mean (SE)	1.45 (0.01) N = 288	1.38 (0.01) N = 267	1.35 (0.01) N = 272	1.37 (0.01) N = 280	1.21 (0.02) N = 133
LS MD (95% CI)		0.06 (0.03 to 0.10) *P* < 0.001	0.09 (0.06 to 0.13) *P* < 0.001	0.07 (0.04 to 0.10) *P* < 0.001	0.24 (0.20 to 0.28) *P* < 0.001
Severe or worse LS mean (SE)	1.45 (0.02) N = 154	1.37 (0.02) N = 168	1.38 (0.02) N = 152	1.37 (0.02) N = 166	1.33 (0.03) N = 58
LS MD (95% CI)		0.08 (0.04 to 0.13) *P* < 0.001	0.08 (0.03 to 0.12) *P* < 0.001	0.08 (0.04 to 0.12) *P* < 0.001	0.12 (0.06 to 0.18) *P* < 0.001
Trough FEV_1 by smoking status					
Former smoker LS mean (SE)	1.46(0.01) N = 264	1.37 (0.01) N = 270	1.37 (0.01) N = 251	1.37 (0.01) N = 272	1.25 (0.02) N = 116
LS MD (95% CI)		0.09 (0.06 to 0.12) *P* < 0.001	0.08 (0.05 to 0.12) *P* < 0.001	0.08 (0.05 to 0.12) *P* < 0.001	0.21 (0.16 to 0.25) *P* < 0.001
Current smoker LS mean (SE)	1.44 (0.02) N = 178	1.39 (0.02) N = 165	1.35 (0.02) N = 173	1.37 (0.02) N = 174	1.24 (0.02) N = 75
LS MD (95% CI)		0.04 (0.00 to 0.09) *P* = 0.042	0.09 (0.05 to 0.13) *P* < 0.001	0.07 (0.02 to 0.11) *P* = 0.002	0.20 (0.14 to 0.25) *P* < 0.001
Trough FEV_1 by FEV_1 reversibility					
≤ 5% LS mean (SE)	1.39 (0.03) N = 75	1.36 (0.02) N = 82	1.34 (0.03) N = 83	1.37 (0.02) N = 91	1.32 (0.04) N = 34
LS MD (95% CI)		0.04 (–0.03 to 0.10) *P* = 0.260	0.05 (–0.01 to 0.11) *P* = 0.109	0.02 (–0.04 to 0.09) *P* = 0.425	0.07 (–0.01 to 0.15) *P* = 0.084
> 5 to ≤ 12% LS mean (SE)	1.45 (0.02) N = 82	1.36 (0.02) N = 83	1.39 (0.02) N = 81	1.34 (0.03) N = 68	1.16 (0.03) N = 42
LS MD (95% CI)		0.09 (0.03 to 0.15) *P* = 0.004	0.06 (0.00 to 0.12) *P* = 0.050	0.11 (0.04 to 0.17) *P* = 0.001	0.29 (0.21 to 0.36) *P* < 0.001
> 12% LS mean (SE)	1.46 (0.01) N = 285	1.38 (0.01) N = 270	1.36 (0.01) N = 260	1.38 (0.01) N = 287	1.25 (0.02) N = 115
LS MD (95% CI)		0.08 (0.04 to 0.11) *P* < 0.001	0.10 (0.07 to 0.14) *P* < 0.001	0.08 (0.05 to 0.11) *P* < 0.001	0.21 (0.17 to 0.25) *P* < 0.001
Trough FEV_1 by age					
< 65 years LS mean (SE)	1.45 (0.01) N = 231	1.39 (0.01) N = 230	1.35 (0.01) N = 214	1.38 (0.01) N = 241	1.25 (0.02) N = 92

