LMMG New Medicine Recommendation

Aclidinium, Glycopyrronium, Indacaterol and Tiotropium Handihaler® for COPD

LMMG Recommendation:
LAMAs:
Tiotropium 18mcg once daily via HandiHaler® remains the preferred LAMA based on its greater body of evidence in moderate, severe and very severe COPD and in patients with a history of exacerbations. **GREEN Recommendation**

Aclidinium and glycopyrronium are only recommended as alternatives where a LAMA is required but tiotropium is contraindicated or its inhalation device cannot be used after initial training and an adequate therapeutic trial. **GREEN with restrictions**

Indacaterol:
Indacaterol is recommended as an alternative to other LABAs. As a once daily LABA it may offer greater convenience than twice daily LABAs, but robust evidence of sustained benefits over formoterol to warrant its significantly greater acquisition costs are currently lacking. There is no robust evidence of sustained benefits of indacaterol over tiotropium. **GREEN with restrictions**

Summary of supporting evidence:

- Tiotropium 18mcg once daily via the HandiHaler® has the greatest body of evidence supporting use in patients with moderate, severe and very severe COPD, including those experiencing exacerbations. Tiotropium appears to have similar efficacy to LABAs in terms of lung function and improving breathlessness, but also appears to reduce exacerbation rates to a greater extent than LABAs, including the once daily LABA indacaterol.
- Aclidinium and glycopyrronium are effective treatments for symptomatic patients with moderate to severe COPD. Based on limited evidence from direct and indirect comparisons, they appear to have broadly similar efficacy to tiotropium in terms of lung function, improvements in breathlessness and health status. However, robust data in patients with severe COPD experiencing exacerbations are lacking for aclidinium and glycopyrronium.
- Indacaterol 150mcg once daily has demonstrated statistically significant improvements in lung function compared with salmeterol 50mcg twice daily in patients with moderate to severe COPD. The clinical significance of the observed differences in lung function is unclear, but short term data suggest significantly more patients using indacaterol 150mch once daily achieved clinically relevant improvements in breathlessness and health status. Evidence for indacaterol 300mcg once daily is more limited than for indacaterol 150mcg, but shows similar improvements over formoterol for breathlessness and health status.
- There are several limitations to the available trial data for all bronchodilators. Most trials are relatively short-term considering the chronic, progressive nature of COPD, and drop-out rates in several trials are high. Patients with cardiovascular disease were generally excluded from trials, and cardiovascular disease is a common co-morbid condition in COPD. In addition, patients in trials often appear not to be treated in line with current

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treatment guidelines; high proportions of patients with moderate to severe COPD appear to use inhaled corticosteroids, despite low rates of previous exacerbations, and comparisons of LAMA against LABA plus inhaled corticosteroids in patients with severe COPD are confounded by high levels of use of inhaled corticosteroids in both treatment arms.
- LMMG will separately review the position of tiotropium Respimat® and Ultibro® fixed combination of indacaterol and glycopyrronium in the future.

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Background and context

Chronic Obstructive Pulmonary Disease (COPD) occurs mainly due to chronic inflammation associated with tobacco smoking. A combination of airway and parenchymal damage leads to chronic, irreversible and progressive airways obstruction, causing breathlessness, disability and impaired quality of life. Exacerbations can occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations, and may require treatment with antibiotics, oral steroids and, if severe, hospitalisation.[1] In the North West, around 157,000 people have diagnosed COPD, and 3,000 people die from COPD each year.[40]

Pharmacological therapy aims to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status. The NICE Clinical Guideline on COPD recommends initial treatment with short-acting inhaled bronchodilators (either short-acting $beta_2$ agonists or muscarinic antagonists) for the relief of breathlessness and exercise limitation. In people with stable COPD who remain breathless or have exacerbations despite use of short-acting bronchodilators as required, maintenance therapy should be offered:

- if forced expiratory volume in 1 second (FEV1) ≥ 50% predicted: either long-acting $beta_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA)
- if FEV1 < 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.

In people with stable COPD and an FEV1 of at least 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:

- consider LABA+ICS in a combination inhaler
- consider LAMA in addition to LABA where ICS is declined or not tolerated.

LAMA in addition to LABA plus ICS should be offered to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV1.[1]

The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.[1]

Several long acting bronchodilators have been licensed for COPD in recent years, including indacaterol (LABA), and aclidinium and glycopyrronium (LAMAs). This evidence review considers the place in therapy of these inhalers in the context of established products, including the LAMA tiotropium delivered vi HandiHaler®.

Ultibro® (a fixed combination of glycopyrronium and indacaterol) is expected to be launched in Q2 2014 [Presonal communication, Novartis, December 2013]; however, at the time of this review, the manufacturer was unable to confirm the price at which the product will be launched. A separate review of Ultibro® will be considered once the price is confirmed.

In 2010 the MHRA issued a safety update advising that tiotropium delivered as a solution for inhalation (Spiriva Respimat®) should be used with caution in patients with cardiac rhythm disorders after a safety study reported an excess risk of mortality in such patients. Several sources of evidence on the safety of tiotropium Respimat® have since become available and will be considered in a separate review of tiotropium Respimat®.

Evidence in Proposed Use

Summary of Efficacy Data:

This review draws largely on evidence from randomised, controlled trials of individual products considered by the Scottish Medicines Consortium and NICE evidence summaries, supplemented with more recent published trial data where available. Summary trial data are provided in Tables 1 to 4.

Aclidinium bromide (Eklira Genuair®):
Key evidence for the licensed dose of twice daily aclidinium is available from a 12-week (ACCORD COPD I, n=561)[2] and a 24-week (ATTAIN, n=828)[3] randomised, double-blind, placebo-controlled trial in patients with moderate to severe COPD. The primary endpoint was change in forced expiratory volume in 1 second (FEV1), which was statistically significantly greater with the licensed dose equivalent of aclidinium than with placebo in both trials. The difference over placebo of 124 and 128mL, respectively, exceeded the 100-120mL considered clinically meaningful. The 24-week ATTAIN trial also explored the impact of aclidinium on symptoms and health status as secondary endpoints. Clinically significant improvements in dyspnoea (measured as a 1-point change on the Transition Dyspnoea Index [TDI]) were observed in 57% of patients using aclidinium and 46% on placebo ($p<0.0001$; NNT 9). Clinically significant improvements in health-status (measured as a 4-point change in the St George's Respiratory Questionnaire [SGRQ] total score) were observed in 57% of patients using aclidinium and 41% on placebo ($p<0.0001$; NNT 6) (Table 1). A one-year extension of the ACCORD COPD I study has been published and demonstrates ongoing efficacy and safety of aclidinium, but does not provide comparative data against placebo or other agents.[41]

