Pharmaceutical Benefits Scheme

Post-market Review of

Chronic Obstructive Pulmonary Disease Medicines

ToR 3

Final Report

August 2017

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Section 3: ToR 3
Review of LAMA and LABA efficacy and safety

Review the evidence on the efficacy and safety of monotherapy and combinations of LABA/LAMA, ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for the treatment of COPD that PBAC has not previously considered.Key findings for ToR 3

The key findings from the systematic literature review conducted in August 2016, identifitied new head-to-head trials as well as a summary of the trials that underpinned previous PBAC decision making (shown in Tables 3.1 to 3.4). Importantly, all of the RCTs excluded patients with a history of asthma; thus, the evidence base presented here has limited applicability to patients with asthma-COPD overlap syndrome (ACOS).

1.1.1 Monotherapy versus monotherapy in patients with COPD

Table 3.1 shows there appear to be no significant differences in efficacy between the PBS-listed LAMA monotherapies, which is consistent with previous PBAC recommendations. Furthermore, there were no noteworthy safety findings and all LAMA monotherapies were well tolerated.

Table 3.1 Summary of evidence for monotherapy versus monotherapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
TIO (HandiHaler): LAMA vs SAMA			
March 2002	BI205.126A BI205.126B	TIO vs IPR	• TIO was considered superior in efficacy and similar in safety to IPR.
New evidence	Not considered	TIO vs IPR	• Comparison of TIO with IPR (i.e. a SAMA) is no longer considered to be clinically relevant.
TIO (Respimat): LAMA vs LAMA			
July 2009	BI205.249 BI205.250 BI205.291	TIO vs TIO[a]	• TIO Respimat was comparable in efficacy and safety to TIO HandiHaler. The two formulations were cost-minimised.
New evidence	TIOSPIR Non-inferiority, double-blind Good quality N=17,135; 2-3 years	TIO vs TIO[a]	• TIO Respimat appears non-inferior to TIO HandiHaler in terms of change from baseline in trough FEV_1. Two post hoc analyses also showed the treatments to be comparable based on mortality and exacerbation outcomes.
GLY (Seebri Breezhaler: LAMA vs LAMA			
November 2013	$GLOW_5$, $GLOW_2$ SPARK SHINE A network analysis for add-on to LABA was also considered	GLY vs TIO	• GLY was considered non-inferior in comparative effectiveness and similar in safety to TIO. GLY was cost-minimised to TIO. • No head-to-head trials of GLY versus other LAMAs were considered by the PBAC at the time.
New evidence	NCT02236611 (unpublished) Non-inferiority, open-label Quality not assessed N=1,037; 12 weeks	GLY vs UME	• UME appears non-inferior to GLY based on least squares mean change from baseline in trough FEV_1. • No other head-to-head trials of GLY versus other LAMAs were identified.
ACL: LAMA vs LAMA			

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
March 2014	LAS-39 An indirect comparison via placebo as common comparator also considered	ACL vs TIO	• ACL was considered non-inferior in term of comparative effectiveness and similar in safety to TIO and was cost-minimised. • No head-to-head trials of ACL versus other LAMAs were considered by the PBAC at the time.
New evidence	Beier (2013) Superiority, double-blind, double-dummy Fair quality N=414; 6 weeks	ACL vs TIO	• There were no significant differences between TIO and ACL in terms of efficacy or safety. Both TIO and ACL were associated with improvements from baseline in trough FEV_1 that met the MCID.
	Manoharan (2016) Superiority, open-label, cross-over Poor quality N=15; 2-3 weeks	ACL vs TIO	• No difference was observed between TIO and ACL in terms of trough FEV_1 when used as triple therapy with ICS/LABA. • No other head-to-head trials of ACL versus other LAMAs were identified.
UME: LAMA vs LAMA			
July 2014	No head-to-head trials Indirect comparison via placebo as common comparator	UME vs TIO	• UME was considered non-inferior in terms of comparative effectiveness and of similar safety to TIO, and was cost-minimised. • No head-to-head trials of UME versus other LAMAs were considered by the PBAC at the time.
New evidence	Feldman (2016) Non-inferiority, double-blind, double-dummy Good quality[b] N=1,017; 12 weeks	UME vs TIO	• UME was superior to TIO based on trough FEV_1; however, there were no significant differences between UME and TIO based on other efficacy outcomes including TDI, SGRQ and CAT scores. • UME non-inferior to TIO based on other efficacy outcomes including TDI, SGRQ and CAT scores.
	Donohue (2012) Dose-ranging study Double-blind, cross-over Fair quality N=176; 2 weeks	UME vs TIO	• The results for the UME (blinded) and TIO (open-label) were not directly compared (UME and TIO were both compared with placebo). However, UME resulted in a numerically greater change in trough FEV_1 from baseline than TIO.
	See trial NCT02236611 (above)	UME vs GLY	• UME appears non-inferior to GLY based on least squares mean change from baseline in trough FEV_1.

Abbreviations: ACL, aclidinium; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FLU, fluticasone; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; IPR, ipratropium; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; PBAC, Pharmaceutic Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium; UME, umeclidinium.
a Respimat versus HandiHaler.
b Overall the study was deemed to be of good quality (see Appendix M); however, concerns have been raised about whether differences in the markings between TIO and placebo capsules may have impacted on the blinding of treatment assignment (discussed further in Section 3.4.1).

1.1.2 Monotherapy versus dual therapy in patients with COPD

There is evidence of a modest benefit in stepping up from LAMA monotherapy to LAMA/LABA dual therapy (see Table 3.2) in patients with COPD with reduced numbers of exacerbations observed. However, it should be noted that many of the studies summarised in Table 3.2 were only powered to detect a difference between LAMA/LABA dual therapy and placebo and not to detect differences between LAMA/LABA dual therapy and LAMA monotherapy. No studies were identified that examined the benefits of stepping up from LABA monotherapy to LAMA/LABA dual therapy.

The INSPIRE 2008 study aimed to compare LAMA monotherapy to ICS/LABA dual therapy (fluticasone/salmeterol versus tiotropium). Comparable healthcare utilisation exacerbations per year and a statistically significant lower risk of all-cause mortality in the ICS/LABA dual therapy group (fluticasone/salmeterol) were observed. Covelli (2016) compared LAMA monotherapy to ICS/LABA dual therapy (fluticasone/vilanterol vs tiotropium). No clinically meaningful difference in trough FEV_1 was observed across treatment groups. An increased

rate of pneumonia and numerically fewer COPD exacerbations was observed in the ICS/LABA group.

No studies were identified that examined the benefits of stepping up from LABA monotherapy to ICS/LABA dual therapy. The INSTEAD 2014 study assessed the effect of switching patients who are at low risk of COPD exacerbations from fluticasone propionate/salmeterol to indacaterol monotherapy. No clinically relevant differences between fluticasone propionate/salmeterol and indacaterol for dyspnoea (TDI), health status (SGRQ) and use of rescue medication were observed suggesting patients can be switched from ICS/LABA to indacaterol with no loss of efficacy and without triggering exacerbations.

These findings are generally consistent with previous PBAC decision making, where LAMA/LABA dual therapy was considered superior to LAMA monotherapy (July 2014), and ICS/LABA FDC was considered non-inferior to LAMA monotherapy (March 2007).

Table 3.2 Summary of new evidence for monotherapy versus dual therapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
UME/VIL: LAMA/LABA vs LAMA or LABA			
New evidence	Maleki-Yazdi (2014) Superiority, double-blind, double-dummy Good quality N=905; 24 weeks	UME/VIL vs TIO	• UME/VIL resulted in statistically significant and clinically meaningful improvements in trough FEV1 compared with TIO monotherapy. The time to first on-treatment exacerbation also favoured UME/VIL.[a]
	Maltais (2014) Superiority, double-blind, cross-over Fair quality N=657; 12 weeks	UME/VIL vs UME	• The results for trough FEV_1 numerically favoured UME/VIL over UME monotherapy; however, no statistical comparisons of these active treatments were conducted and it is unlikely that the study was adequately powered for this comparison.
GLY/IND: LAMA/LABA vs LAMA or LABA			
July 2014	SHINE, SPARK	GLY/IND vs GLY or IND	• For trough FEV_1, GLY/IND was statistically superior to its monocomponents but the difference did not exceed the accepted MCID.[1] • GLY/IND was cost-minimised to UME/VIL.
New evidence	BRIGHT Superiority, double-blind, cross-over Fair quality N=85; 3 weeks	GLY/IND vs TIO[b]	• GLY/IND was statistically superior to TIO based on trough FEV1; however the study was only powered to detect a difference between GLY/IND and PBO.
TIO/OLO: LAMA/LABA vs LAMA or LABA			
July 2015	TONADO 1 & 2 (Indirect comparison vs other FDCs via TIO monotherapy as common comparator)	TIO/OLO vs TIO or OLO	• For trough FEV_1, TIO/OLO was statistically superior to its monocomponents but the difference did not exceed the MCID.
New evidence	TONADO 1 & 2[c] Superiority, double-blind Fair quality N=5,163; 52 weeks	TIO/OLO vs TIO	• TIO/OLO significantly improved lung function over TIO (Respimat) monotherapy in patients with GOLD 2 and 3-4 disease. There were no notable differences in lung function responses according to whether patients were naïve or experienced to LAMA or LABA therapy at baseline.
	OTEMTO 1 & 2 Superiority Double-blind Fair quality N=1,623; 12 weeks	TIO/OLO vs TIO	• Treatment with TIO/OLO resulted in numerically greater improvements in trough FEV_1 compared with TIO (Respimat) monotherapy; however, it is unlikely that the observed differences would be considered clinically relevant.[d]
FLU/SAL: ICS/LABA vs LAMA			

[1] Noted in March 2014 PSD for glycopyrronium/indacaterol FDC. The MCID was 100-140 mL.

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
March 2007	Trial 40036, plus two supportive trials (unpublished)	FLU/SAL vs TIO	• FLU/SAL was considered non-inferior to TIO on the basis of comparative efficacy and similar safety. FLU/SAL was cost-minimised to TIO.
New evidence	INSPIRE Superiority, double-blind, double-dummy Good quality N=1,323; 2 years	FLU/SAL vs TIO	• FLU/SAL and TIO were found to be comparable with respect to healthcare utilisation exacerbations per year; however, the risk of all-cause mortality was 52% lower in the FLU/SAL group, representing a statistically significant difference between the treatments.
	Sarac (2016) Superiority, open-label Poor quality N=44; 1 year	FLU/SAL vs TIO	• The mean number of exacerbations and number of severe exacerbations both numerically favoured FLU/SAL over TIO monotherapy; however, the differences were not statistically significant.
FLU/VIL: ICS/LABA vs LAMA			
New evidence	Covelli (2016) Superiority, double-blind, double-dummy Good quality N=623; 12 weeks	FLU/VIL vs TIO	• No statistically significant or clinically meaningful difference between FLU/VIL and TIO in terms of trough FEV_1. Safety results were comparable, with minor differences in rates of pneumonia and COPD exacerbations.
IND: LABA vs LABA			
July 2011	No head-to-head trials Indirect comparison via TIO as common comparator	IND vs FLU/SAL	• IND in combination with TIO was considered non-inferior in comparative effectiveness and similar in safety to FLU/SAL plus TIO by the PBAC. IND was cost-minimised to FLU/SAL.
New evidence	INDORSE Superiority, double-blind Good quality N=415; 52 weeks	IND 150 µg vs IND 300 µg	• The two PBS-listed doses of indacaterol were associated with similar magnitudes of improvement from baseline in trough FEV_1 compared with placebo and were comparable in terms of risk of exacerbations.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FLU, fluticasone; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IND, indacaterol; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; OLO, olodaterol; PBAC, Pharmaceutic Benefits Advisory Committee; PBO, placebo; SAL, salmeterol; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol; FLU/SAL, fluticasone propionate/salmeterol; FLU/VIL, fluticasone furoate/vilanterol.

a Over half of the patients in each treatment arm were using ICS therapies at baseline and continued use of ICS throughout the study; thus, approximately half of the study participants were on triple therapy or dual (ICS + LAMA) therapy.

b Patients who were on ICS therapy at baseline were permitted to continue use of ICS; therefore, a subset of patients were on triple therapy, while others were on dual ICS + LAMA therapy during the treatment period.

c New evidence refers to a post hoc analysis based on disease severity and treatment intensity.

d The study was powered to detect differences between TIO/OLO and PBO, not TIO/OLO and TIO monotherapy.

1.1.3 Dual therapy versus dual therapy in patients with COPD

Only two RCTs were identified that compared two LAMA/LABA dual therapy combinations (umeclidinium/vilanterol FDC versus tiotropium plus indacaterol) and (indacaterol/glycopyrronium FDC versus tiotropium plus eformoterol) as outlined in Table 3.3. Despite the limited body of evidence, the findings of these studies were consistent with previous PBAC recommendations; that is, there appears to be no significant difference in efficacy (based on primary end points) or safety between PBS-listed LAMA/LABA FDC s.