	SHINE				
	IG N = 474	I N = 476	G N = 473	TIO N = 480	PLA N = 232
LS MD (95% CI)		0.07 (0.03 to 0.10) *P* < 0.001	0.10 (0.06 to 0.14) *P* < 0.001	0.07 (0.04 to 0.11) *P* < 0.001	0.20 (0.16 to 0.25) *P* < 0.001
65 to < 75 years LS mean (SE)	1.44 (0.02) N = 150	1.36 (0.02) N = 159	1.37 (0.02) N = 152	1.37 (0.02) N = 150	1.23 (0.02) N = 76
LS MD (95% CI)		0.07 (0.03 to 0.12) *P* = 0.001	0.07 (0.03 to 0.12) *P* = 0.002	0.07 (0.02 to 0.11) *P* = 0.004	0.21 (0.15 to 0.26) *P* < 0.001
≥ 75 years LS mean (SE)	1.45 (0.03) N = 61	1.36 (0.03) N = 46	1.38 (0.03) N = 58	1.35 (0.03) N = 55	1.28 (0.04) N = 23
LS MD (95% CI)		0.09 (0.02 to 0.17) *P* = 0.019	0.07 (0.00 to 0.14) *P* = 0.060	0.10 (0.03 to 0.17) *P* = 0.008	0.18 (0.08 to 0.27) *P* < 0.001

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; G = glycopyrronium; I = indacaterol; IG = indacaterol + glycopyrronium; LAMA = long-acting antimuscarinic agent; LS = least squares; MD = mean difference; PLA = placebo; SE = standard error; TIO = tiotropium.
Source: Clinical study report for SHINE.[13]

TABLE 67: SUBGROUP ANALYSIS OF FEV_1 (0 HOURS TO 12 HOURS): ICS/LABA-CONTROLLED

	ILLUMINATE	
	IG N = 258	FP/S N = 264
FEV_1 (0 hours to 12 hours) by age		
< 65 years LS mean (SE)	1.67 (0.03) N = 135	1.52 (0.03) N = 133
LS MD (95% CI)		0.15 (0.10 to 0.19), *P* < 0.001
65 to < 75 years LS mean (SE)	1.67 (0.03) N = 81	1.56 (0.03) N = 87
LS MD (95% CI)		0.12 (0.06 to 0.18), *P* < 0.001
≥ 75 years LS mean (SE)	1.70 (0.06) N = 16	1.55 (0.06) N = 16
LS MD (95% CI)		0.15 (0.01 to 0.29), *P* = 0.031
FEV_1 (0 hours to 12 hours) by smoking status		
Former smoker LS mean (SE)	1.68 (0.03) N = 114	1.56 (0.03) N = 122
LS MD (95% CI)		0.12 (0.07 to 0.17), *P* < 0.001
Current smoker LS mean (SE)	1.67 (0.03) N = 118	1.52 (0.03), N = 114
LS MD (95% CI)		0.15 (0.10 to 0.21), *P* < 0.001
FEV_1 (0 hours to 12 hours) by COPD severity		
Moderate LS mean (SE)	1.68 (0.03) N = 183	1.53 (0.03) N = 191
LS MD (95% CI)		0.15 (0.11 to 0.19), *P* < 0.001

	ILLUMINATE	
	IG N = 258	**FP/S N = 264**
Severe LS mean (SE)	1.66 (0.04) N = 49	1.56 (0.04) N = 45
LS MD (95% CI)		0.10 (0.02 to 0.18), *P* = 0.016
FEV_1 (0 hours to 12 hours) by FEV_1 reversibility		
≤ 5% LS mean (SE)	1.71 (0.05) N = 28	1.65 (0.05) N = 28
LS MD (95% CI)		0.06 (–0.04 to 0.17), *P* = 0.249
> 5 to ≤ 12% LS mean (SE)	1.66 (0.04) N = 58	1.51 (0.04) N = 46
LS MD (95% CI)		0.15 (0.07 to 0.22), *P* < 0.001
> 12% LS mean (SE)	1.68 (0.03) N = 146	1.53 (0.03) N = 162
LS MD (95% CI)		0.15 (0.10 to 0.19), *P* < 0.001

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FP/S = fluticasone propionate + salmeterol; ICS = inhaled corticosteroid; IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LS = least squares; MD = mean difference; SE = standard error.
Source: Clinical study report for ILLUMINATE.[14]

TABLE 68: SUBGROUP ANALYSIS FOR ENLIGHTEN

	ENLIGHTEN	
	IG N = 225	**PLA N = 113**
No subgroup data located		

IG = indacaterol + glycopyrronium; PLA = placebo.
Source: Clinical study report for ENLIGHTEN.[15]