Direct comparative data against other agents are limited to a small (n=30), randomised, double-blind, 15-day cross-over trial against tiotropium 18mcg once daily,[4] and a larger (n=414), short-term, randomised, double-blind trial of aclidinium and tiotropium against placebo. The latter observed no statistically significant difference between aclidinium twice daily and tiotropium 18mcg once daily for the primary endpoint of change from baseline in FEV1 (normalised over 24 hours) at six weeks (differences over placebo: 150mL and 140mL, respectively), or for the secondary endpoint of change from baseline in normalised FEV1 over the night-time period (differences over placebo: 160mL and 123mL, respectively) at six weeks.[5]

Glycopyrronium bromide (Seebri Breezhaler®):
Key evidence for glycopyrronium 50mcg once daily is available from a 26-week (GLOW 1, n=822)[6] a 52-week (GLOW 2, n=1,066)[7] randomised, double-blind, placebo-controlled trial in patients with moderate to severe COPD. GLOW 2 also included an open-label tiotropium 18mcg once daily arm Table 2). Both trials assessed the primary endpoint of trough FEV1 at 12 weeks and demonstrated statistically significant improvements for glycopyrronium over placebo (108mL in GLOW 1 and 97mL in GLOW 2). There was no significant difference between glycopyrronium and tiotropium for trough FEV1 at 12 weeks or at 52 weeks. Clinically significant improvements in dyspnoea (1-point change on the TDI) were observed for more patients using glycopyrronium over placebo in both trials (NNT 8 at 26 weeks in GLOW 1 and 9 at 52 weeks in GLOW 2), and for more patients using tiotropium over placebo (NNT 11 at 52 weeks). Clinically significant improvements in health-status (4-point change on SGRQ) were observed for more patients using glycopyrronium over placebo in GLOW 1 (NNT 10 at 26 weeks) but not for either glycopyrronium or tiotropium over placebo in GLOW 2. The annualised rate of moderate or severe exacerbations per patient was significantly lower for glycopyrronium than for placebo (0.54 vs. 0.80; relative risk 0.66, $p=0.003$), but not for tiotropium vs. placebo. There were no significant differences between glycopyrronium and tiotropium for dyspnoea, health status or exacerbation rates at 52 weeks[7] (Table 2).

A further, 21-day cross over trial (GLOW 3, n=108)[8] in patients with moderate to severe COPD observed glycopyrronium to increase endurance time by 89 seconds compared with placebo during submaximal ergometry tests, but adds little over the other available data for glycopyrronium.

Indacaterol maleate (Onbrez Breezhaler®):
There have been several trials of once daily indacaterol 150mcg and 300mcg against placebo and active comparators (salmeterol, formoterol [LABAs] and tiotropium [LAMA]), over varying durations (Table 3). All but one (INVIGORATE[9]) have been conducted in patients with moderate to severe COPD and low exacerbation rates, and all have assessed FEV1 impact at 12 weeks as the primary endpoint.

Compared with placebo, indacaterol at doses of 150mcg and 300mcg once daily statistically significantly improved trough FEV1 by 130-180mL,[10-13] which exceeds the 100-120mL considered clinically meaningful. However, evidence of clinically meaningful differences in patient-orientated outcomes of dyspnoea, health status and exacerbation rates appears mixed in these placebo-controlled trials.

Two published trials of indacaterol 150mcg once daily against salmeterol 50mcg twice daily have been identified. INLIGHT 2 (n=1,002)[13] and INSIST (n=1,123)[15] both observed changes from baseline in FEV1 at 12 weeks to be statistically significantly greater with indacaterol by 57-60mL; however, the clinical significance of this improvement is unclear. Clinically significant improvements in health-status (4-point change on SGRQ) were observed for more patients using indacaterol over salmeterol in INLIGHT 2 (NNT 9 at 12 weeks), and in dyspnoea (1-point change on the TDI) in both trials (NNT 15 at 12 weeks in INSIST). Impact on exacerbation rates is not assessed in these short-term (12- and 26-week) trials.

One published trial (INVOLVE, n=1,732) of indacaterol 300mcg once daily against formoterol 12mcg twice daily observed changes from baseline in FEV1 at 12 weeks to be statistically significantly greater with indacaterol by 100mL, which is approaching a clinically relevant difference and was maintained at 52 weeks.[12] The proportion of patients achieving a clinically important improvement in dyspnoea was greater than placebo at 12 weeks for both indacaterol 300mcg (NNT 4) and formoterol (NNT 8); however, despite the differences in FEV1 in favour of indacaterol, the mean improvement in dyspnoea and health status scores at 52 weeks was not significantly different between indacaterol 300mcg and formoterol. The annual rate of exacerbations was statistically significantly lower with formoterol compared with placebo (relative risk 0.75, $p<0.05$) but not for indacaterol; however, exacerbation event rates were generally low in the trial.[12]

Two key trials have compared indacaterol against tiotropium 18mcg once daily in patients with moderate to severe COPD. INHANCE (n=1,665)[10] observed indacaterol at doses of 150mcg and 300mcg once daily to be statistically but not clinically superior to tiotropium for trough FEV1 at 12 weeks as a secondary endpoint (mean difference 40mL), and INTENSITY (n=1,598[14]) observed indacaterol 150mcg once daily to be non-inferior to tiotropium for trough FEV1 as the primary endpoint. A higher proportion of patients using indacaterol 150mcg achieved a clinically significant improvement in dyspnoea and health status compared with tiotropium at 12 weeks in INTENSITY[14] (NNTs 13), but there were no clinically relevant differences between indacaterol and tiotropium for dyspnoea at 26 weeks in INHANCE[10], and neither indacaterol nor tiotropium significantly reduced annualised exacerbation rates compared with placebo.[10]

The most recent and largest indacaterol trial to be published compared indacaterol 150mcg once daily against tiotropium 18mcg once daily in patients with severe COPD and a recent history of exacerbations (INVIGORATE, n=3,444).[16] Indacaterol was non-inferior to tiotropium for the primary endpoint of trough FEV1 at 12 weeks and was statistically but not clinically significantly inferior to tiotropium for trough FEV1 at 52 weeks. There was no statistically significant difference between indacaterol and tiotropium in the proportion of patients achieving a clinically relevant improvement in dyspnoea or health status at 52 weeks, but the overall exacerbation rate was statistically lower (0.90 vs. 0.73; relative risk 1.24 [95%CI 1.12 to 1.37]) and the rate and time to first moderate-to-

severe exacerbation were statistically significantly improved with tiotropium compared with indacaterol.