Table 3.3 also summarises the key findings from several RCTs that examined the comparative efficacy and safety of LAMA/LABA and ICS/LABA FDCs. The FLAME trial is of particular interest as it enrolled patients with a history of at least one exacerbation in the previous 12 months requiring treatment. The FLAME trial demonstrated non-inferiority of glycopyrronium/indacaterol to fluticasone propionate/salmeterol and, on a subsequent

subgroup analysis, superiority of the LAMA/LABA FDC to the ICS/LABA FDC based on exacerbation and lung function outcomes.[2]

The RG also considered the results of a recent Cochrane review published after the search period for the systematic review (Horita et al, 2017). The Cochrane review meta-analysed the results of 11 studies (n=9,839) that compared LAMA plus LABA to LABA plus ICS treatment, predominantly in patients with moderate to severe COPD without recent exacerbations.[3] Horita et al. (2017) found that compared to LABA plus ICS, LAMA plus LABA treatment was associated with greater improvements in FEV_1, fewer exacerbations, more frequent improvement in quality of life (measured by an increase in SGRQ of over four units), and lower risk of pneumonia.

Table 3.3 Summary of new evidence for dual therapy versus dual therapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of findings
GLY/IND: LAMA/LABA vs LAMA/LABA			
July 2014	BEACON An indirect comparison via TIO as common comparator also considered	GLY/IND vs GLY+IND	• GLY/IND was cost-minimised to UME/VIL.
New evidence	QUANTIFY	IND/GLY vs TIO+EFO	• IND/GYL was non inferiority to TIO+EFO based on SGRQ-C in patients had who moderate or severe risk of exacerbations (GOLD II and GOLD III). The non-inferiority margin was predefined as 4 units. IND/GLY showed a significantly increased pre-dose FEV_1 at week 26. Both treatments were well tolerated.
UME/VIL: LAMA/LABA vs LAMA/LABA			
July 2014	No head-to-head trials Indirect comparison via TIO as common comparator	UME/VIL vs TIO+IND	• UME/VIL was cost-minimised to TIO+IND with an adjustment to account for efficacy being less than the sum of components.
New evidence	Kalberg (2016) Non-inferiority, double-blind, triple-dummy Good quality N=961; 12 weeks	UME/VIL vs TIO+IND	• UME/VIL was non-inferior to TIO+IND in terms of trough FEV_1 in patients who were at high risk of exacerbations (over 60% of patients were classified as GOLD Group D; over 50% were receiving ICS at screening).
ACL/EFO: LAMA/LABA vs LAMA/LABA			
July 2015	No head-to-head trials Indirect comparison via placebo as common comparator	ACL/EFO vs GLY/IND ACL/EFO vs UME/VIL	• ACL/EFO was considered non-inferior to GLY/IND and UME/VIL on the basis of comparative efficacy and safety. ACL/EFO was cost-minimised to GLY/IND and UME/VIL.
TIO/OLO: LAMA/LABA vs LAMA/LABA			
July 2015	No head-to-head trials Indirect comparison via TIO monotherapy as common comparator	TIO/OLO vs GLY/IND TIO/OLO vs UME/VIL	• TIO/OLO was considered non-inferior to GLY/IND and UME/VIL on the basis of comparative efficacy and safety. TIO/OLO was cost-minimised to GLY/IND and UME/VIL.
BUD/EFO: ICS/LABA vs ICS/LABA			
November 2010	No head-to-head trials Indirect comparisons with both placebo and TIO as common comparators	BUD/EFO vs FLU/SAL	• BUD/EFO was non-inferior in terms of comparative efficacy and similar safety to FLU/SAL, and was cost-minimised.
UME/VIL: LAMA/LABA vs ICS/LABA			

[2] Note that a subgroup analysis of the FLAME RCT suggests that superiority (in terms of reducing exaccerbations) is primarily driven by patients who had experienced only one exacerbation in the previous year. There was no statistically significant difference between the FDCs in patients who had experienced two or more exaccerbations in the previous year.

[3] The PBS restrictions for ICS/LABAs limit use for COPD treatment to patients with a history of two or more exacerbations in the previous year.

PBAC consideration	Head-to-head trials	Comparison	Summary of findings
New evidence	Singh (2015a) Superiority, double-blind, double-dummy Good quality N=716; 12 weeks	UME/VIL vs FLU/SAL	• UME/VIL was found to be statistically superior to FLU/SAL based on change from baseline in trough FEV_1 in patients with no history of exacerbations that required oral corticosteroids, antibiotics and/or hospitalisation in the previous year. However, the trial did not demonstrate any differences between the treatment groups with respect to symptom and quality of life outcomes.
GLY/IND: LAMA/LABA vs ICS/LABA			
New evidence	ILLUMINATE Superiority, double-blind, double-dummy Good quality N=523; 26 weeks	GLY/IND vs FLU/SAL	• GLY/IND provided significantly better and clinically relevant improvements in trough FEV_1 over FLU/SAL in patients who had not experienced an exacerbation requiring treatment with antibiotics, systemic corticosteroids, or hospitalisation in the previous year.
	LANTERN Non-inferiority, double-blind, double-dummy Good quality N=744; 26 weeks	GLY/IND vs FLU/SAL	• In patients with low risk of exacerbations, GLY/IND was shown to be non-inferior and, on a subsequent superiority analysis, superior to FLU/SAL on the basis of trough FEV_1 and was also associated with statistically significant improvements in time to first moderate or severe exacerbation. Several patient-reported outcomes were also assessed in the study, and failed to demonstrate a significant difference between treatments.
	FLAME Non-inferiority, double-blind, double-dummy Good quality N=3,362; 52 weeks	GLY/IND vs FLU/SAL	• In patients with a history of at least one exacerbation during the previous year, GLY/IND achieved non-inferioty to FLU/SAL on the basis of annual rate of COPD exacerbations. A subsequent superiority analysis showed that GLY/IND was consistently superior to FLU/SAL on the basis of exacerbations, lung function and health status outcomes.
TIO/OLO: LAMA/LABA vs ICS/LABA			
New evidence	ENERGITO Superiority, double-blind, cross-over Fair quality N=229; 6 weeks	TIO/OLO vs FLU/SAL	• TIO/OLO was associated with statistically significant improvements in trough FEV_1 over FLU/SAL; however, the magnitude of the adjusted mean difference between the treatment arms (58 mL) is unlikely to represent a clinically meaningful difference.
ICS/LABA vs ICS/LABA			
July 2014	HZC113107	FLU/VIL vs FLU/SAL	• No evidence was shown for triple therapy with FLU/VIL. • FLU/VIL was considered non-inferior in terms of comparative effectiveness and safety to FLU/SAL. FLU/VIL was cost-minimised to FLU/SAL.

Abbreviations: ACL, aclidinium; BUD, budesonide; COPD, chronic obstructive pulmonary disease; EFO, eformoterol; FEV_1, forced expiratory volume in one second; FLU, fluticasone; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS; inhaled corticosteroid; IND, indacaterol; LABA; long-acting beta-2 agonist; OLO, olodaterol; PBAC, Pharmaceutic Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; RCT, randomised controlled trial; SAL, salmeterol; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol; FLU/SAL, fluticasone propionate/salmeterol; FLU/VIL, fluticasone furoate/vilanterol.

1.1.4 Dual therapy versus triple therapy in patients with COPD

Table 3.4 shows studies that investigated the benefit of adding a LAMA to ICS/LABA dual therapy which showed that the step up from dual to triple therapy results in statistically significant and clinically meaningful improvements in trough FEV_1. The PBAC has previously seen evidence from the GLISTEN trial that demonstrated that glycopyrronium plus fluticasone propionate/salmeterol is statistically superior to fluticasone propionate/salmeterol alone in terms of trough FEV_1 (November 2015 PSD for glycopyrronium).

Table 3.4 Summary of new evidence for dual therapy versus triple therapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of findings
ICS/LABA + LAMA vs ICS/LABA			
July 2014	GLISTEN (2015)	GLY+ FLU/SAL vs FLU/SAL	• Interim results presented to the PBAC from the study up to Week 12 indicated that triple therapy provided statistically significant improvements in trough FEV_1 compared to fluticasone propionate/salmeterol alone.
New evidence	Siler (2015) Superiority, double-blind Good quality N=1,239; 12 weeks	FLU/VIL+PBO vs FLU/VIL+ UME	• Triple therapy with FLU/VIL plus UME was associated with clinically meaningful improvements in trough FEV_1 compared with FLU/VIL (plus placebo).
	Sousa (2016) Superiority, double-blind Fair quality N=236; 12 weeks	ICS/LABA+ PBO vs ICS/LABA+ UME	• The addition of UME to ICS/LABAs produced statistically significant and clinically meaningful improvements over dual therapy with ICS/LABA (plus placebo), based on trough FEV_1.

Abbreviations: FEV_1, forced expiratory volume in one second; FLU, fluticasone; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; PBAC, Pharmaceutic Benefits Advisory Committee; PBO, placebo; UME, umeclidinium; VIL, vilanterol, FLU/SAL, fluticasone propionate/salmeterol; FLU/VIL, fluticasone furoate/vilanterol.

No RCTs or large observational studies were identified that examined the comparative efficacy and safety of ICS + LAMA/LABA versus LAMA/LABA. A recent Cochrane review also failed to identify any ongoing or completed RCTs comparing the treatment of stable COPD with ICS plus combination LAMA/LABA inhalers against combination LAMA/LABA inhalers alone (Tan et al, 2016).

New inhaled ICS/LABA/LAMA FDCs, including fluticasone furoate/vilanterol/umeclidinium, budesonide/formoterol/glycopyrronium and beclometasone/formoterol/glycopyrronium, are in Phase III of clinical development for COPD.

1.1.5 Stakeholder views (Forum and public consultations)

- The FLAME trial included patients with predominately a history of one exacerbation. Superiority of the LAMA/LABA compared to the ICS/LABA was not established in patients with a history of two or more excerbations.
- The authors of the AFFIRM trial (recently published) claim that combined therapy with aclidinium/formoterol demonstrated superiority over salmeterol/fluticasone in peak FEV_1. Improvements in dyspnoea and symptom control were comparable between treatment groups.
- The GOLD Strategy Report (2017) recommends that where dual therapy is appropriate, LAMA/LABA is preferred to ICS/LABA. Many stakeholders considered that further evidence is required to establish the comparative effectiveness of ICS/LABA to LAMA/LABA therapies, and amend Australian clinical guidelines and PBS restrictions.
- Recent post hoc analysis of the WISDOM study indicates that withdrawel of ICS from triple therapy (ICS/LAMA/LABA) increased the risk of excerbations in a small group of patients with high eosinophil counts and history of two or more exacerbations.
- The IMPACT study will evaluate the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol versus ICS/LABA or LAMA/LABA therapy over a 52-week treatment period.
- ICS monotherapy is not TGA indicated for COPD. Restricting PBS access to ICS/LABA to patients with asthma or combined asthma/COPD is problematic given the low use of spirometry and misdiagnosis of COPD.

- A culture change is already occurring and clinicians are prescribing LAMA/LABA in preference to ICS/LABA in COPD only patients to reduce the risk of pneumonia.
- For further information, the Stakeholder Forum Summary is available at Appendix F.
- Additional recent published references were provided by stakeholders (see Appendix U).

1.2 Background

The aim of ToR 3 of this review is to update the evidence base for LAMA and LABA monotherapy and combinations of LAMA/LABA, ICS/LABA and LAMA plus ICS/LABA therapies for the treatment of COPD. A systematic literature review was undertaken to locate additional evidence for efficacy and safety that has been published since the PBS listing of these medicines and that could inform the PBAC on both short and longer term outcomes. The methodology and results of the systematic literature search are presented in Section 3.3.

In order to provide context for the interpretation of the recently published evidence, the PBS listing history for each class of COPD medicines is described below. Further information is provided in Appendix D, which presents a summary of PBAC decision making for COPD medicines, including the trials and outcomes that were considered.

1.2.1 LAMAs

In March 2002, the PBAC considered the clinical evidence for tiotropium (Spiriva HandiHaler) for the treatment of COPD. As there were no other long-acting bronchodilators (LABA or LAMA) listed on the PBS at the time, the submission chose the short-acting antimuscarinic agent, ipratropium bromide in the inhaler dosage form as the comparator. [redacted] Tiotropium was recommended by the PBAC based on an acceptable [redacted] incremental cost-effectiveness ratio. Further details about the clinical evidence and economic evaluation that were presented to the PBAC for their consideration of tiotropium are available in Appendix J.

Glycopyrronium, aclidinium and umeclidinium were all recommended by the PBAC on the basis of non-inferiority against tiotropium, in November 2013, March 2014, and July 2014, respectively, and were cost-minimised to tiotropium.

1.2.2 LABAs

The first consideration of indacaterol was at the November 2010 PBAC meeting. According to the PSD, tiotropium was the nominated comparator, with evidence presented from an RCT (and a supportive cross-over RCT) that compared indacaterol at various doses with

tiotropium and placebo. On the basis of the evidence presented, the submission claimed that indacaterol is non-inferior in terms of efficacy and comparable in terms of safety with the main comparator tiotropium. The Committee was satisfied that the clinical evidence presented in the submission was adequate to support the efficacy claim. However, the PBAC considered the safety of indacaterol in COPD to be particularly important as the use of single agent LABA treatment in asthma had been associated with hospitalisation, intubation and sudden death. Around 15% of COPD patients have concomitant asthma so serious asthma related events are a potential risk if indacaterol was used in this patient group. The relative paucity of long-term safety data for indacaterol also made it hard for PBAC to assess the magnitude of these risks.