TABLE 69: SUBGROUP ANALYSIS OF TROUGH FEV_1: COMPONENT-CONTROLLED STUDY

	BEACON	
	IG N = 90	I and G (Individual Components) N = 103
Trough FEV_1 by age		
< 65 years LS mean (SE)	1.441 (0.030) N = 34	1.476 (0.026) N = 44
LS MD (95% CI)		–0.035 (–0.106 to 0.035) *P* = 0.324
≥ 65 years LS mean (SE)	1.472 (0.024) N = 47	1.455 (0.024) N = 52
LS MD (95% CI)		0.017 (–0.044 to 0.078) *P* = 0.585
Trough FEV_1 by smoking status		
Former smoker LS mean (SE)	1.468 (0.025) N = 46	1.471 (0.023) N = 57
LS MD (95% CI)		–0.003 (–0.063 to 0.056) *P* = 0.912
Current smoker LS mean (SE)	1.450 (0.028) N = 35	1.459 (0.026) N = 39
LS MD (95% CI)		–0.008 (–0.079 to 0.062) *P* = 0.817

FEV_1 = forced expiratory volume in one second; IG = indacaterol + glycopyrronium; LS = least squares; MD = mean difference; SE = standard error.
Source: Clinical study report for BEACON.[16]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

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

- Forced expiratory volume in one second (FEV_1)
- Chronic Respiratory Disease Questionnaire Self-Administered Scale (CRQ-SAS)
- St. George's Respiratory Questionnaire (SGRQ).

Findings

FEV_1, CRQ-SAS, and SGRQ are briefly summarized in Table 70:

TABLE 70: VALIDITY AND MCID OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
FEV_1	FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second.	Yes	0.10 L to 0.14 L	[39]
CRQ-SAS	Self-administered. CRQ-SAS consists of 20 items measuring four domains: dyspnea, fatigue, emotional function, and mastery. Patients rate their experience on a 7-point scale, ranging from 1 to 7, where a higher score indicates less severe symptoms or better quality of life.	Yes	0.5 per item	[40-43]
SGRQ	The SGRQ is a disease-specific measure of HRQoL that consists of 50 items and was specifically developed for patients with chronic airflow limitation. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD. The questionnaire is divided into three dimensions: symptoms, activity, and impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst impairment.	Yes	4.0 points	[44-47]

CRQ-SAS = Chronic Respiratory Disease Questionnaire Self-Administered Scale; FEV1 = forced expiratory volume in one second; HRQoL = health-related quality of life; MCID = minimal clinically important difference; SGRQ = St. George's Respiratory Questionnaire-COPD.

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 COPD outcomes.[48,49] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[50] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L.[39] 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%.[48] 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 Initiative for Chronic Lung Disease (GOLD) criteria indicate that post-bronchodilator values should be used.[50] This is supported by evidence from a prospective study of 300 patients with COPD who were followed for at least one and a half years and who were evaluated every three months until the end of the study.[50] 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 percent predicted FEV_1 was a significant independent predictor of both all-cause mortality and respiratory-cause mortality, whereas the pre-bronchodilator percent 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 pre-bronchodilator percent predicted FEV_1 ($P = 0.009$ versus 0.131).

Normalized AUC FEV_1 is an average of the measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation.[51] No information regarding the validity of this outcome or the MCID was identified.

Chronic Respiratory Disease Questionnaire

Chronic Respiratory Disease Questionnaire (CRQ) was developed by Guyatt et al. in 1987.[52] CRQ examines four aspects of patients' lives: dyspnea, fatigue, emotional function, and mastery (the feeling of control over the disease and its effects). It was originally administered by a clinician, but it has been modified to a self-administered scale (CRQ-SAS) since.[40,43,52-55] The CRQ-SAS consists of 20 items that measure physical and emotional function, divided into the same four dimensions: dyspnea, fatigue, emotion, and mastery. Each patient is asked to choose five activities from a list of 25 or he/she can mention other activities that are not on the list. This means that the dimension "dyspnea" is strictly individualized. When completing CRQ-SAS, patients rated their experience on a seven-point scale, ranging from 1 (maximum impairment) to 7 (no impairment), where higher score indicate less severe symptoms or better quality of life.[41,56,57] The validity, sensitivity, internal consistency, and test-retest reliability were studied and reported for each of the four dimensions.[53-55,58,59] A mean change of 0.5 per item was considered to be the MCID for dyspnea, fatigue, or emotional function score in patients with COPD.[40,42,43]