Other Comparative Efficacy data:

Tiotropium vs. LABA:
Tiotropium is a well-established LAMA in the treatment of COPD. A 2012 Cochrane review identified seven randomised controlled trials of tiotropium 18mcg once daily compared against LABA: four studies against salmeterol, one study against formoterol and two studies against indacaterol.[22] The INVIGORATE trial of indacaterol against tiotropium was not published at the time of the review.

The studies used similar designs and were generally of good methodological quality. However, studies varied in terms of smoking history and COPD severity of participants, and a high level of heterogeneity amongst studies meant it was not possible to pool data for the SGRQ quality of life score, which was the primary endpoint of the review. Tiotropium reduced the number of participants experiencing one or more exacerbations compared with all LABAs (odds ratio 0.86; 95% CI 0.79 to 0.93); there was no difference seen among the different types of LABA. Tiotropium was also associated with a reduction in the number of COPD exacerbations leading to hospitalisation compared with LABA treatment (odds ratio 0.87; 95%CI 0.77 to 0.99), but not in the overall rate of all-cause hospitalisations. There was no statistically significant difference in FEV1 or symptom score between tiotropium and LABA treated patients.[22] The results of the INVIGORATE trial of indacaterol against tiotropium (above) appear broadly comparable with these findings.[16]

Aclidinium vs. Glycopyrronium vs. Tiotropium:
There are no direct comparative data for aclidinium versus glycopyrronium. The Centre for Reviews and Dissemination (CRD) at the University of York has critiqued a published systematic review and network meta-analysis that provides indirect comparisons of aclidinium, glycopyrronium and tiotropium.[23, 24]

The systematic review identified 21 studies: three studies of aclidinium 400mcg twice daily, two studies of glycopyrronium 50mcg once daily, 13 studies of tiotropium 18mcg once daily, and three studies of tiotropium 5 mcg once daily. All but one trial was placebo-controlled. Bayesian network meta-analyses, with adjustment for some potential confounding effects of patient characteristics, were conducted. There were no statistically or clinically significant differences between aclidinium and glycopyrronium or tiotropium 18mcg for trough FEV1, dyspnoea measure using TDI scores or health status measured using SGRQ, at either 12 or 24 weeks.[23] The CRD critique notes that not all potential confounding factors could be controlled for within the analyses and there were some clinical and methodological differences between the included trials. The lack of direct comparative trials precluded assessment of inconsistency, and so the robustness of the results is uncertain. Overall, the study reflects the available evidence and the conclusions are moderately reliable.[24]

Dual bronchodilation with Tiotropium plus LABA vs. Tiotropium alone:
A 2012 Cochrane review[25] identified 5 randomised controlled trials of the addition of LABA to tiotropium in patients with moderate to severe COPD: two studies used indacaterol, two studies used formoterol and one study used salmeterol as the LABA. Compared to tiotropium alone, LABA plus tiotropium resulted in a small mean increase in trough FEV1 (mean difference 0.07 L; 95% CI 0.05 to 0.09), and a slightly larger improvement in mean health-related quality of life measured using SGRQ (4.5 units vs. 6.1 units, respectively; mean difference -1.61; 95% CI -2.93 to -0.29). There were no significant differences in hospital admissions, exacerbation rates, symptom scores, serious adverse events, and withdrawals. Heterogeneity and high withdrawal rates were noted among the trials, and confidence intervals around estimates were wide. There were insufficient data available from the literature review to determine the relative efficacy of tiotropium plus LABA compared with LABA alone.[25]

Summary of Safety Data:

LAMAs:
The safety profile of tiotropium 18mcg once daily, delivered as a dry powder via a HandiHaler® is well established. Aclidinium and glycopyrronium share similar anticholinergic effects to tiotropium, such as dry mouth, and all LAMAs should be used with caution in patients with urinary retention, and narrow-angle glaucoma.[26-29] The Summary of Product Characteristics (SPC) for tiotropium notes that in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) tiotropium should be used only if the expected benefit outweighs the potential risk.[26,27] The SPC for glycopyrronium notes the same for patients with severe renal impairment,[29] but the SPC for aclidinium notes that renal clearance plays only a minor role in its elimination, and no renal cautions are listed.[28]

Patients with a recent history of cardiovascular disease were excluded from the aclidinium and glycopyrronium trials, and the SPCs for both these LAMAs advise caution in use in patients with cardiovascular disease/conditions.[28,29] Although the tiotropium SPCs do not specifically refer to cardiovascular effects,[26,27] in 2010 the MHRA issued a safety update advising that tiotropium solution for inhalation (Spiriva Respimat®) should be used with caution in patients with cardiac rhythm disorders after a safety study reported an excess risk of mortality in such patients.[30] Several new sources of evidence regarding the safety of tiotropium Respimat® have since become available, and will be considered in a separate LMMG review of tiotropium Respimat®.

LABAs:
Indacaterol appears to have a similar safety profile to salmeterol and formoterol, which are well established treatments. As sympathomimetic agents, LABAs may induce tremor, increase systolic blood pressure and heart rate, and induce ECG changes. Hyperglycaemic effects have also been reported. LABAs should be used with caution in patients with cardiovascular disease or rhythm disorders, and in patients with diabetes. No renal effects are reported in SPCs.[32-34]

The Cochrane review of trials of tiotropium and LABAs reported a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA (odds ratio 0.88; 95% CI 0.78 to 0.99). The tiotropium group was also associated with a lower rate of study withdrawals (OR 0.89; 95% CI 0.81 to 0.99).[22] However, in the 52-week INVIGORATE trial of indacaterol versus tiotropium in patients with severe COPD, there was no significant difference in rates of any adverse events, serious adverse events or withdrawals due to adverse events.[16]

Summary of Evidence on Cost Effectiveness:

The Scottish Medicines Consortium (SMC) accepted the use of indacaterol, aclidinium and glycopyrronium on the basis of cost minimisation analyses. Indacaterol was compared against salmeterol and tiotropium, and aclidinium and glycopyrronium were compared against tiotropium only.[35-37] The implicit assumption of the cost minimisation approach is that these agents are therapeutically equivalent.