The PBAC also commented that the submission did not provide data on add-on use where indacaterol would be added to regimens of tiotropium monotherapy rather than replacing tiotropium outright. The PBAC considered that in clinical practice, indacaterol would replace tiotropium as the initial treatment in some newly diagnosed patients, but would be added to tiotropium in many other patients in place of ICS/LABA. No data were provided by the submission to establish that the efficacy and safety of indacaterol was non-inferior to a ICS/LABA. The PBAC therefore rejected the submission because of uncertainty about the clinical place of indacaterol in the treatment of COPD, because of concerns about the long-term safety of LABA without ICS therapy in COPD, and because the submission did not provide any data on the comparative efficacy and safety of indacaterol and LABA/ICS combinations.

In July 2011, the PBAC considered a resubmission for indacaterol that appropriately nominated fluticasone propionate/salmeterol FDC as the main comparator. According to the PSD, the resubmission compared indacaterol added to tiotropium versus fluticasone propionate/salmeterol FDC added to tiotropium, on the basis of an indirect comparison of change in trough FEV_1 using the common comparator tiotropium. The PBAC accepted the submission's claim that indacaterol in combination with tiotropium is non-inferior in terms of comparative effectiveness and similar safety to fluticasone propionate/salmeterol in combination with tiotropium. Although there was some uncertainty regarding the comparability of the trials used in the indirect comparison, the PBAC considered that this was a valid comparison.

The equi-effective doses were considered to be indacaterol 150 micrograms daily, fluticasone propionate with salmeterol 250/25 µg , two puffs twice daily and tiotropium 18 micrograms daily. As the original submission demonstrated comparative clinical efficacy of the two doses of indacaterol (150 µg and 300 µg once daily), and the sponsor did not request a price differential between the doses, the PBAC considered both indacaterol 150 µg and 300 µg to be equivalent to tiotropium 18 µg.

The PBAC considered that the additional safety data provided to address concerns raised in November 2010 about serious adverse events occurring with LABA monotherapy use in asthma, was supportive of monotherapy LABA use in COPD only. They recommended the addition of a NOTE to the restriction stating that indacaterol is not PBS-subsidised in asthma to minimise use for this indication.

1.2.3 LAMA/LABA dual therapy

The first LAMA/LABA FDC listed on the PBS was umeclidinium/vilanterol, which was first considered by the PBAC in March 2014. According to the PSD, the submission nominated indacaterol 150 µg plus tiotropium 18 µg as the main comparator, and glycopyrronium/indacaterol FDC as a supportive comparator. The clinical claim was that combination therapy with umeclidinium/vilanterol has comparable effectiveness to indacaterol plus tiotropium at 12 weeks, and has a similar safety profile. The PBAC rejected the submission as the FDC was cost-minimised to the sum of the component products and this was not justified by the evidence presented as the price of the FDC would be approximately twice the cost of monotherapy in the absence of evidence to demonstrate an incremental benefit of that magnitude.

As the incremental gain in FEV_1 of the FDC was not able to be translated into more clinically relevant measures of effect (e.g. frequency of exacerbations, hospitalisations), the PBAC considered it was unable to determine and value the incremental benefit associated with use of the FDC compared with use of components given concurrently. Therefore, the Committee was unable to determine an appropriate price for the FDC.

In July 2014, the PBAC considered a minor submission for umeclidinium/vilanterol with a similar clinical claim to the March 2014 major submission. According to the PSD, the minor submission presented a new trial that claimed an incremental benefit in FEV_1 of 112 mL over tiotropium monotherapy. As a minor submission, this trial was not evaluated. However, the PBAC considered that the claim of non-inferior comparative effectiveness and safety to indacaterol plus tiotropium was reasonable.

The submission attempted to address the PBAC concerns regarding price determination by calculating the incremental benefit of the FDC using a price per mL improvement in FEV_1 over monotherapy and then discounting the resulting price to deal with some of the uncertainty in this approach. The PBAC considered that the approach used assumptions that were not appropriately justified, but accepted that under the proposed approach, the listing of the FDC would be associated with both benefits and cost savings for patients who are already using individual LAMA and LABA in separate devices.

The PBAC subsequently recommended umeclidinium/vilanterol FDC at the July 2014 meeting on a cost-minimisation basis compared with tiotropium and indacaterol with a price adjustment to account for FEV_1 efficacy being less than the sum of components (equi-effective doses: umeclidinium/vilanterol 62.5/25 µg, tiotropium 18 µg and indacaterol 150 µg).

At the same meeting, the PBAC recommended glycopyrronium/indacaterol on the basis of non-inferiority to umeclidinium/vilanterol. Tiotropium/olodaterol and aclidinium/eformoterol were recommended at the July 2015 meeting on the basis of non-inferiority to the two LAMA/LABA FDCs that were already listed at the time of submission (glycopyrronium/indacaterol and umeclidinium/vilanterol FDCs).

1.2.4 ICS/LABA dual therapy

The March 2007 submission for fluticasone propionate/salmeterol claimed that Seretide is more effective than tiotropium with similar toxicity. The clinical claim was based on one key RCT comparing fluticasone propionate/salmeterol 500/50 µg twice daily with tiotropium 18 µg once daily in patients with COPD over 104 weeks. Two supportive trials comparing the same drugs in a similar population over 12 weeks and 3 weeks respectively were also provided. None of the trials were published at the time of the submission.

According to the PSD, there was no statistically significant difference between treatments in the rate of health care utilisation exacerbations, which was the primary outcome of the trial. All-cause mortality, which was one of the safety outcomes in the trial, had been relied on in the economic evaluations. There were more death events in the tiotropium group than in the fluticasone propionate/salmeterol group. The majority of the fatalities were associated with cardiac disorders, with a greater percentage occurring in the tiotropium group compared with the fluticasone propionate/salmeterol group.

The PBAC considered that there was no plausible biological mechanism to support such a difference. Further, the all-cause mortality data could be considered an unexpected finding because the trial had not predefined the hypothesis that fluticasone propionate/salmeterol has a role in the prevention of mortality in patients with COPD.

The PBAC did not accept the clinical claim that fluticasone propionate/salmeterol had significant advantages in terms of clinical effectiveness and toxicity over tiotropium. Therefore, its use as the foundation of an economic claim was not appropriate. In the pre-PBAC response, the sponsor accepted a therapeutic relativity of no difference in effectiveness and safety between fluticasone propionate/salmeterol and tiotropium, based on the results of the key RCT (trial 40036).

In November 2010, the PBAC considered and recommended a submission for budesonide/eformoterol (Symbicort Turbuhaler), which was considered non-inferior to fluticasone propionate/salmeterol. A second formulation of budesonide/eformoterol (Symbicort Rapihaler) was recommended by the PBAC in July 2013, cost-minimised against Symbicort Turbuhaler. In July 2014, fluticasone furoate/vilanterol was recommended by the PBAC on the basis of non-inferiority to fluticasone propionate/salmeterol.

1.3 Methodology

This section outlines the methodology that underpinned the evidence review undertaken to address ToR 3. Throughout Chapter 3, newer studies that add to the existing evidence base are discussed in light of findings previously submitted to the PBAC, with consideration of whether the newer evidence provides support for previous PBAC decision making.

1.3.1 Identification of relevant studies

The peer-reviewed literature was systematically searched for clinical studies that evaluated the safety and effectiveness of LAMA and LABA monotherapy as well as combinations of LAMA, LABA and ICS at the doses and formulations listed on the PBS for COPD treatment.

Systematic searches were conducted in the following electronic databases: Medline, EMBASE and the Cochrane Library, using the search strategies outlined in Appendix K. Restrictions were placed on the time period searched to capture evidence that has not previously been considered by the PBAC. The reference lists of relevant papers were scanned for other studies potentially missed in the searches, and any additional evidence (published or unpublished) provided by the sponsors in their public consultation submissions on the final ToR for this review was also considered for inclusion.

Table 3.5 summarises the literature search criteria that was used to address ToR 3. The table also describes the eligibility criteria that were applied to the titles and abstracts of identified citations. Literature identified as opinion pieces, editorials or other papers without a clear study design and description of method and results were not included. Conference abstracts and studies that are not published in the English language were excluded.

Where the citation appeared to meet the eligibility criteria, full articles were retrieved for further assessment. The same criteria were applied to the full articles. Those publications that initially met the eligibility criteria, but were later excluded, were documented with the reasons for exclusion (see Appendix N).

Table 3.5 Literature search criteria for ToR 3

Limit	Eligibility criteria
Databases of peer-review literature	• EMBASE • Medline • Cochrane Library
Other means to identify evidence	• Scan of HTA websites for relevant reports: AHRQ, CADTH, KCE, NHS HTA/NCCHTA, NHS CRD, NICE. • Scan of reference lists of relevant systematic reviews, selected narrative reviews, primary articles and evidence-based clinical practice guidelines. • Scan of public consultation submissions.
Publication types	• Full text studies of the efficacy and safety of COPD medicines in humans. • English language only.
Study types	• A hierarchical stepwise method will be used to identify and select studies according to study design, as determined by the NHMRC Evidence Hierarchy for intervention questions (Appendix L). The search strings for each study type are shown in Appendix K. • If there are no systematic reviews of RCTs available, then RCTs alone will be selected. Should these be unavailable, or not adequately address the research question, then systematic reviews of non-randomised comparative studies will be selected. If these are not available, then large, high-quality non-randomised comparative studies alone will be selected. • Level III-3 and Level IV studies will not be included.

Limit	Eligibility criteria
Search period	The review will focus on evidence that has not previously been considered by the PBAC. Studies will be eligible if they fall within the date ranges below: [a] • Sep 2001 – August 2016: tiotropium • Sep 2006 – August 2016: fluticasone propionate/salmeterol • Mar 2010 – August 2016: budesonide/eformoterol • Nov 2010 – August 2016: indacaterol • Mar 2013 – August 2016: glycopyrronium • Sep 2013 – August 2016: aclidinium; fluticasone furoate/vilanterol • Nov 2013 – August 2016: umeclidinium; glycopyrronium/indacaterol; umeclidinium/vilanterol • Nov 2014 – August 2016: present: aclidinium/eformoterol; tiotropium/olodaterol
Study exclusion criteria	• Not a clinical study: exclude narrative reviews, editorials, letters, conference abstracts, protocols, animal studies, in vitro studies, case reports. • Wrong patient population: does not include patients with COPD or mixed airways disease (e.g. ACOS). • Wrong intervention: does not include a PBS-listed treatment for COPD. • Wrong comparator: does not include a relevant pharmacological comparator or placebo. • Wrong outcomes: does not report relevant efficacy and safety outcomes (e.g. exacerbations, FEV_1, QoL, mortality, hospitalisations, symptoms, AEs).

Source: Final Research Protocol, approved by RG 2nd August 2016
Abbreviations: ACOS, asthma- COPD overlap syndrome; AE, adverse event; AHRQ, Agency for Healthcare Research and Quality; CADTH, Canadian Agency for Drugs and Technologies in Health; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HTA, health technology assessment; ICS, inhaled corticosteroid; KCE, Belgian Health Care Knowledge Centre; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; NCCHTA, National Coordinating Centre for Health Technology Assessment; NHS CRD, University of York NHS Centre for Reviews and Dissemination; NHS HTA, National Health Service Health Technology Assessment (UK); NHMRC, National Health and Medical Research Council; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; QoL, quality of life; RCT, randomised controlled trial; ToR, Term of Reference.
a The literature search start date is approximately eight months prior to the positive PBAC recommendation for that medicine.

Where possible, study eligibility (and interpretation) was guided by the evidence reported in the COPD-X guidelines,[4] which are updated regularly by a committee of Australian experts in COPD. The guideline development process is underpinned by quarterly systematic literature searches conducted in PubMed and the Cochrane Library to identify relevant systematic reviews, meta-analyses, RCTs, cohorts and case-control studies.

While device type may be important in clinical practice, it was out-of-scope for this review. Studies that assessed patient or clinician preferences for different devices were excluded.

1.3.2 Search results and selection of evidence

A total of 4,467 citations were identified through the systematic literature search. There were 1,681 duplicates within and across the three databases, leaving 2,786 unique citations that were screened using the aforementioned selection criteria. Table 3.6 shows that the review of titles and abstracts yielded a subset of 381 potentially relevant citations including: 16 Health Technology Assessments (HTAs); 139 systematic reviews/meta-analyses (SR/MA); 200 RCTs; and 26 observational studies.

[4] COPD-X Plan 2016

Table 3.6 Study selection process

Description	Medline	EMBASE	Cochrane Library
Number of citations retrieved by search	948	1,851	1,668
Total		4,467	
Duplicates within and across sets removed		1,683	
Additional studies found through handsearching		1	
Number of citations screened		2,785	
Excluded at title/abstract review:			
Wrong publication type		1,329	
Wrong population		102	
Wrong intervention		349	
Wrong comparator		103	
Wrong outcomes		192	
Not in English		108	
Superseded		10	
Previously considered by PBAC		100	
Dose differs from PBS dose		59	
Withdrawn		1	
Duplicate data		2	
Considered more relevant to ToR4		35	
Observational studies with less than 500 participants		14	
Total		2,404	
Number citations potentially relevant after title/abstract review:		381	
Health technology assessments		16	
Systematic reviews and/or meta-analyses		139	
Randomised controlled trials		200	
Observational studies		26	

Abbreviations: PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; ToR, Term of Reference.