In one study,[52] Guyatt at al. studied the reproducibility tested and responsiveness (sensitivity to change) of CRQ-SAS in 100 patients with chronic airflow limitation. The authors concluded that the changes in questionnaire score were correlated with changes in spirometric values, exercise capacity, and patients' and physicians' global ratings. Thus, it has been shown that the questionnaire is precise, valid, and responsive.[52] It can therefore serve as a useful disease-specific measure of quality of life for clinical trials. CADTH consulting clinical experts also indicated that the CRQ-SAS used to be frequently applied to assess quality of life in patients with COPD, but it has not been used in recent years. The reliability and validity of this questionnaire have been investigated by Wijkstra et al. in the four separate dimensions of the CRQ in 1994.[55] In the study by Wijkstra, the internal consistency and reliability of each dimension of CRQ was investigated and it was found that items of the dimensions fatigue, emotion, and mastery of the CRQ are reliable and valid and can be used to assess quality of life in patients with severe airway obstruction. Items of the dyspnea dimension are less reliable and should not be included in the overall score of the CRQ in comparative research.[55] However, by scoring the items of dyspnea separately, they may be useful for the evaluation of the effects of intervention in a specific patient.[55] In another study,[58] CRQ-SAS and St. George's Respiratory Questionnaire (SGRQ) were compared. It was found that the internal consistency was good for both questionnaires (Cronbach's alpha coefficients > 0.84 for the

CRQ and > 0.76 for the SGRQ).[58] It was concluded by the author that, since this analysis of reliability, validity, and responsiveness to change did not clearly favour one instrument above the other, the choice between the CRQ and the SGRQ can be based on other considerations such as the required sample size.[58]

St. George's Respiratory Questionnaire

The 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.[44] It was developed in 1992 to measure impaired health and perceived well-being in patients with airways disease, and to meet the need for a sensitive measure of HRQoL.[60] The instrument has been used worldwide in studies and in clinical settings.[60] The SGRQ includes questions regarding sleep disturbances, public embarrassment, panic (which can be signs of depression or anxiety), feeling like a nuisance to friends and family, employment, and recreation activities (which are indicative of social impact).[61]

The 50 items of the questionnaire are divided into three dimensions: symptoms (eight items measuring 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).[47] 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.[46,47] The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units of change, a decrease in scores indicating an increase in HRQoL.[45] These have been examined as within-group measures, not between-group measures. As all estimates of clinical significance are subject to measurement and sample error and require value judgments, MCID should be interpreted with caution,[45] and 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 five-point scale, where a low score indicates less severe symptoms and a high score indicates more severe symptoms.[47] A number of items in the symptoms component relate to the frequency of symptoms over the previous year.[62] 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.[47] Impacts covers aspects involved in social functioning and psychosocial disturbances resulting from obstructive airways disease (employment, panic, medication, and side effects).[47] Social functioning and psychosocial disturbances have been identified by patients as particularly troubling aspects of COPD. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD.[46] A difference of four points or more in the SGRQ total score versus placebo at study end, or four points or more from baseline, is considered the MCID for this measure.[63]

Summary

FEV_1, SGRQ, and CRQ-SAS have all been shown to be valid outcome measure for patients with COPD. The suggested MCIDs for FEV_1, SGRQ, and CRQ-SAS were 0.10 L to 0.14 L, four units' change from baseline, and 0.5 point change per item, respectively. Since similar reliability, validity, and sensitivity, the choice between the CRQ-SAS and the SGRQ (SGRQ-C) were based on other considerations such as the required sample size. However, CRQ-SAS used to be frequently used in the clinical trials, but has not been used in recent years.

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