Evidence to support this assumption for indacaterol was a short-term direct comparison against salmeterol, and a secondary direct comparison against tiotropium 18mcg, which showed indacaterol to be comparable to these agents in terms of FEV1 in patients with moderate to severe COPD .[35] Since the SMC advice, a cost utility analysis of indacaterol compared against salmeterol and tiotropium in UK patients with moderate to severe has been published.[38] This estimates indacaterol to be both more effective and less costly than both salmeterol and tiotropium; however, it is not clear that the comparative data against tiotropium used in the model are the most relevant, as it excludes data available from the INTENSITY trial (showing no difference in trough FEV1 at 12 weeks between indacaterol and tiotropium in moderate to severe COPD) . The recently

published INVIGORATE trial data in patients with severe COPD also showed tiotropium to be non-inferior to indacaterol for trough FEV1 at 12 weeks, and tiotropium to be statistically superior to indacaterol at 52 weeks for both trough FEV1 and moderate to severe exacerbation rates.[16] The reliability of the cost utility analysis is therefore unclear.

Evidence to support the assumption of therapeutic equivalence of aclidinium and glycopyrronium compared to tiotropium, accepted in the SMC advice, was obtained from indirect comparisons of trial data using network meta-analyses.[36,37]

Key Points to Note from the Available Evidence:

- Aclidinium and glycopyrronium are effective treatments for symptomatic patients with moderate to severe COPD. Based on limited evidence from direct and indirect comparisons, they appear to have broadly similar efficacy to tiotropium in terms of lung function, improvements in breathlessness and health status. However, robust data in patients with severe COPD experiencing exacerbations are lacking for aclidinium and glycopyrronium.
- Tiotropium 18mcg once daily via the HandiHaler® has the greatest body of evidence supporting use in patients with moderate, severe and very severe COPD, including those experiencing exacerbations. Tiotropium appears to have similar efficacy to LABAs in terms of lung function and improving breathlessness, but also appears to reduce exacerbation rates to a greater extent than LABAs, including the once daily LABA indacaterol.
- Indacaterol 150mcg once daily has demonstrated statistically significant improvements in lung function compared with salmeterol 50mcg twice daily in patients with moderate to severe COPD. The clinical significance of the observed differences in lung function is unclear, but short term data suggest significantly more patients using indacaterol 150mch once daily achieved clinically relevant improvements in breathlessness and health status. Evidence for indacaterol 300mcg once daily is more limited than for indacaterol 150mcg, but shows similar improvements over formoterol for breathlessness and health status.
- There are several limitations to the available trial data for all bronchodilators. Most trials are relatively short-term considering the chronic, progressive nature of COPD, and drop-out rates in several trials are high. Patients with cardiovascular disease were generally excluded from trials, and cardiovascular disease is a common co-morbid condition in COPD. In addition, patients in trials often appear not to be treated in line with current treatment guidelines; high proportions of patients with moderate to severe COPD appear to use inhaled corticosteroids, despite low rates of previous exacerbations, and comparisons of LAMA against LABA plus inhaled corticosteroids in patients with severe COPD are confounded by high levels of use of inhaled corticosteroids in both treatment arms.

Productivity, Service Delivery and Implementation Considerations:
The launch of the newer long-acting bronchodilators is not anticipated to have significant productivity or service delivery impacts. No changes to the treatment pathway outlined in the current NICE Clinical Guideline on COPD[1] are anticipated.

The newer long-acting bronchodilators are all formulated as dry powder for inhalation. Glycopyrronium and indacaterol (and the fixed combination of these, Ultibro®) are delivered via the same Breezhaler® device, and aclidinium is delivered via a Genuair® device. These devices differ from those of established agents. The NICE Clinical Guideline recommends that inhalers should be prescribed only after patients have received training in the use of the device and have demonstrated satisfactory technique.[1]

Innovation, Need and Equity Considerations:
There is no evidence to suggest that the newer long-acting bronchodilators are innovative or address significant unmet needs compared with the well-established existing agents. No equity considerations are anticipated.

Comparative unit costs:
Table 5 provides example comparative unit costs for newer and existing long-acting bronchodilators. As there are several formulations and brands of existing agents, the range of the most and least costly products is provided.

Currently, the acquisition costs of aclidinium and glycopyrronium are lower than for tiotropium by around £60-70 per patient per year. The patent on tiotropium is anticipated to expire in 2015, which may result in generic versions at lower acquisition cost.

The acquisition costs of indacaterol are similar to the lower cost salmeterol products, which are over £200 greater per year than the lowest cost formoterol product.

The manufacturer of Ultibro® (fixed combination of glycopyrronium and indacaterol) has been unable to confirm the price at which this product will be launched in the UK. Ultibro® is therefore excluded from Table 5.

Table 5. Example minimum and maximum annual acquisition costs of long-acting bronchodilators

Drug name	Example regimen	Pack cost	Annual maintenance cost per patient (ex VAT)
LABA			
Formoterol 12mcg (Easyhaler Formoterol™) 120 dose dry powder	12mcg twice daily	£23.75	£142.50
Formoterol 12mcg (Oxis Turbohaler®) 60 dose dry powder	12mcg twice daily	£24.80	£297.60
Indacaterol 150mcg, or 300mcg (Onbrez Breezhaler®) 30 dose dry powder	150mcg or 300mcg once daily	£29.26	£351.12
Salmeterol 25mcg (Neovent/non-proprietary) 120 dose pMDI	25mcg x 2 puffs twice daily	£27.80	£333.60
Salmeterol 50mcg (Serevent Diskhaler®) 60 dose dry powder	50mcg twice daily	£35.15 (refill)	£422.44*
LAMA			
Aclidinium 322mcg (Eklira Genuair®) 60 dose dry powder	322mcg twice daily	£28.60	£343.20
Glycopyrronium 50mcg (Seebri Breezhaler®) 30 dose dry powder	50mcg once daily	£27.50	£330.00
Tiotropium 18mcg (Spiriva®) 30 dose dry powder via HandiHaler®	Once daily	£33.50 (refill)	£403.37*
Tiotropium 2.5mcg (Spiriva Respimat®) 30 dose solution for inhalation	2.5mcg x 2 puffs once daily	£35.50	£426.00
Costs based on MIMS list prices as of October 2013, assuming 12 x 30 day periods. This table does not imply therapeutic equivalence of drugs or doses. *This cost includes 1 starter and 11 refills per year			

Recommended Place in Therapy

LAMAs:
Tiotropium 18mcg once daily via HandiHaler® remains the preferred LAMA based on its greater body of evidence in moderate, severe and very severe COPD and in patients with a history of exacerbations.

Aclidinium and glycopyrronium are only recommended as alternatives where a LAMA is required but tiotropium is contraindicated or its inhalation device cannot be used after initial training and an adequate therapeutic trial.

Indacaterol:
Indacaterol is recommended as an alternative to other LABAs. As a once daily LABA it may offer greater convenience than twice daily LABAs, but robust evidence of sustained benefits over formoterol to warrant its significantly greater acquisition costs are currently lacking.