As stipulated in the protocol, studies were to be assessed for eligibility for inclusion in the systematic review using a staged approach; that is, the highest level of evidence available to answer the individual research questions would be considered initially before moving to lower levels of evidence (determined by the NHMRC Evidence Hierarchy for interventional evidence, as described in Appendix L). The use of a staged approach targeted the research most likely to provide unbiased evidence as a consequence of how the research was designed. However, other factors must also be taken into consideration when assessing the reliability of study findings, such as study quality, size of the treatment effect, generalisability and applicability of the evidence.

Although a very large body of Level I evidence was identified (139 SR/MAs), a closer inspection of these studies revealed that the applicability of their findings to the Australian setting was often limited. Many of the Level I studies had broad eligibility criteria in terms of the range of COPD medicines and doses that were included. Furthermore, the pooled estimates of effect provided in these studies often included numerous therapies and doses of therapies within a drug class, not all of which are necessarily PBS-listed medicines or doses. For instance, the therapeutic effect and safety of indacaterol would be difficult to disentangle from evidence relating to salmeterol and eformoterol, which are not PBS listed as monotherapy for COPD. Similarly, non-PBS listed doses of fluticasone propionate/salmeterol (e.g. 250/50 µg) were often included in meta-analyses with PBS-listed doses. Such pooling of data generally compromised the applicability to the Australian setting and also precluded the ability to confirm therapeutic non-inferiority within drug classes where it has previously been established.

In light of these challenges, the evidence base underpinning ToR 3 focuses exclusively on Level II (RCT) studies that examine PBS-listed medicines at the approved dose(s). In the absence of RCT evidence, the search was extended to high-quality observations studies.

In addition to a focus on Level II evidence, head-to-head evidence was favoured over indirect comparisons (or network meta-analyses). As such, a large proportion of the 200 potentially relevant RCTs were excluded, as they were comparisons of one active COPD medicine versus placebo. In any studies with multiple active treatment groups, only the treatment groups with PBS-listed doses were included in results tables.

An additional three key questions were drafted in order to guide the evidence review. The questions outlined below were intended to provide clarity around the type of comparisons that the PBAC would be particularly interested in seeing:

- Does the recent evidence support non-inferiority of medicines within the same class (i.e. comparisons of LAMAs with other LAMAs; LAMA/LABAs with other LAMA/LABAs; and ICS/LABAs with other ICS/LABAs)? If one medicine or combination is shown to be superior or inferior to the others within the same class, are these differences only applicable to certain patients?
- Is there evidence that patients benefit from initiating on dual or triple therapy rather than monotherapy? If so, in which patients is this appropriate?
- What is the additional benefit of moving from monotherapy to dual therapy, or from dual to triple therapy? In which patients is this appropriate?

Finally, as noted in Section 3 (ToR 2), there are a large number of relevant outcomes in COPD, including various measures of lung function, COPD exacerbations, symptoms and HRQoL. A pragmatic approach to reporting of results was necessitated due to the large number of medicines and included RCTs. As a result, the review focuses on several key outcomes that are relevant to decision making, namely, trough FEV_1, exacerbations, hospitalisation, and safety.

On the basis of this refined approach, a total of 24 RCTs (reported in 28 separate publications) were considered eligible for inclusion in the review. Appendix N provides citation details for the remaining 172 RCTs, together with the reason for exclusion.

1.3.3 Critical appraisal and data extraction

Studies were critically appraised according to the likelihood that bias had affected their findings. The execution of RCTs and observational studies was evaluated using quality appraisal checklists adapted from the NHMRC and SIGN (see Appendix M).

Relevant data was extracted from included studies, including study design, eligibility criteria (noting any studies that included patients with mixed airways disease), intervention drug and dosage details, comparator drug and dosage details, relevant outcome measures and results, and follow-up period.

Where appropriate, data extracted from the included studies were to be combined in a meta-analysis, using Review Manager software from the Cochrane Collaboration. For each review question, the findings were synthesised into an overall narrative, with better quality studies given greater weight in the formulation of conclusions.

1.4 Summary of evidence from randomised controlled trials

The following sections summarise the evidence from RCTs that compare the efficacy and safety of COPD medicines within the same class (Sections 3.4.1 to 3.4.3) and across different classes (Sections 3.4.4 to 3.4.8). In line with the aim of ToR 3, this section only includes evidence that the PBAC has not previously considered.

It should be noted that the comparison of LAMA and LABA monotherapy was not considered to be clinically relevant in the context of this review. Therefore, studies that only compared those two therapies were excluded.

1.4.1 LAMA versus LAMA

Since the listing of tiotropium, three other LAMAs (glycopyrronium, aclidinium and umeclidinium) have been listed on the PBS for the treatment of COPD, all of which were listed on a cost-minimisation basis with tiotropium.

One of the intentions of this evidence review is to determine whether recent evidence supports non-inferiority of the four LAMAs that are PBS listed (and if one medicine or combination is shown to be superior or inferior to the others, whether these differences are only applicable to certain patients). Six RCTs that compared two or more LAMA therapies were identified in the literature search and are listed in Table 3.7. The study characteristics of the six relevant studies, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.8. The results reported in each study that are of relevance to this review are then outlined in subsections according the specific treatment comparisons.

Table 3.7 List of randomised controlled trials comparing two or more LAMA therapies

Trial ID	Citation	Description
Beier (2013)	Beier J, Kirsten AM, Mruz R, Segarra R, Chuecos F, Caracta C, et al (2013). 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: Journal of Chronic Obstructive Pulmonary Disease 10 (4):511-522.	Key publication
Donohue (2012)	Donohue JF, Anzueto A, Brooks J, Mehta R, Kalberg C and Crater G (2012). A randomized, double-blind dose-ranging study of the novel LAMA GSK573719 in patients with COPD. Respiratory Medicine 106 (7):970-979.	Key publication
Feldman (2016)	Feldman G, Maltais F, Khindri S, Vahdati-Bolouri M, Church A, Fahy WA, et al (2016). A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 mug compared with tiotropium 18 mug in patients with COPD. International Journal of COPD 11 (1):719-730.	Key publication
Manoharan (2016)	Manoharan A, Morrison AE and Lipworth BJ (2016). Effects of Adding Tiotropium or Aclidinium as Triple Therapy Using Impulse Oscillometry in COPD. Lung 194 (2):259-266.	Key publication
NCT02236611	A 12-week Study to Evaluate the Efficacy and Safety of Umeclidinium 62.5 Microgram (mcg) Compared With Glycopyrronium 44 mcg in Subjects With Chronic Obstructive Pulmonary Disease (COPD). Sponsor: GlaxoSmithKline. Study results received: 18 January 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02236611?term=NCT02236611&rank=1.	Unpublished results from a completed trial

Trial ID	Citation	Description
TIOSPIR	Anzueto A, Wise R, Calverley P, Dusser D, Tang W, Metzdorf N, et al (2015). The Tiotropium Safety and Performance in Respimat (TIOSPIR) Trial: Spirometry Outcomes. Respiratory Research 16 (1) (no pagination)(107).	Substudy of spirometry outcomes
	Dahl R, Calverley PMA, Anzueto A, Metzdorf N, Fowler A, Mueller A, et al (2015). Safety and efficacy of tiotropium in patients switching from HandiHaler to Respimat in the TIOSPIR trial. BMJ Open 5 (12) (no pagination)(e009015).	Post hoc analysis of patients previously on HandiHaler and switching to Respimat
	Wise R, Calverley PM, Dahl R, Dusser D, Metzdorf N, Muller A, et al (2015). Safety and efficacy of tiotropium Respimat versus HandiHaler in patients naive to treatment with inhaled anticholinergics: A post hoc analysis of the TIOSPIR trial. NPJ Primary Care Respiratory Medicine 25 (no pagination)(15067).	Post hoc analysis of patients naïve to treatment with inhaled anticholinergics

Abbreviations: LAMA, long-acting muscarinic antagonist.

Table 3.8 Details of randomised controlled trials comparing two or more LAMAs

Trial ID 1. Publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
ACL vs TIO						
Manoharan (2016) 1. N/A 2. Poor quality 3. UK 4. Almirall	15	Superiority. Open-label, cross-over.	TIO 18 µg qd + any ICS/LABA (n=13) ACL 322 µg bid + any ICS/LABA (n=13)	Inclusion (1) Age 40-80 years, (2) moderate to severe COPD, (3) currently taking ICS/LABA combination therapy,[5] (4) FEV_1 30-80%. Exclusion (1) Other significant respiratory disease, (2) a COPD exacerbation or respiratory tract infection requiring systemic steroids and/or antibiotics within 1 month of study commencement (or within 3 months if hospitalisation was required). Other (1) Previously prescribed LAMA were stopped at the screening visit.	2-3 weeks per treatment; 1-2 week washout.	Primary Change in trough R5 (airway resistance at 5 Hz, measured by IOS). Secondary Remaining IOS variables (central airway resistance at 20 Hz, peripheral resistance, reactance at 5 Hz, area under the reactance curve); trough FEV_1; FVC; RVC; 6-minute walk test; SGRQ; BDI-TDI.
Beier (2013) 1. N/A 2. Fair quality 3. Germany, Poland, Hungary, Czech Republic 4. AstraZeneca	414	Superiority. Double-blind, double-dummy.	ACL 400 µg bid[6] (n=171) TIO 18 µg qd (n=158) PBO (n=85)	Inclusion (1) Age ≥40 years, (2) clinical diagnosis of stable moderate-to-severe COPD, (3) post-bronchodilator FEV_1/FVC <70%, and FEV_1 ≥30% and <80%. Exclusion (1) History or current diagnosis of asthma or other clinically relevant respiratory or CV conditions, (2) respiratory tract infection or COPD exacerbation ≤6 weeks before screening (or ≤3 weeks if hospitalised), (3) current use of other methylxanthines other than theophylline. Other (1) Relief medication (SAMA) provided for additional symptoms control as needed (except ≤6 hours before each visit), (2) permitted to continue stable use of oral sustained-release theophylline, ICS, and oral or parenteral CS (except ≤6 hours before each visit) and/or oxygen therapy (except ≤2 hours before each visit).	6 weeks	Primary Change from baseline in normalised FEV_1 AUC for 24 hrs post-morning dose at Week 6 (FEV_1 AUC_{0-24}). Secondary FEV_1 AUC_{0-12}; FEV_1 AUC_{12-24} (night time period); morning pre-dose (trough) and peak FEV_1 and FVC; EXACT-RS total score; additional symptoms questionnaire; safety (AEs, vital signs).

[5] Fluticasone propionate/salmeterol, budesonide/formoterol, or beclomethasone/formoterol.
[6] Metered dose of aclidinium bromide; equivalent to a delivered dose containing 322 µg of aclidinium (the PBS-listed dose).

Trial ID 1. Publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
UME vs TIO						
Feldman (2016) 1. N/A 2. Good quality 3. Canada, Chile, Denmark, France, Germany, Italy, Romania, Korea, South Africa, the Russian Federation, Ukraine, US 4. GlaxoSmithKline	1,017	Non-inferiority. Double-blind, double-dummy.	UME 62.5 µg qd (n=509) TIO 18 µg qd (n=508)	Inclusion (1) Age ≥40 years, (2) diagnosis of COPD, (3) pre- and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of 30%-70% of predicted normal values, (4) dyspnoea score of ≥2 on the modified Medical Research Council Dyspnea Scale at Visit 1. Exclusion (1) Current diagnosis of asthma or other significant respiratory disorder or other condition that may affect respiratory function, (2) pregnancy, (3) lung volume reduction surgery, or hospitalisation for COPD/pneumonia within 12 weeks prior to Visit 1, (4) long-term oxygen therapy (prescribed for >12 hrs per day) and use of COPD maintenance medications other than study medication, with the exception of ICS. Other (1) Albuterol/salbutamol use was permitted as rescue medication.	12 week	Primary Trough FEV_1 on Day 85 (mean of values obtained 23 and 24 hours after dosing on Day 84, PP population). Secondary Trough FEV_1 on Day 85 (ITT population); trough FEV_1 on Days 2, 28, 56 and 84; trough FVC on Days 2, 28, 56, 84 and 85; weighted mean FEV_1 over 0-12, 12-24 and 0-24 hours post-dose; TDI focal score; TDI responders; SGRQ; CAT score; rescue medication, safety (AEs, vital signs).
Donohue (2012)[7] 1. N/A 2. Fair quality 3. US, Germany 4. GlaxoSmithKline	176	Dose-ranging study. Double-blind,[8] three-way cross-over.	UME 62.5 µg qd[9] (n=35) TIO 18 µg qd (n=35) PBO (n=158)	Inclusion (1) Age 40-80 years, (2) history of COPD, (3) post-albuterol FEV_1/FVC ratio of ≤0.70 and a post-albuterol FEV_1 of ≥35 and ≤70% of predicted normal. Exclusion (1) Current diagnosis of asthma, (2) lower respiratory tract infection or recent COPD exacerbation, (3) α1-antitrypsin deficiency, (4) any clinically significant uncontrolled disease. Other (1) Albuterol was provided to use as required to relieve breakthrough symptoms, (2) Concurrent use of systemic corticosteroids, long-acting bronchodilators, including theophyllines, and inhaled ipratropium was not allowed, but patients were permitted to use ICS at a stable dose (and patients on an ICS/LABA combination were allowed to switch to ICS monotherapy).	2 weeks (for each of the three treatment arms); 10-14 day washout.	Primary Change from baseline in trough FEV_1 on Day 15. Secondary 0-6 and 0-24 hr weighted mean FEV_1 at Day 14; serial FEV_1 values at each time point over 28 hrs at Day 14; peak FEV_1; FVC; rescue medication use; safety.

[7] The umeclidinium (Incruse Ellipta) submission, considered by the PBAC in July 2014, presented safety data from this study in Section B.7.2, pp. 144-5.
[8] Investigators and participants were blinded to umeclidinium/placebo assignment. Open-label tiotropium was included as a positive control.
[9] The study also examined doses of umeclidinium 125, 250, 500 and 1000 µg qd and 62.5, 125 and 250 µg bid.

Trial ID 1. Publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
UME vs GLY						
NCT02236611 1. N/A 2. Not assessable 3. Argentina, Chile, Czech Republic, Germany, Hungary, Norway, Romania, Russia, Spain, Sweden 4. GlaxoSmithKline	1,037	Non-inferiority. Open-label.	UME 62.5 µg qd (n=516) GLY 44 µg qd (n=518)[10]	Inclusion (1) Age ≥40 years, (2) established clinical history of COPD, (3) a score of ≥2 on the mMRC Dyspnea Scale, (4) pre- and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≥30% and ≤70% of predicted normal values at Visit 1. Exclusion (1) Current diagnosis of asthma, (2) hospitalisation for COPD or pneumonia within 12 weeks prior to Visit 1, (3) other clinically significant respiratory disorders including bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease. Other (1) Patients were required to discontinue most COPD maintenance therapies prior to Visit 1, (2) patients were provided with albuterol/salbutamol for as-needed use throughout the study, except within the 4 hr period prior to spirometry.	12 weeks	Primary Change from baseline in trough FEV_1 on Day 85.[11]
TIO HandiHaler vs Respimat						
TIOSPIR 1. Anzueto (2015); Dahl (2015); Wise (2013); Wise (2015) 2. Good quality 3. Various, including six Australian sites 4. Boehringer Ingelheim	17,135[12]	Non-inferiority. Double-blind. Event-driven.[13]	TIO HandiHaler 18 µg qd (n=445) TIO Respimat 5 µg qd (n=461) TIO Respimat 2.5 µg qd (n=464)	Inclusion (1) Age ≥40 years, (2) diagnosis of COPD, (3) post-bronchodilator FEV_1/FVC ratio ≤0.70, and an FEV_1 ≤70% predicted. Exclusion (1) Recent or unstable concomitant cardiac disease, (2) other clinically significant lung disease or a COPD exacerbation within the last month, (3) moderate or severe renal impairment, (4) cancer requiring therapy within the last 5 years, (5) drug or alcohol abuse within the last year. Other (1) All COPD medications except other inhaled anticholinergic agents were allowed; however, there were rules in place regarding washout periods prior to pulmonary function tests.	Up to 3 years (final visit 30 days after last treatment; all followed up for vital signs until end of study)	Primary Time to all-cause mortality; time to first COPD exacerbation. Secondary Trough FEV_1; number of COPD exacerbations; hospitalisations associated with exacerbations; time to onset/time to death from MACE.

Note: N refers to number randomised unless otherwise specified.
Abbreviations: AUC, area under the curve; ACL, aclidinium; AE, adverse event; BDI, Basline Dyspnoea Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CS, corticosteroid; EXACT-RS, EXAcerbations of Chronic pulmonary disease Tool-Respiratory Symptoms; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HH, HandiHaler; ICS, inhaled corticosteroid; IOS, impulse oscillometry; ITT, intention-to-treat; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event; PP, per protocol; Resp, Respimat; RVC, relaxed vital capacity; SAMA, short-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium; TIOSPIR, TIOtropium Safety and Performance In Respimat; UME, umeclidinium.

[10] Refers to the delivered dose of glycopyrronium; capsule contains 50 µg of glycopyrronium, in line with PBS-listed dose.
[11] Mean of values obtained 23 and 24 hours after dosing on Day 84.
[12] Each of the studies presented in this review are sub-studies/post hoc analyses of the TIOSPIR study.
[13] The trial was designed to end when approximately 1,266 deaths were reported.

Aclidinium versus tiotropium

Manoharan (2016)

In a recent cross-over study conducted by Manoharan et al (2016), patients were randomised to undergo treatment periods with tiotropium 18 µg once daily and aclidinium 322 µg twice daily for 2-3 weeks each. In this study, the LAMAs were used as add-on therapy to pre-existing ICS/LABA therapy in eligible patients with moderate to severe COPD.

Table 3.9 shows that trough FEV_1 significantly improved from baseline with both aclidinium and tiotropium (P=0.009 and P<0.0001, respectively). Both treatments met the MCID of 100-140 mL; however, it was unclear whether the MCID was defined a priori.

Table 3.9 Change from baseline to 2-3 weeks in trough FEV_1 – ACL vs TIO

Change from baseline	ACL 322 µg	TIO 18 µg	Δ mL (95% CI)	p-value
Trough FEV_1 at 2-3 weeks, mL	110	150	–40 (–130, 50)	0.36

Source: Manoharan et al (2016), Table 1.
Note: Trough FEV_1 was measured at 12 hrs for aclidinium and 24 hrs for tiotropium.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ns, non-significant; HH, HandiHaler; Resp, Respimat; TIO, tiotropium.

Importantly, there was no significant difference between aclidinium and tiotropium when used as triple therapy in patients with COPD. The authors noted that baseline values prior to randomised treatments were not significantly different, and there were also no significant differences in baselines according to visit sequence.

Beier (2013)

An earlier study by Beier et al (2013) also assessed the comparative efficacy of aclidinium and tiotropium; however, the primary analysis was a comparison of aclidinium and placebo. Unlike Manoharan et al (2016), not all patients in Beier et al (2013) were undergoing triple therapy for COPD. While patients were not required to discontinue treatment with ICS during the study period, the proportion of patients taking ICS therapies at baseline and throughout the study was unclear.

Treatment with both aclidinium and tiotropium resulted in improvements from baseline in trough FEV_1 that were statistically significant compared with placebo (see Table 3.10). On Day 1, the mean improvement with aclidinium was statistically significantly greater than tiotropium, but did not meet the proposed MCID for this parameter of 100-140 mL. By Week 6 the treatments were comparable, suggesting that the difference on Day 1 may be attributable to differences in pharmacokinetics, whereby aclidinium reaches steady state faster than tiotropium (Beier et al, 2013).

Table 3.10 Least squares mean difference from placebo in trough FEV_1 – ACL vs TIO

LS mean difference from placebo in trough FEV_1	ACL (n=171)	TIO (n=158)	Treatment difference, Δ (95% CI)	p-value
Day 1, mean difference (95% CI), mL	141 (NR)[a]	93 (NR)[b]	48 (NR)	<0.05
Week 6, mean difference (95% CI), mL	141 (NR)[a]	102 (NR)[b]	38 (NR)	ns

Source: Beier et al (2013), Table 2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; LS, least squares; NR, not reported; ns, non-significant.
a p<0.0001 versus placebo.
b p<0.001 versus placebo.
c p<0.01 versus placebo.

While not the focus of this review, the authors noted that "the trend towards greater symptomatic improvement with aclidinium over tiotropium observed in this study may be related to differences in dosing frequency", while noting that the improvement in night time and early morning symptoms under clinical trials conditions should be considered against the potential disadvantages of twice- versus once-daily dosing in real world scenarios (Beier et al, 2013).

In addition to the comparable efficacy results, the incidence of adverse events was balanced between the treatment groups, with 27.5% of patients in the aclidinium group experiencing an adverse event, 29.7% in the tiotropium group, and 25.9% of patients who received placebo.

Umeclidinium versus tiotropium

Feldman (2016)

In a recent non-inferiority trial, patients with symptomatic moderate-to-severe COPD (GOLD Grade 2-3 and GOLD Groups B and D) were randomised to receive umeclidinium or tiotropium for 12 weeks. The MCID was defined as an increase of ≥100 mL above baseline in trough FEV_1, with the non-inferiority margin set at half of the MCID (i.e. –50 mL). As such, umeclidinium was considered non-inferior to tiotropium if the lower boundary of the 95% confidence interval (CI) around the treatment difference was greater than –50 mL, and considered superior if it was greater than 0 mL.

Table 3.11 shows an extensive list of analyses of change from baseline in trough FEV_1, including the primary analysis: LS mean change from baseline at Day 85. The authors noted that the per protocol (PP) population was used for analysis of the primary outcome to avoid bias of the results towards equivalence. Importantly, patients experiencing a COPD exacerbation were excluded from the PP analysis from the onset of the exacerbation, owing to the potential impact that treatments administered for the exacerbation, or the exacerbation itself, may have had on efficacy findings.

Table 3.11 Least squares mean change from baseline in trough FEV_1 – UME vs TIO

LS mean change from baseline	UME 62.5		TIO 18		Δ (95% CI)	p-value
	n	Mean (SE)	n	Mean (SE)		
Trough FEV_1 Overall population						
Day 2, mL	485	103 (8)	484	91 (8)	13 (–9,35)	0.254
Day 28, mL	485	144 (10)	484	102 (10)	42 (14,69)	0.003
Day 56, mL	485	136 (11)	484	89 (11)	46 (17,76)	0.002
Day 85, mL (primary outcome; PP analysis)	485	154 (11)	484	95 (11)	59 (29,88)	<0.001
Day 85, mL (ITT analysis)	508	147 (10)	504	94 (10)	53 (25,81)	<0.001
Subgroup analyses – trough FEV_1 on Day 85[a] GOLD Grade						
GOLD Grade 2	281	177 (14)	281	114 (14)	63 (25,100)	0.001
GOLD Grade 3	226	108 (16)	223	69 (16)	39 (–4,82)	0.074
GOLD Group						
GOLD Group B	244	171 (15)	227	114 (16)	57 (16,98)	0.006
GOLD Group D	263	124 (15)	277	78 (14)	46 (7,85)	0.020
ICS use at screening						

ICS users at screening	246	147 (15)	229	81 (15)	66 (25,107)	0.002
ICS non-users at screening	262	146 (14)	275	104 (14)	42 (3,81)	0.035
ICS use and GOLD grade at screening						
GOLD Grade 2 and ICS users at screening	122	172 (21)	114	108 (21)	64 (6,122)	0.030
GOLD Grade 2 and ICS non-users at screening	159	181 (19)	167	119 (18)	62 (13,111)	0.013
GOLD Grade 3 and ICS users at screening	124	118 (22)	115	53 (22)	65 (7,123)	0.028
GOLD Grade 3 and ICS non-users at screening	102	97 (24)	108	88 (23)	9 (–55,72)	0.784

Source: Feldman (2016), Figure 2 (p 724), Table 2 (p 724), Table S4 (online).
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for chronic Obstructive Lung Disease; ITT, intention-to-treat; LS, least squares; NR, not reported; ns, non-significant; PP, per protocol; SE, standard error; TIO, tiotropium; UME, umeclidinium.
Note: Results are based on the PP population unless otherwise specified (PP: all patients in the ITT population, including those who did not complete the study, who did not have a protocol deviation considered to impact efficacy).
a All post hoc analyses were performed using a repeated measures model with covariates of treatment, baseline FEV_1 (mean of the two assessments made 30 min and 5 min pre-dose on Day 1), centre group, 24 hr subset flag, GOLD grade/GOLD group/ICS use, day, day-by-baseline and day-by-GOLD grade/GOLD group/ICS use and Day by GOLD grade/GOLD group/ICS use by treatment interactions.

The results shown above demonstrate that umeclidinium was found to be non-inferior and, on a subsequent superiority analysis, superior to tiotropium, based on trough FEV_1. Similar differences were observed in the PP and intention-to-treat (ITT) populations. Superiority was shown after four weeks of treatment and maintained until the end of the 12-week study.

The subgroup analyses in Table 3.11 generally favoured umeclidinium over tiotropium; however, the treatment difference was more pronounced in some subgroups than others. For instance, a statistically significant difference was observed in the least squares mean change from baseline in trough FEV_1 in favour of umeclidinium versus tiotropium for patients with GOLD Grade 2 COPD, but not for patients with GOLD Grade 3 COPD at Day 85.

An analysis of responders was conducted that also showed a statistically significant difference, in favour of umeclidinium, in the proportion of patients with an increase of ≥100 mL above baseline in trough FEV_1 (see Table 3.12).

Table 3.12 Proportion of patients with an increase of ≥100 mL above baseline in trough FEV_1 – UME vs TIO

Trough FEV_1 increase ≥100 mL above baseline	UME (n=485)	TIO (n=484)	OR (95% CI)	p-value
Proportion of responders on Day 2, %	51	48	1.13 (0.88, 1.45)	ns
Proportion of responders of Day 28, %	58	47	1.51 (1.18, 1.93)	<0.05
Proportion of responders on Day 56, %	52	41	1.52 (1.18, 1.95)	<0.05
Proportion of responders on Day 84, %	50	43	1.30 (1.01, 1.66)	<0.05
Proportion of responders on Day 85, n (%)	268 (53)	228 (45)	1.35 (1.06, 1.74)	<0.05

Source: Feldman (2016), Figure 4.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ns, non-significant; OR, odds ratio; TIO, tiotropium; UME, umeclidinium.