There is no robust evidence of sustained benefits of indacaterol over tiotropium.

Financial and Service Implications

Anticipated patient numbers and net budget impact:
The costing report accompanying the NICE Clinical Guideline indicates a prevalence of diagnosed COPD in the North West of around 2%.[39] This would equate to around 30,000 people with COPD in Lancashire.

Prescribing data for Lancashire for the 12 months to September 2013 indicates a spend on COPD-specific long acting bronchodilators of around £6.64million. This excludes prescribing of the LABAs salmeterol or formoterol, and inhaled corticosteroids, as it is not possible to differentiate their use in COPD from that in asthma.

Tiotropium 18mcg via the HandiHaler® accounts for around 88% of all prescribing of COPD-specific long-acting bronchodilators, and tiotropium 2.5mcg solution for inhalation via Respimat® accounts for around 9%. Current use of aclidinium and glycopyrronium is low (<2%) but has been growing over the last 12 months, and current use of indacaterol is low and stable.

The acquisition costs of aclidinium and glycopyrronium are currently around 14-18% lower than those for tiotropium (see Table 5). A 10% shift in prescribing from tiotropium 18mcg to aclidinium or glycopyrronium would lead to savings in the prescribing budget of around £88,000 to £107,000 per year across Lancashire; however, this assumes that other costs related to exacerbations and follow on treatments are unchanged.

COPD-related prescribing data for established LABAs used alone, in combination with inhaled corticosteroids or alongside LAMAs are not available. It is therefore difficult to estimate a potential net budget impact of the use of indacaterol as an alternative individual LABA.

References

1. National Institute for Health and Clinical Excellence. COPD Clinical Guideline 101; 2010. Accessed 12 November 2013 at: http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-cg101 .
2. Kerwin EM, D'Urzo AD, Gelb AF et al. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). COPD: Journal of Chronic Obstructive Pulmonary Disease 2012; 9: 90–101.
3. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. European Respiratory Journal 2012; 40: 830–6.
4. Fuhr R, Magnussen H, Sarem K, et al. Efficacy of aclidinium bromide 400mg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. Chest 2012; 141:745–52.
5. Beier J, Kirsten A-M, Mróz R, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled phase IIIb study. COPD 2013; DOI: 10.3109/15412555.2013.814626.

6. D'Urzo A, Ferguson GT, van Noord JA, et al. Efficacy and safety of once-daily NVA237 inpatients with moderate-to-severe COPD: the GLOW1 trial. Respiratory Research 2011; 12: 156.
7. Kerwin E, Hébert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. European Respiratory Journal 2012; 40:1106–14.
8. Beeh KM, Singh D, Di Scala L, et al. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. International Journal of COPD 2012; 7: 503–13.
9. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. The Lancet Respiratory Medicine 2013; 1: 524-33.
10. Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med 2010; 182: 155–62.
11. Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulmonary Medicine 2010;10: 11
12. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 2010;65:473-9.
13. Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011; 37: 273–9.
14. Buhl R, Dunn LJ, Disdier C, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J 2011; 38: 797–803.
15. Korn S, Kerwin E, Atis S, et al. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: A 12-week study. Respiratory Medicine 2011; 105: 719-26.
16. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respiratory 2013; 1: 524-13.
17. Dahl R, Jadayel D, Alagappan VKT, et al. Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. International Journal of COPD 2013:8 501–8.
18. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013; 42:1484-94.
19. European Medicines Agency. Ultibro Breezhaler - European Public Assessment Report; July 2013. Accessed 20 December 2013 at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002679/WC500151257.pdf.
20. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respiratory Medicine 2013; 1: 199-209.
21. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol–fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respiratory Medicine 2013; 1: 51-60.
22. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD009157. DOI: 10.1002/14651858.CD009157.pub2.
23. Karabis A, Lindner L, Mockarski M, et al. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. International Journal of COPD 2013; 8: 405-23.
24. Centre for Reviews and Dissemination. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. University of York; November

2013. Accessed 22 December 2013 at: http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=12013055521&UserID=0.
25. Karner C, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD008989. DOI: 10.1002/14651858.CD008989.pub2.
26. Boehringer Ingelheim Ltd. Summary of Product Characteristics - Spiriva 18mcg inhalation powder; October 2013. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/.
27. Boehringer Ingelheim Ltd. Summary of Product Characteristics - Spiriva Respimat 2.5mcg solution for inhalation; October 2013. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/20134/SPC/Spiriva+Respimat+2.5+micrograms+solution+for+inhalation/.
28. Almirall Ltd. Summary of Product Characteristics -Eklira Genuair 322mcg inhalation powder; December 2013. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/27001/SPC/Eklira+Genuair+322+micrograms+inhalation+powder/.
29. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics -Seebri Breezhaler inhalation powder 44mcg; November 2012. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/27138/SPC/Seebri+Breezhaler+Inhalation+Powder%2c+Hard+Capsules+44mcg/.
30. MHRA. Tiotropium: safety studies of Spiriva Respimatq. Drug Safety Update 2010; 4 (4). Accessed 20 December 2013 at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON099869.
31. Dong H-Y, Lin H-H, Shau W-Y, et al. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax 2013; 68: 48–56.
32. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics - Onbrez Breezhaler inhalation powder 44mcg; October 2013. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/23260/SPC/Onbrez+Breezhaler+150+and+300+microgram+inhalation+powder%2c+hard+capsules/.
33. Allen & Hanburys Ltd. Summary of Product Characteristics - Serevent Accuhaler; May 2012. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/91/SPC/Serevent+Accuhaler/.
34. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics - Foradil; October 2013. Accessed 20 December 2013 at: http://www.medicines.org.uk/emc/medicine/1286/SPC/Foradil/.
35. Scottish Medicines Consortium. Indacaterol 150 and 300 micrograms inhalation powder hard capsules (Onbrez Breezhaler®) (No.619/10); June 2010.
36. Scottish Medicines Consortium. Aclidinium 322 micrograms inhalation powder (Eklira Genuair®) SMC No. (810/12); October 2012.
37. Scottish Medicines Consortium. Glycopyrronium 44 micrograms hard capsules of inhalation powder (Seebri Breezhaler®) SMC No. (829/12); December 2012.
38. Price D, Asukai Y, Ananthapavan J, et al. A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD, using real world evidence on resource use. Appl Health Econ Health Policy 2013; 11:259–74.
39. National Institute for Health and Clinical Excellence. Costing report: Chronic obstructive pulmonary disease, clinical Guideline 101; February 2011. Accessed 23 December 2013 at: http://www.nice.org.uk/nicemedia/live/13029/53292/53292.pdf.
40. NHS North West Respiratory Clinical Pathway Team. North West COPD Report, November 2011. Accessed 23 December 2013 at: http://www.networks.nhs.uk/nhs-networks/respiratory-leads/documents/North%20West%20COPD%20Report%20final%20v1.pdf.