Umeclidinium was generally found to have superior efficacy to tiotropium when assessed by trough FEV_1, and was also well tolerated (see Table 3.13); however, it is important to note that no significant differences were found between the treatment groups for several other efficacy outcomes, including TDI, SGRQ and COPD Assessment Test (CAT) scores (data not presented in this review).

Table 3.13 Incidence of adverse events and other safety outcomes for UME vs TIO – ITT population

Safety outcome	UME 62.5 (N=509)	TIO 18 (N=508)
AE incidence, n (%)	165 (32)	153 (30)

On-treatment exacerbations[a], n (%)	58 (11)	48 (9)
Cardiovascular events, n (%)	9 (2)	10 (2)
Pneumonia, n (%)	2 (<1)	2 (<1)
LRTI, n (%)	5 (<1)	3 (<1)
Death, n (%)	0	2 (<1)[b]

Source: Feldman et al (2016), Table 5.
Abbreviations: AE, adverse event; LRTI, lower respiratory tract infection; TIO, tiotropium; UME, umeclidinium.
a Defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study medication or rescue albuterol/salbutamol.
b Neither of the two events (alcohol poisoning, seizure) were considered related to study drug by the reporting investigator.

Some important limitations of this study were acknowledged, most of which are broadly applicable across many COPD studies:

1. It is not possible to determine whether the differences in bronchodilator effect observed are due to pharmacologic effects of the drugs themselves or to differences in the devices that might have influenced inhalation technique and/or drug absorption and lung deposition.
2. This was a controlled, short-term study in which patients were supervised while administering their study medication. Therefore, patients were expected to have minimal critical errors in device handling.
3. While this study reported on-treatment exacerbations as a safety outcome, the duration of the study was too short to evaluate the comparative efficacy of umeclidinium and tiotropium on exacerbation rate.
4. There were differences in the markings between the tiotropium and placebo capsules which may have may have impacted on the blinding of treatment assignment. Specifically, tiotropium capsules had trade marking but placebo capsules did not.[14] In an attempt to mask this discrepancy, blister packages for both tiotropium and placebo were covered with opaque over-labels in order to cover the appearance of the commercial blister packing of tiotropium. Any identifying marks on the inhaler were also covered.

Donohue (2012)

Donohue et al (2012) undertook a dose-response study that evaluated once-daily and twice-daily doses of umeclidinium with daily doses ranging from 62.5 µg (the PBS dose) to 1000 µg. While the primary aim of the study was not to compare umeclidinium and tiotropium, an open-label tiotropium arm was included in the trial, allowing for a basic assessment of the comparative efficacy of the two LAMA therapies.

As outlined in Table 3.8, concurrent use of ICS was permitted during the study. Across the treatment groups, between 21% and 39% of patients were also treated with ICS throughout the treatment period. Overall, the authors concluded that doses of umeclidinium ranging from 62.5 to 1000 µg once-daily were well tolerated, with efficacy comparable to tiotropium. The results for umeclidinium 62.5 µg and tiotropium 18 µg (the PBS-listed doses) are shown in Table 3.14.

[14] Patients randomised to umeclidinium also received placebo via the HandiHaler inhaler; patients randomised to tiotropium received placebo via the Ellipta dry power inhaler.

Table 3.14 Changes in trough FEV_1 on Day 15 – UME vs TIO

Trough FEV_1 on Day 15	UME (n=35)		TIO (n=35)	
	Mean (SE)	p-value	Mean (SE)	p-value
Adjusted mean change from baseline, mL	81 (33)	-	58 (33)	-
Adjusted mean difference versus placebo, mL	128	≤0.001	105	0.003

Source: Donohue (2012), pg 973.
Note: Mean change from baseline in the placebo arm was –47 mL (SE: 17).
Abbreviations: FEV_1, forced expiratory volume in one second; SE, standard error; TIO, tiotropium; UME, umeclidinium.

Umeclidinium versus glycopyrronium

NCT02236611

This recently completed RCT was not identified in the systematic literature review, as there were no peer-reviewed publications of the trial at the time of the search. However, the study was cited and briefly summarised in the GlaxoSmithKline response to the final ToR for this review (dated 22 April 2016). The study characteristics and results presented here for trial NCT02236611 were collated from the public submission as well as the study results that were available on ClinicalTrials.gov as of 10 November 2016.

The primary aim of the study was to determine non-inferiority of umeclidinium to glycopyrronium. The non-inferiority margin was set at –50 mL, meaning that umeclidinium was considered non-inferior to glycopyrronium if the lower boundary of the 95% CI around the treatment difference was greater than –50 mL.

Based on both per protocol and ITT analyses, shown in Table 3.15, the results showed that umeclidinium was non-inferior to glycopyrronium. The safety results shown in Table 3.16 indicate that both umeclidinium and glycopyrronium were generally well tolerated.

Table 3.15 Least squares mean change from baseline for trough FEV_1 – UME vs GLY

Trough FEV_1	UME (n=431)	GLY (n=425)	Treatment difference, Δ (95% CI)	p-value
LS mean (SE) change from baseline on Day 85, L				
Per protocol population	0.123 (0.0105)	0.099 (0.0105)	0.024 (–0.005, 0.054)	0.100
Intention-to-treat population	NR	NR	0.033 (0.005, 0.061)	NR

Source: NCT02236611. Results available at: https://clinicaltrials.gov/ct2/show/results/NCT02236611?sect=X70156&term=NCT02236611&rank=1#outcome1.
Note: Based on a mixed models analysis.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; GLY, glycopyrronium; LS, least squares; NR, not reported; SE, standard error; UME, umeclidinium.

Table 3.16 Safety outcomes for the comparison of UME and GLY

Safety outcome	UME (N=516)	GLY (N=518)
Total AEs not including SAEs, n (%)	77 (14.9)	80 (15.4)
Total SAEs, n (%)	17 (3.3)	15 (2.9)
Cardiac disorders	2 (0.4)	3 (0.6)
Respiratory, thoracic and mediastinal disorders	7 (1.4)	6 (1.2)

Source: NCT02236611. Results available at: https://clinicaltrials.gov/ct2/show/results/NCT02236611?sect=X70156&term=NCT02236611&rank=1#outcome1.
Abbreviations: AE, adverse event; GLY, glycopyrronium; SAE, serious adverse event; UME, umeclidinium.

Tiotropium Respimat versus tiotropium HandiHaler

TIOSPIR study

The TIOSPIR study was a large RCT that compared the safety and efficacy of the two PBS-listed tiotropium formulations, HandiHaler and Respimat, over a 2-3 year period. The primary safety outcome was time to death of any cause (non-inferiority of Respimat versus HandiHaler), and the primary efficacy outcome was time to first COPD exacerbation (superiority for Respimat versus HandiHaler).

The primary safety outcomes were reported by Wise et al (2013) and were considered by the PBAC as part of the tiotropium/olodaterol (Spiolto Respimat) submission in July 2014. Subsequently, several post hoc analyses of the TIOSPIR study have been published that focus on the comparative efficacy of Respimat and HandiHaler and the comparative safety in particular patient subgroups. Three of those publications, with findings of relevance to this review, are summarised below.

It should be noted that several of the post hoc TIOSPIR publications emphasise the liberal eligibility criteria of the study, noting that patients with a wide range of disease severities and those with a history of cardiac disorders were included. As a result, TIOSPIR is likely to be more representative of a typical COPD population than some clinical studies (although patients with severe, unstable cardiovascular disease or moderate-to-severe renal impairment were not eligible).

Anzueto et al (2015) undertook a subgroup analysis of spirometry outcomes on a subset of 1,370 patients who underwent spirometry at baseline and every 24 weeks throughout the study. The non-inferiority margin for trough FEV_1 was set at 50 mL and, based on that criteria, tiotropium Respimat 5 µg was shown to be non-inferior to HandiHaler (see Table 3.17).[15]

Table 3.17 Adjusted mean change from baseline in trough FEV_1 – Respimat vs HandiHaler

	Respimat (n=461)	HandiHaler (n=445)	Δ mL (95% CI)	p-value
Adjusted mean trough FEV_1 (average 24-120 weeks), mL	1,285	1,295	–10 (–38, 18)	ns

Source: Anzueto (2015), p110.
Note: Trough FEV_1 (24 to 120 weeks) was analysed between treatment groups using a mixed model repeated measures model with an autoregression-1 covariance structure and the Kenwood–Roger approximation to estimate denominator degrees of freedom. Analyses included the fixed terms for treatment, investigative site, visit, treatment-by-visit interaction, baseline FEV_1, and baseline FEV_1-by-visit interaction, and a random term for patient.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ns, non-significant.

In another subgroup analysis, Dahl et al (2015) examined the results for 2,782 patients who had stable HandiHaler use for at least two months prior to study enrolment. The aim of the study was to determine whether there was a difference in risk for patients who switched from HandiHaler to Respimat in terms of time to death (safety) and time to first COPD exacerbation (efficacy).

Of the patients included in this post hoc analysis, 952 were randomised to HandiHaler; 918 to Respimat 5 µg; and 914 to Respimat 2.5 µg.[16] In addition to pre-existing LAMA therapy, 68.7%

[15] In this predefined substudy, 464 patients were randomised to tiotropium Respimat 2.5 µg qd. Results are not shown for this treatment group, as it is not a PBS-listed dose.
[16] This is a non-PBS dose. No results are presented for this treatment group.

of patients in this substudy were taking a LABA at baseline, and 66.5% were being treated with ICS. A high proportion of patients (60.1%) were also receiving cardiovascular medications and 16.2% had a history of cardiac arrhythmia.

Non-inferiority testing was undertaken for the time to death endpoint, using HandiHaler as the reference group. Rate ratios and 95% CIs were used to compare incidence rates, with the non-inferiority margin set at 1.25; consequently, if the upper limit of the 95% CI was below 1.25, the null hypothesis was rejected (Wise et al, 2013).

Table 3.18 indicates that there were numerically fewer mortality events in the Respimat group than the HandiHaler group in all but one of the relevant analyses, which included subgroup analyses of cardiac history, treatment history and COPD severity. The one exception was in patients with two or more exacerbations in the previous year, where the results numerically favoured HandiHaler. Nevertheless, the criteria for non-inferiority was met, demonstrating that across an extensive range of mortality outcomes, Respimat is non-inferior to HandiHaler. Additional safety findings for non-fatal adverse events are presented in Table 3.20.

There was no significant difference in the co-primary end point of time to first COPD exacerbation in Respimat versus HandiHaler, with a similar number of exacerbations, including severe exacerbations, being observed between the two treatment groups (see Table 3.19).

Table 3.18 Incidence of mortality and fatal MACE in treated with tiotropium HandiHaler at baseline who continue to receive HandiHaler or switch to Respimat in the TIOSPIR study

	N for both groups	Respimat (n=918)	HandiHaler (n=952)	Rate ratio (95% CI)
Overall				
All-cause mortality, n (rate per 100 patient-years)	-	71 (3.3)	92 (4.1)	0.79 (0.58, 1.07)
Cardiac disorders	-	2 (0.1)	5 (0.2)	0.41 (0.08, 2.10)
Respiratory, thoracic and mediastinal disorders	-	26 (1.2)	33 (1.5)	0.80 (0.46, 1.78)
Fatal MACE[a]	-	13 (0.6)	20 (0.9)	0.66 (0.33, 1.33)
All-cause mortality, total incidence (%)	-	7.7	9.7	0.79 (0.58, 1.07)
Subgroup analyses, total incidence (%) **Baseline cardiac arrhythmia**				
No	1,571	6.8	8.7	0.77 (0.54, 1.10)
Yes	296	12.3	14.6	0.83 (0.44, 1.56)
Cardiac history[b]				
No	1,282	5.6	8.0	0.69 (0.45, 1.05)
Yes	585	12.4	13.2	0.93 (0.59, 1.46)
ICS				
No	630	7.2	8.3	0.86 (0.49, 1.51)
Yes	1,238	8.0	10.4	0.75 (0.52, 1.09)
LABA				
No	593	7.0	8.5	0.82 (0.46, 1.47)
Yes	1,275	8.1	10.2	0.77 (0.53, 1.11)
GOLD Grade				
I-II	773	6.0	7.5	0.80 (0.46, 1.38)

	N for both groups	Respimat (n=918)	HandiHaler (n=952)	Rate ratio (95% CI)
III	841	6.5	8.4	0.77 (0.46, 1.27)
IV	241	17.9	21.0	0.82 (0.46, 1.46)
Exacerbation episodes in last year				
0 or 1	1,561	6.8	9.8	0.68 (0.48, 0.97)
2 or more	306	11.6	9.3	1.26 (0.63, 2.53)

Source: Dahl et al (2015), Table 2 and e-figure 2b.
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting beta-2 agonist; MACE, major adverse cardiovascular event.
a Stroke, transient ischaemic attack, myocardial infarction, sudden death, cardiac death, sudden cardiac death or fatal event in the system organ classes for cardiac and vascular disorders.
b Defined as history of myocardial infarction, ischaemic heart disease/coronary artery disease, cardiac arrhythmia or heart failure.

Table 3.19 Risk and rate of exacerbations, on-treatment analysis[a] – Respimat vs HandiHaler

	Respimat (n=918)	HandiHaler (n=952)	HR (95% CI)	p-value
Any exacerbation[b]				
Patients with event, n (%)	560 (61.1)	578 (60.8)	0.96 (0.86, 1.08)	0.517
Number of events	1,508	1,548	-	-
Adjusted rate of events per patient-year (95% CI)	0.83 (0.76, 0.90)	0.81 (0.74, 0.87)	-	-
Severe (hospitalised) exacerbation				
Patients with event, n (%)	173 (18.9)	172 (18.1)	1.03 (0.84, 1.28)	0.760
Number of events	283	267	-	-
Adjusted rate of events per patient-year (95% CI)	0.16 (0.13, 0.19)	0.14 (0.12, 0.17)	-	-

Source: Dahl et al (2015), Table 3.
Abbreviations: CI, confidence interval; HR, hazard ratio.
Note: HRs and 95% CIs for time-to-event end points were calculated using a Cox proportional hazards regression model (with no covariate adjustment). Negative binomial regression models were used to compare annual exacerbation rates.
a Includes first day after treatment stop.
b Defined as the worsening of two or more major respiratory symptoms (dyspnoea, cough, sputum, chest tightness of wheezing) with a duration of at least 3 days and requiring specified treatment changes.

Table 3.20 Safety outcomes relating to tiotropium Respimat and HandiHaler

	Respimat (N=917)	HandiHaler (N=951)
Any AE, n (%)	721 (78.6)	737 (77.5)
Drug-related AE, n (%)	66 (7.2)	75 (7.9)
Serious AE, n (%)	399 (43.5)	409 (43.0)
Patients with MACE[a], n (%)	31 (3.4)	57 (6.0)

Source: Dahl et al (2015), Table 4.
Abbreviations: AE, adverse event; MACE, major adverse cardiovascular event.
a As determined by the investigator.

Based on their findings, Dahl et al (2015) concluded that it is safe to switch patients from HandiHaler to Respimat, including those with a history of cardiac disorders, and that efficacy is maintained over the switch.

Conversely, Wise et al (2015) conducted a post hoc analysis of patients who were naïve to anticholinergic therapy prior to the study (N=6,966). The patients in this subgroup analysis had less severe disease than the total TIOSPIR population and had not received short- or long-acting inhaled anticholinergics during the two months prior to randomisation. Again, this post hoc analysis focused on the aforementioned co-primary endpoints: risk of death from any cause (measured as time to death) and risk of COPD exacerbation (measured as time to first exacerbation).

Patients naïve to anticholinergic treatment at baseline were randomised to tiotropium HandiHaler 18 µg (n=2,309) or Respimat 5 µg (n=2,312).[17] Importantly, while all patients in this post hoc analysis were naïve to LAMAs, 50.2% and 51.6% of patients were taking ICS and LABA treatments, respectively, at baseline.

Overall, risk of death and the specific causes of death were similar between the Respimat and HandiHaler treatment groups, as shown in Table 3.21. The authors also noted that subgroup analyses (including cardiac history at baseline and pulmonary co-medication at baseline) showed no difference between groups; however, these data were not published.

Table 3.21 Incidence of mortality and fatal MACE in anticholinergic-naïve patients treated with tiotropium Respimat versus tiotropium HandiHaler in the TIOSPIR study

	Respimat (n=2,312)	HandiHaler (n=2,309)	Rate ratio (95% CI)
Overall			
All-cause mortality, n (rate per 100 patient-years)	149 (2.8)	159 (3.0)	0.93 (0.75, 1.17)
Cardiac disorders	13 (0.2)	5 (0.1)	2.59 (0.92, 7.27)
Respiratory, thoracic and mediastinal disorders	34 (0.6)	36 (0.7)	0.94 (0.59, 1.50)
Fatal MACE[a]	49 (0.9)	43 (0.8)	1.14 (0.75, 1.71)

Source: Wise et al (2015), Table 2.
Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular event.
a Stroke, transient ischaemic attack, myocardial infarction, sudden death, cardiac death, sudden cardiac death or fatal event in the system organ classes for cardiac and vascular disorders.

There were no significant differences between Respimat and HandiHaler with respect to the risk of exacerbations. Exacerbation rates were similar between the treatment arms across the spectrum of exacerbation severities (any, moderate-to-severe or severe) as shown in Table 3.22. A subgroup analysis of less severe patients, classified as GOLD Stage II, also demonstrated comparable efficacy results for Respimat and HandiHaler (data not presented).

[17] In addition, 2,345 patients were randomised to tiotropium Respimat 2.5 µg qd. Results are not shown for this treatment group, as it is not a PBS-listed dose.

Table 3.22 Risk of exacerbation in anticholinergic naïve patients – Respimat vs HandiHaler

	Respimat (n=2,309)	HandiHaler (n=2,307)	HR (95% CI)	p-value
Any exacerbation; all patients				
Patients with event, n (%)	923 (40.0)	948 (41.1)	0.99 (0.90, 1.08)	0.829
Number of events	2,022	1,955	-	-
Adjusted rate of events per patient-year (95% CI)	0.45 (0.42, 0.48)	0.44 (0.41, 0.47)	-	-
Moderate-to-severe exacerbations; all patients				
Patients with event, n (%)	902 (39.1)	926 (40.1)	0.99 (0.90, 1.09)	0.840
Number of events	1,956	1,902	-	-
Adjusted rate of events per patient-year (95% CI)	0.44 (0.41, 0.47)	0.43 (0.40, 0.46)	-	-
Severe (hospitalised) exacerbation; all patients				
Patients with event, n (%)	250 (10.8)	255 (11.1)	0.99 (0.83, 1.18)	0.917
Number of events	376	363	-	-
Adjusted rate of events per patient-year (95% CI)	0.09 (0.08, 0.10)	0.08 (0.07, 0.10)	-	-

Source: Wise et al (2015), Table 3.
Abbreviations: CI, confidence interval; HR, hazard ratio.
Note: HRs and 95% CIs for time-to-event end points were calculated using a Cox proportional hazards regression model (with no covariate adjustment). Negative binomial regression models were used to compare annual exacerbation rates.

Overall, the post hoc analysis of anticholinergic naïve patients showed that those who were treated with tiotropium Respimat and HandiHaler were at a similar risk of mortality, adverse cardiac events and exacerbations.

Summary of findings

- Overall, all LAMA therapies were well tolerated and no new safety concerns were identified. The findings presented throughout this section are consistent with evidence previously considered by the PBAC that demonstrated non-inferiority between all PBS-listed LAMA therapies with respect to efficacy.
- Manoharan et al (2016; poor quality) conducted a short-term cross-over study that compared the efficacy and safety of aclidinium and tiotropium in patients with moderate to severe COPD who were already on ICS/LABA therapy. Tiotropium and aclidinium were found to be comparable in terms of both efficacy (based on trough FEV_1) and safety when used as triple therapy.
- Beier et al (2013; fair quality) also compared the effect of treatment with aclidinium and tiotropium on trough FEV_1 in patients with moderate to severe COPD. Patients were permitted to stay on ICS (and some other therapies) if they were already taking them at baseline. The proportion of patients who were taking concomitant ICS was not reported and it is possible that in this study a large proportion of patients were using tiotropium and aclidinium as monotherapy. By Week 6, both treatments had reached the MCID (i.e. both ≥100 mL improvement from baseline), but no significant difference was observed between tiotropium and aclidinium.
- Feldman et al (2016; good quality) confirmed the non-inferiority of umeclidinium to tiotropium. Based on the primary outcome (least squares mean change from baseline in trough FEV_1 at 12 weeks) umeclidinium was also found to be superior to tiotropium across a range of patient subgroups; however, no significant differences were found between the treatments groups for several other efficacy outcomes, including TDI, SGRQ and CAT score.

- An unpublished RCT (NCT02236611; quality not assessed) demonstrated non-inferiority of umeclidinium to glycopyrronium based on least squares mean change from baseline for trough FEV_1. Short-term data (12 weeks) indicated that umeclidinium and glycopyrronium are also comparable in terms of safety.
- Despite earlier safety concerns, the largest COPD study conducted to date (TIOSPIR study; good quality) found that tiotropium Respimat was non-inferior to HandiHaler across a broad range of safety outcomes, including overall risk of death. Earlier safety concerns about a possible increased risk of mortality with tiotropium Respimat (particularly in patients with a history of cardiac arrhythmia) were not supported by longer-term evidence from this large, high-quality RCT. Tiotropium Respimat also demonstrated comparable efficacy to HandiHaler with respect to both risk of exacerbations and change from baseline in trough FEV_1.

1.4.2 LABA versus LABA

Indacaterol is the only LABA currently listed on the PBS for COPD; however, it is available in two doses, 150 µg once-daily and 300 µg once-daily. The body of evidence comparing the doses is limited and only one RCT, listed in Table 3.23, was identified that provided additional evidence about the comparative efficacy and safety of the two doses. The characteristics of the included study are summarised in Table 3.24.

Table 3.23 List of randomised controlled trials comparing two doses of indacaterol

Trial ID	Citation	Description
INDORSE	Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C and Kramer B (2011). Long-term safety and efficacy of indacaterol, a long-acting $beta_2$-agonist, in subjects with COPD: A randomized, placebo-controlled study. Chest 140 (1):68-75.	Key publication

The original submissions that supported the listing of indacaterol (Onbrez) demonstrated comparative clinical efficacy of the two doses of indacaterol (150 µg and 300 µg once-daily) that are now PBS listed for COPD. On the basis of results from the pivotal clinical study that showed similar results for both doses, the sponsor did not request a price differential between the doses. Therefore, based on the evidence previously considered, the PBAC considered both indacaterol 150 µg and 300 µg to be equivalent to tiotropium 18 µg. The study characteristics of the one included study are summarised in Table 3.24.

Table 3.24 Details of RCTs comparing indacaterol 150 µg and indacaterol 300 µg

Trial ID 1. Publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period (LOF)	Outcomes reported
INDORSE 1. Chapman (2011) 2. Good quality 3. US, Argentina, Canada, Germany, India, Italy, Spain, Sweden, Turkey 4. Novartis	415	Double-blind, extension study.	IND 150 µg qd (n=144) IND 300 µg qd (n=146) PBO (n=125)	Inclusion (1) Completed the core 26-week study, (2) age ≥40 years, (3) moderate-to-severe COPD, (4) post-bronchodilator FEV_1 <80% and ≥30% predicted, and post-bronchodilator FEV_1/FVC <70%. Exclusion (1) History of asthma, (2) respiratory tract infection or hospitalisation for COPD exacerbation within 6 weeks before the core study. Other (1) Subjects were supplied with albuterol for use as needed, (2) other bronchodilators were discontinued before the study, (3) treatment with fixed combinations of LABAs and ICS was replaced with ICS monotherapy at equivalent doses and regimens prior to the core study (subjects already on ICS monotherapy at the start of the core study could continue their ICS medication).	52 weeks (26-week RCT with 26-week extension)	Primary Safety over 52 weeks, including AEs, vital signs, ECGs, serum potassium and blood glucose levels. Secondary Trough FEV_1 at 52 weeks;[18] time to first COPD exacerbation;[19] albuterol use; rate of exacerbations; SGRQ.

Note: N refers to number randomised unless otherwise specified.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; LOF, length of follow up; PBO, placebo; qd, once daily; RCT, randomised controlled trial; SGRQ, St George's Respiratory Questionnaire; US, United States.

[18] Mean of measurements at 23 hrs 10 mins and 23 hrs 45 mins postdose. A difference in trough FEV_1 of 120 mL between indacaterol and placebo was considered clinically relevant.
[19] COPD exacerbations were defi ned as onset or worsening of more than one respiratory symptom (dyspnea, cough, sputum purulence/volume, or wheeze) for 3 consecutive days, plus intensified treatment (eg, systemic steroids, antibiotics, oxygen) and/or hospitalisation or ED visit.