41. D'Urzo A, Kerwin E, Rennard S, et al. One-year extension study of ACCORD COPD I: safety and efficacy of two doses of twice-daily aclidinium bromide in patients with COPD. COPD 2013; 10:1–11.

Table 1 Summary of key Aclidinium bromide RCTs

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison*	Outcomes: Primary endpoint	Outcomes: Key secondary / exploratory endpoints
ACCORD COPD I [2]	12-week, double-blind, placebo controlled, Parallel-group study (with 2-week run-in)	≥40 yrs (mean 64 yrs) Male: 53% Caucasian: 93.8% Current or former cigarette smokers ≥ 10 pack years Moderate to severe COPD Mean % predicted FEV_1: 47% Before screening use of COPD medications: 64% SABAs, 38% LABA+ICS, 30% LAMA, 8% ICS, 5% LABA, 5% SAMA (only SABAs & ICS continued throughout study) Excluded unstable , recent CV disease	Aclidinium 400mcg b.d. (n=190; 166 completed study) Placebo (n=186; 149 completed study). All using a multiple-dose dry powder inhaler (Genuair)	LS mean change from baseline to week 12 in morning pre-dose (trough) FEV_1: Aclidinium 400mcg: 99ml Placebo: -25ml LS mean difference over placebo: 124ml (95%CI 83 to164ml, p<0.0001)	LS mean change from baseline to week 12 in peak FEV_1 (within 3 hours of morning dose) LS mean difference over placebo: Aclidinium 400mcg: 192ml (95% CI 148 to 236ml, p<0.0001)
ATTAIN[3]	24-week, double-blind, placebo controlled, Parallel-group study (with 2-week run-in)	≥40 yrs (mean 62 yrs) Male: 67.4% Caucasian: 95.2% Current or former cigarette smokers ≥ 10 pack years Moderate to severe COPD Mean % predicted FEV_1: 52% Before screening use of COPD medications: 50% SABAs, 38% ICS, 30% LABA, 27% LAMA, 16% SAMA, 14% LABA + ICS, 11% SABA + SAMA (only SABAs & ICS continued throughout the study)	Aclidinium 400mcg b.d.(n=272; 252 completed study) Placebo (n=276; 232 completed study) All using a multiple dose dry powder inhaler (Genuair)	LS mean change from baseline to week 24 in morning pre-dose (trough) FEV_1: Aclidinium 400mcg: 55ml Placebo: -73ml LS mean difference over placebo: 128ml (95%CI 85 to 170ml, p<0.0001)	LS mean change from baseline to week 24 in peak FEV_1 (within 3 hours of morning dose): LS mean difference over placebo: 209ml (SE $\pm$24ml, p<0.0001) % achieving clinically significant improvements in SGRQ total score at week 24: Aclidinium 400mcg: 57.3% Placebo: 41.0% (OR 1.87; p<0.0001; NNT=6) % achieving clinically significant improvement in TDI focal score at week 24:

					Aclidinium 400mcg: 56.9% Placebo: 45.5% (OR 1.68; p<0.01; NNT=9) Annualised rate of moderate or severe COPD exacerbations: Aclidinium400mcg: 0.34 Placebo: 0.47 (RR: 0.72, 95% CI: 0.51 to 1.02, p=0.06).
5	6-week, double-blind, placebo and active controlled, parallel-group study (with 2-3-week run-in)	≥40 yrs (mean 62 yrs) Male: approx. 66% Caucasian: 99.5% Current or former cigarette smokers ≥ 10 pack years Moderate (66%) to severe (37%) COPD Mean % predicted FEV_1: 56% Before screening use of COPD medications: LAMA 25.6%, SAMA 18.8%, SABA+ SAMA 5.3%, ICS?	Aclidinium 400mcg b.d.(n=171; 166 completed study) Tiotropium 18mcg o.d. (n=158; 154 completed study) Placebo (n=85; 80 completed study)	Mean change from baseline to week 6 in 24-hour normalised FEV_1: Aclidinium 400mcg: 65mL Tiotropium 18mcg: 55mL Placebo: -85ml LS mean difference over placebo: Aclidinium 400mcg: 150mL (95%CI 94 to 205mL; p<0.0001) Tiotropium 18mcg: 140mL (95%CI 83 to 196mL; p<0.0001)	Mean change from baseline to week 6 in night-time normalised FEV_1 (12-24 hours): LS mean difference over placebo: Aclidinium 400mcg: 160mL (95%CI 103 to 207mL; p<0.0001) Tiotropium 18mcg: 123mL (95%CI 65 to 181mL; p<0.0001) LS mean difference: Aclidinium 400mcg vs. Tiotropium 18mcg: NS
*Only data for licensed aclidinium dose presented. Aclidinium 400mcg equivalent to licensed 322mcg inhalation powder. 95%CI=95% confidence interval; AUC=Area under curve; b.d. = twice daily; CV=cardiovascular; ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist; LS mean = least squares mean; o.d.=once daily; OR=odds ratio; RR=Rate ratio; SABA=short-acting beta-agonist; SE=standard error; SGRQ=St Georges Respiratory Questionnaire (4 point difference minimal clinically important difference); TDI=Transition Dyspnoea Index (1 unit difference minimal clinically important difference).					

Table 2. Summary of key Glycopyrronium bromide RCTs

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint	Outcomes: Key secondary / exploratory endpoints
GLOW 1[6]	26-week, double blind placebo-controlled study. (Primary endpoint assessed at 12 weeks)	Patients > 40 yrs (Mean 64yrs) Male: 81% Caucasian: 63% Asian: 35% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 54% % previous exacerbations: 21% ICS use: 52% (could continue if stable doses)	Glycopyrronium 50mcg o.d (n=552; 450 completed) Placebo (n=270; 212 completed) Administered via Breezhaler.	Trough FEV_1 at week 12: Glycopyrronium 50mcg: 1.408L Placebo: 1.301L LS mean difference over placebo: 108ml (SE± 14.8ml); p<0.001	% achieving clinically significant improvements in SGRQ total score at week 26: Glycopyrronium 50mcg: 56.8% Placebo: 46.3% (OR 1.58; p=0.006; NNT=10) % achieving clinically significant improvement in TDI focal score at week 26: Glycopyrronium 50mcg: 61.3% Placebo: 48.3% (OR 1.7; p=0.001; NNT=8)

GLOW 2[7]	52-week, double-blind, placebo-controlled trial, with open-label tiotropium arm, parallel group study (Primary endpoint assessed at 12 weeks)	Patients > 40 yrs (mean 64yrs) Male: 64% Caucasian:87% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 54% % previous exacerbations: 27% ICS use: 53% (could continue if stable doses)	Glycopyrronium 50mcg o.d (n=529; 411 completed) Placebo (n=269; 193 completed) Tiotropium 18mcg o.d. (n=268; 206)	Trough FEV_1 at week 12 Glycopyrronium 50mcg: 1.469L Placebo: 1.372L Tiotropium 18mcg: 1.455L LS mean difference for Glycopyrronium over placebo: 97ml (95% CI 64.6 to 130.2ml; p<0.001) LS mean difference for Tiotropium over placebo: 83ml (95% CI 45.6 to 121.4; p<0.001)	% achieving clinically significant improvements in SGRQ total score at week 52: Glycopyrronium 50mcg: 54.3% (NS) Placebo: 50.8% Tiotropium: 59.4% (NS) % achieving clinically significant improvement in TDI focal score at week 52: Glycopyrronium 50mcg: 55.3% Placebo: 44.2% Tiotropium: 53.4% (OR Glycopyrronium vs. placebo 1.58; p=0.01; NNT=9) (OR Tiotropium vs. placebo 1.54; p=0.032; NNT=11) Annualised rate of moderate or severe COPD exacerbations: Glycopyrronium 50mcg: 0.54 Placebo: 0.80 (RR: 0.66, 95% CI: 0.496 to 0.869, p=0.003) (Tiotropium vs placebo RR: 0.80, 95% CI: 0.586 to 1.104, NS).
95%CI=95% confidence interval; b.d. = twice daily; ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist; LS mean = least squares mean; NS=not statistically significantly different; NNT=number needed to treat; o.d.=once daily; OR=odds ratio; RR=Rate ratio; SABA=short-acting beta-agonist; SE=standard error; SGRQ=St Georges Respiratory Questionnaire (4 point difference minimal clinically important difference); TDI=Transition Dyspnoea Index (1 unit difference minimal clinically important difference).					

Table 3. Summary of key Indacaterol RCTs

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison*	Outcomes: Primary endpoint	Outcomes: Key secondary / exploratory endpoints
B2335S INHANCE[10]	26-week, double-blind, double dummy placebo-controlled parallel group, 2 stage trial (Primary endpoint assessed at week 12) N= 1683	Patients > 40 yrs (mean 64yrs) Male: 63% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 56% ICS use: 37%	Stage 1: patients randomised to indacaterol 75, 150, 300, 600mcg o.d., formoterol 12 mcg b.d., or open label tiotropium 19mcg o.d. for 2 weeks Stage 2: Indacaterol 150mcg (n=416) Indacaterol 300mcg (n=416) Tiotropium 18mcg (n=415) Placebo (n=418) Continued to total 26 weeks 77% patients completed study	Trough FEV_1 at week 12: Indacaterol 150mcg: 1.46L Indacaterol 300mcg: 1.46L Placebo: 1.28L Tiotropium 18mcg: 1.42L LS mean difference: Indacaterol 150 and 300mcg vs. placebo: 180mL (p<0.001) Tiotropium vs. placebo: 140mL (p<0.001)	Trough FEV_1 at week 12 Indacaterol vs. tiotropium: test for non-inferiority, p<0.001; test for superiority, p≤0.01 LS mean difference in TDI vs. placebo at 26 weeks: Indacaterol 150mcg: 1.0 (p<0.001) Indacaterol 300mcg: 1.18 (p<0.001) Tiotropium: 0.87 (p<0.001) LS mean difference in SGRQ vs. placebo at 26 weeks: Indacaterol 150mcg: -3.3 (p<0.01) Indacaterol 300mcg: -2.4 (p<0.01) Tiotropium: 0.87 (NS) Exacerbation rates per year (imputed for missing data): Indacaterol 150mcg: 0.95 Indacaterol 300mcg:0.86 Tiotropium 18mcg:0.0.93 Placebo:1.33 RR vs. placebo: Indacaterol 150mcg: 0.71 (NS) Indacaterol 300mcg:0.65 (NS) Tiotropium 18mcg:0.0.69 (NS)
INDORSE [11]	26-week, double-blind, extension of INHANCE	Patients > 40 yrs (mean 63yrs) Male: 61% Moderate to severe COPD Smoking history of >10 pack	Indacaterol 150mcg (extension phase n =144, 126 completed) Indacaterol 300mcg (extension phase n=146, 135 completed)	Trough FEV_1 at week 52: LS mean difference vs. placebo: Indacaterol 150mcg: 170mL	Exacerbation ratesper year (imputed for missing data): Indacaterol 150mcg: 0.43 Indacaterol 300mcg:0.40 Placebo: 0.57

		years Mean % predicted FEV_1: 56% ICS use: 36%	Placebo (extension phase n=125, 105 completed)	(95%CI 110 to 230mL; p<0.001) Indacaterol 300mcg: 180mL (95%CI 120 to 240mL; p<0.001)	RR vs. placebo: Indacaterol 150mcg: 0.67 (95%CI 0.45 to 1.01; NS) Indacaterol 300mcg:0.66 (95%CI 0.44 to 0.98; p=0.042)
B2346 INLIGHT 1[11]	12-week, double-blind, double dummy placebo-controlled trial	Patients > 40 yrs (mean 63 yrs) Male: 52% Caucasian: 93% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 55% ICS use: 32%	Indacaterol 150mcg o.d. (n=211, 186 completed) Placebo (n=205, 178 completed)	Trough FEV_1 at week 12: Indacaterol 150mcg: 1.48L Placebo: 1.35L LS Mean difference vs. placebo: 130mL (SE $\pm$ 24ml; p<0.001)	No validated symptom measures employed.
B2334 INVOLVE[12]	52-week, double blind, double dummy placebo controlled trial (primary endpoint assessed at week 12)	Patients > 40 yrs (mean age 64yrs) Male: 80% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 52% ICS use: 53%	Indacaterol 300mcg o.d. (n=437, 338 completed) Placebo (n=432, 295 completed) Formoterol 12mcg b.d. (n=435, 323 completed)	Trough FEV_1 at week 12: Indacaterol 300mcg: 1.48L Placebo: 1.31L Formoterol: 1.38L LS Mean difference vs. placebo: Indacaterol 300mcg: 170mL (95%CI 130 to 200mL; p<0.001) Formoterol: 70mL (95%CI 40 to 100mL; p<0.001)	LS mean difference in trough FEV_1 at week 12: Indacaterol 300mcg vs. Formoterol: 100mL (95%CI 70 to 130mL; p<0.001) % achieving clinically significant improvement in TDI focal score at week 12: Placebo:40% Indacaterol 300mcg: 63% (NNT vs. placebo: 4) Formoterol: 53% (NNT vs placebo: 8) LS mean difference in TDI score vs. placebo at 52 weeks: Indacaterol 300mcg: 1.0 (p<0.001) Formoterol: 0.71 (p<0.01) LS mean difference in SQRQ score vs. placebo at 52 weeks: Indacaterol 300mcg: -4.7 (p<0.001) Formoterol: -4.0 (p<0.001) Annual rate of exacerbations: Indacaterol 300mcg: 0.60

					Placebo: 0.74 Formoterol: 0.56 RR exacerbation vs. placebo: Indacaterol 300mcg: 0.82 (95%CI 0.63 to 1.06; NS) Formoterol: 0.75 (95%CI 0.58 to 0.99; p<0.05)
INLIGHT 2 [13]	26-week, double blind, double-dummy, controlled trial (primary endpoint assessed at week 12)	Patients > 40 yrs (mean age 63yrs) Male: 75% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 53% ICS use: 44%	Indacaterol 150mcg o.d. (n=333; 289 completed) Placebo (n=335,264 completed) Salmeterol 50mcg b.d. (n=334; 284 completed)	Trough FEV_1 at 12 weeks: Change from baseline: Indacaterol150mcg: 150mL Placebo: -30mL Salmeterol: 90mL Indacaterol 150mcg vs. Placebo: 170mL; p<0.001)	Trough FEV_1 at 12 weeks: Indacaterol 150mcg vs. Salmeterol: 60mL; p<0.001 Salmeterol vs. Placebo: 110mL; p<0.001) % achieving clinically significant improvements in SGRQ total score at week 12: Indacaterol 150mcg: 57.9% Placebo: 39.1% Salmeterol: 46.8% OR Indacaterol 150mcg vs. Placebo 2.41; p<0.001; NNT=5 (OR Indacaterol 150mcg vs. Salmeterol 1.59; p<0.01; NNT=9) % achieving clinically significant improvements in TDI focal score at week 12, indacaterol 150mcg vs. salmeterol: OR=2.13, p≤0.01
INTENSITY[14]	12-week, double blind, double-dummy, controlled trial	Patients > 40 yrs (mean age 64yrs) Male: 68% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 54%	Indacaterol 150mcg o.d. (n=797, 737 completed) Tiotropium 18mcg o.d. (n=801, 740 completed)	Trough FEV_1 at week 12 (Per protocol population): Indacaterol 150mcg: 1.44L Tiotropium: 1.43L LS Mean difference Indacaterol	% achieving clinically significant improvements in SGRQ total score at week 12: Indacaterol 150mcg: 50.5% Tiotropium: 42.5%

		ICS use: 55%		150mcg vs. Tiotropium: 0mL (95%CI -20 to 20mL)	(OR Indacaterol 150mcg vs. Tiotropium 1.43; p<0.001; NNT=13) % achieving clinically significant improvement in TDI focal score at week 12: Indacaterol 150mcg: 57.9% Tiotropium: 50.1% (OR Indacaterol 150mcg vs. Tiotropium 1.49; p<0.001; NNT=13)
INSIST[15]	12-week, double blind, double-dummy, controlled trial	Patients > 40 yrs (mean age 63yrs) Male: 70% Caucasian: 84% Moderate to severe COPD Smoking history of >10 pack years Mean % predicted FEV_1: 52% ICS use: 46%	Indacaterol 150mcg o.d. (n=560; 511 completed) Salmeterol 50mcg b.d. (n=563; 523 completed)	Mean change from baseline in FEV_1 standardised AUC 5mins to 11hrs 45mins at 12 weeks: Indacaterol 150mcg: 0.19L Salmeterol:0.13L Indacaterol 150mcg vs. salmeterol: 57mL (95%CI 35 to 79mL; p<0.001)	Trough FEV_1 at week 12: Indacaterol 150mcg vs. salmeterol: 60mL (95%CI 37 to 83mL; p<0.001) % achieving clinically significant improvement in TDI focal score at week 12: Indacaterol 150mcg: 69.4% Salmeterol:62.7% (OR 1.41; 95% CI 1.07 to 1.85; p < 0.05; NNT=15)
INVIGORATE[17]	52-week, double blind, double-dummy, controlled, non-inferiority trial (Primary endpoint assessed at 12 weeks)	Patients > 40 yrs (mean age 64yrs) Male: 77% Caucasian: 77% Asian: 16% Severe COPD Smoking history of >10 pack years Exacerbations in last 12 months:100% Mean % predicted FEV_1: 41% ICS use: 72%	Indacaterol 150mcg o.d. (n=1723; 1337 completed) Tiotropium 18mcg o.d. (n=1721; 1379 completed)	LS mean trough FEV_1 at week 12 (Per protocol population): Indacaterol 150mcg: 1.134L Tiotropium: 1.145L LS Mean difference Indacaterol 150mcg vs. Tiotropium: -11mL (lower limit 95%CI: -26mL; p<0.0001 for non-inferiority)	LS mean difference in trough FEV_1 at week 52 (Full analysis set) Indacaterol 150mcg vs. Tiotropium: -20mL, p=0.022 Exacerbation rate (Full analysis set): Indacaterol 150mcg: 0.90 Tiotropium: 0.73 (RR 1.24, 95% CI 1.12 to 1.37; p<0.0001) Rate of moderate to severe exacerbations reported to be

					higher for indacaterol vs tiotropium. Time to first moderate or severe exacerbation: tiotropium vs. indacaterol: HR 1.20 (95%CI 1.0173 to 1.332; p=0.0012) % achieving clinically significant improvement in TDI focal score at week 52: Indacaterol 150mcg: 58% Tiotropium:55% (NS) % achieving clinically significant improvement in SGRQ score at week 52: Indacaterol 150mcg: 49% Tiotropium:49% (NS)
*Only data for licensed indacaterol doses presented. 95%CI=95% confidence interval; AUC=Area under curve; b.d. = twice daily; HR=hazard ratio; ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist; LS mean = least squares mean; o.d.=once daily; OR=odds ratio; RR=Rate ratio; SABA=short-acting beta-agonist; SE=standard error; SGRQ=St Georges Respiratory Questionnaire (4 point difference minimal clinically important difference); TDI=Transition Dyspnoea Index (1 unit difference minimal clinically important difference).					

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