Indacaterol 150 µg once-daily versus indacaterol 300 µg once-daily

INDORSE study

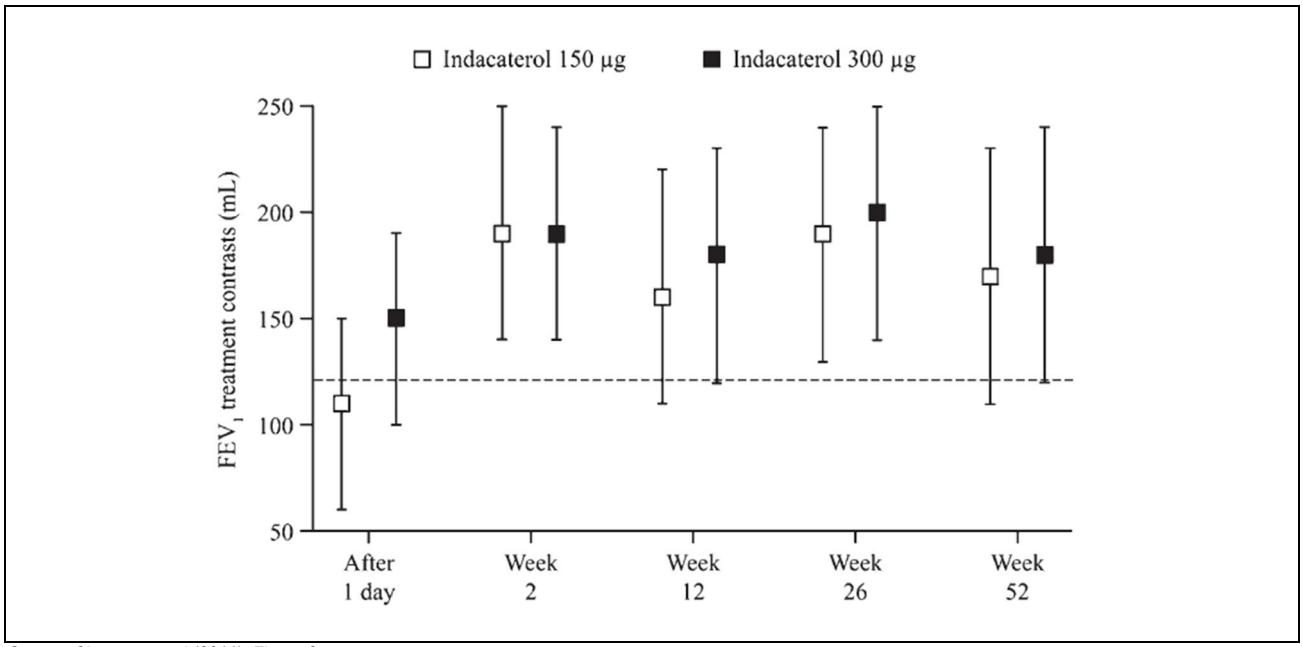
In this study, patients were randomised (1:1:1:1) to treatment with indacaterol 150 µg or 300 µg, placebo, or open-label tiotropium for 26 weeks. Patients who were assigned to either of the indacaterol groups or placebo, and who completed the core study, were eligible for a 26-week extension study in which they continued their existing treatment. The double-blind was maintained throughout the entire study period and the primary end point was safety at 52 weeks.

In relation to baseline characteristics, the treatment groups were generally comparable. In both of the indacaterol groups, 34% of patients were using ICS medications at baseline compared with 40% in the placebo group.

The differences between indacaterol and placebo in trough FEV_1 were fairly consistent from Week 2 to Week 52, with differences of ≥160 mL compared with placebo for both doses at each time point (all $p<0.001$). Although no statistical analyses were conducted to compare the two doses of indacaterol, it is apparent from the data presented in Figure 3.1 and Table 3.25 that the two doses of indacaterol were associated with similar magnitudes of improvement from baseline and compared with placebo.

The results shown in Table 3.26 demonstrate very similar findings for the two indacaterol doses in relation to risk of exacerbations; however, the authors acknowledged that the study was not sufficiently powered for a comparison of exacerbation rates.

Figure 3.1 Differences between active treatments and placebo for trough FEV_1 up to Week 52



Source: Chapman et al (2011), Figure 2.
Note: Data are presented as LS means with 95% CIs. An indacaterol-placebo difference of 120 mL (broken line) was taken as the threshold for a clinically relevant effect.
Abbreviations: FEV_1, forced expiratory volume in 1 second.

Table 3.25 Change in trough FEV_1 at Week 52 – IND 150, IND 300 and PBO

Trough FEV_1 at Week 52	IND 150	IND 300	PBO	p-value
Change relative to placebo, LS mean (95% CI), mL	170 (110, 230)	180 (120, 240)	-	both p<0.001
Change relative to baseline, LS mean (% change), mL	120 (10)	130 (10)	–40 (–3)	-

Source: Chapman et al (2011), pg 71-2 and Figure 2.
Note: Efficacy was analysed for the ITT population, comprising all randomised subjects who received at least one dose of study drug, and subjects were analysed according to their randomised treatment. The analysis was conducted using a mixed model analysis of covariance.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; IND, indacaterol; LS, least squares; PBO, placebo.

Table 3.26 Rate of COPD exacerbations – IND 150 µg, IND 300 µg versus placebo

	IND 150 (n=144)	IND 300 (n=146)	PBO (n=124)
Without imputation			
Exacerbations per year	0.39	0.38	0.54
Rate ratio compared with placebo (95% CI)	0.64 (0.43, 0.96); p=0.029	0.62 (0.42, 0.92); p=0.018	-
With imputation			
Exacerbations per year	0.43	0.40	0.57
Rate ratio compared with placebo (95% CI)	0.67 (0.45, 1.01); p=0.054	0.66 (0.44, 0.98); p=0.042	-

Source: Chapman et al (2011), Table 3.
Note: Time to first exacerbation was analysed using a Cox regression model, and exacerbation rates were analysed using a Poisson regression model without imputation (a sensitivity analysis with imputation of an additional exacerbation for prematurely discontinuing subjects was also performed).
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; IND, indacaterol; PBO, placebo.

The primary objective of the INDORSE study was to evaluate the long-term safety of indacaterol. The safety outcomes summarised in Table 3.27 demonstrate that both doses of indacaterol were well tolerated over a one year period and there were no concerning safety signals in either of the indacaterol groups, compared with placebo.

Table 3.27 Safety outcomes relating to IND 150 µg, IND 300 µg and placebo – safety population[a]

	IND 150 (n=144)	IND 300 (n=146)	PBO (n=124)
AEs, n (%)	110 (76.4)	112 (76.7)	84 (67.7)
COPD worsening, n (%)	35 (24.3)	39 (26.7)	34 (27.4)
LRTI, n (%)	5 (3.5)	11 (7.5)	8 (6.5)
Death, n (%)	0	1 (<1)	1 (<1)
AE leading to discontinuation, n (%)	4 (2.8)	2 (1.4)	7 (5.6)
SAE, n (%)	15 (10.4)	18 (12.3)	13 (10.5)

Source: Chapman et al (2011), pg 70; e-Table 1 (Online supplement).
Note: Both deaths were due to myocardial infarction, and both were suspected to be related to study treatment (note: investigators were blinded to treatment assignment).
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; IND, indacaterol; LRTI, lower respiratory tract infection; PBO, placebo; SAE, serious adverse event.
a All subjects who received at least one dose of the study drug.

Summary of findings

- The previously established comparable clinical efficacy of indacaterol 150 µg and indacaterol 300 µg (both once daily) is supported by newer evidence from the INDORSE study (Chapman et al, 2011; good quality). Indacaterol demonstrated good overall tolerability and long-term safety in patients with moderate to severe COPD.

1.4.3 LAMA/LABA versus LAMA/LABA

One recently published RCT was identified that examined the comparative efficacy and safety of two different LAMA/LABA combination therapies. The publication details are shown in Table 3.28 and the study characteristics, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.29.

Table 3.28 List of randomised controlled trials comparing two LAMA/LABA combination therapies

Trial ID	Citation	Description
Kalberg (2016)	Kalberg C, O'Dell D, Galkin D, Newlands A and Fahy WA (2016). Dual Bronchodilator Therapy with Umeclidinium/Vilanterol Versus Tiotropium plus Indacaterol in Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. Drugs in R and D 16 (2):217-227.	Key publication
QUANTIFY	Buhl, R., Gessner, C., Schuermann, W., Foerster, K., Sieder, C., Hiltl, S. & Korn, S. (2015a). Efficacy and safety of orce-daily QVA149 compared with the free combination of once-daily tiotropium plus twice-daily formoterol in patients with moderate-to-severe COPD (QUANTIFY): a randomised, non-inferiority study. Thorax, 70, 311-9.	Key publication

Table 3.29 Details of RCTs comparing two LAMA/LABA combinations in patients with COPD

Trial ID 1. Publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period (LOF)	Outcomes reported
Kalberg (2016) 1. N/A 2. Good quality 3. Germany, Russia, Hungary, Argentina, Romania and others. 4. GlaxoSmithKline	961	Non-inferiority. Double-blind,[20] triple-dummy.	UME/VIL 62.5/25 µg qd (n=482) TIO 18 µg qd + IND 150 µg qd (n=479)	Inclusion (1) Age ≥40 years, (2) clinical history of COPD, (3) pre- and post-bronchodilator FEV_1 values of ≤70% predicted normal, (4) pre- and post-bronchodilator FEV_1/FVC ratio <0.70, (5) score of ≥2 on the mMRC Dyspnea Scale. Exclusion (1) Current diagnosis of asthma, (2) alpha-1 antitrypsin deficiency, (3) active lung infection, (4) lung cancer, (5) abnormal or significant electrocardiogram finding, (6) hospitalised for COPD or pneumonia within 12 weeks of visit 1, (7) current oxygen therapy or pulmonary rehabilitation. Other (1) The use of ICS/LABAs, phosphodiesterase-4 inhibitors, theophyllines, oral β_2-agonists, LAMAs, LABAs, and LAMA/LABA combinations (other than those under study) was not allowed, (2) patients were randomised to treatment only if they had not experienced COPD exacerbation between visits 1 and 2 and if they had not used any prohibited medication during the run-in period to visit 2, (3) all patients had albuterol provided for as-needed use.	12 weeks	Primary Trough FEV_1 on Day 85. Secondary Trough FEV_1 on Days 28 and 56, weighted mean FEV_1 over 0-6 hours on Day 84, serial and trough FVC, rescue medication, TDI focal score, SGRQ, safety (AEs, vital signs, COPD exacerbations).
QUANTIFY 1. Buhl (2015a) 2. Good quality 3. Germany (164 centres) 4. Novartis Pharma AG, Boeheringer Ingelheim	934	Non-inferiority blinded, triple-dummy, parallel.	IND/GLY 110/50 µg qd (n=476) TIO 18 µg qd + EFO 112 µg qd (n=479)	Inclusion (1 Adults aged ≥40 years, (2) moderate-to-severe stable COPD, (3) current or ex-smokers with a smoking history of at least 10 pack-years, (4) patients with a post-bronchodilator bronchodilator FEV_1 values ≥ 30% and < 80% of the predicted normal, and post-bronchodilator FEV_1/FVC < 0·7 at Visit 2), (5) Patients receiving ICS continued treatment at the same dose. Exclusion (1) Patients with any history of asthma (2) COPD exacerbation that needed treatment with antibiotics, systemic corticosteroids or hospitalisation in the 6 weeks before pre-screening.and patients who developed a COPD exacerbation between the pre-screening and randomisation visits (3) Patients who had a respiratory tract infection within 6 weeks prior to pre-screening. Other	26 weeks	Primary SGRQ-C Secondary Trough FEV_1 and FVC on week 12 and 26, rescue medication, TDI focal score, safety (AEs, vital signs, COPD moderate and severe exacerbations resulting in hospitalisations).

Note: N refers to number randomised unless otherwise specified.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; EFO, Eformoterol, FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LOF, length of follow up; mMRC, modified Medical Research Council; N/A, not applicable; PBO, placebo; qd, once daily; RCT, randomised controlled trial; SGRQ, St George's Respiratory Questionnaire; SGRQ-C, St George's Respiratory Questionnaire COPD, TDI, Transition Dyspnea Index; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol,.

[20] Exact physical placebo matches for the tiotropium and indacaterol capsules and for the indacaterol blister packs were not available, although they were closely matched in colour.

Umeclidinium/vilanterol versus tiotropium + indacaterol

Kalberg (2016)

The authors stated that umeclidinium/vilanterol has previously been investigated in comparison with umeclidinium, vilanterol, or tiotropium monotherapy; however, this non-inferiority trial is the first to evaluate the FDC in comparison with another combination of a LAMA and LABA (i.e. tiotropium and indacaterol at PBS-listed doses, in separate inhalers).

In both treatment groups, the majority of patients were symptomatic with a high risk of exacerbations, with 61% and 60% of patients in the umeclidinium/vilanterol and tiotropium plus indacaterol groups, respectively, being classified as GOLD Group D. Over half of the patients in both the umeclidinium/vilanterol (56%) and tiotropium plus indacaterol (51%) arms were also receiving ICS at screening.

As in several of the aforementioned studies, the non-inferiority margin was set at –50 mL (i.e. if the lower limit of the 95% confidence interval (CI) fell above –50 mL but below 0, then umeclidinium/vilanterol could be considered statistically non-inferior to tiotropium plus indacaterol). On this basis, the results presented in Table 3.30 for trough FEV_1 at Day 85 demonstrate non-inferiority of the two treatments.

Table 3.30 Change from baseline to Day 85 in trough FEV_1 – UME/VIL vs TIO+IND

LS mean change from baseline	UME/VIL 62.5/25		TIO 18 + IND 150		Δ	p-value
	N	mL (SE)	N	mL (SE)	mL (95% CI)	
Trough FEV_1 on Day 85 – PP	392	172 (11)	392	171 (11)	1 (–29, 30)	NR
Trough FEV_1 on Day 85 – ITT	482	NR	479	NR	7 (–22, 35)	NR

Source: Kalberg et al (2016), Table 2.
Note: The authors noted that use of the ITT population (i.e. inclusion of data from protocol deviators) would tend to bias the results towards equivalence.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; IND, indacaterol; ITT, intention-to-treat; LS, least squares; NR, not reported; PP, per protocol; SE, standard error; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

While the focus of this review is on a small number of outcomes, the authors highlighted that umeclidinium/vilanterol and tiotropium plus indacaterol were comparable across a range of lung function, patient-reported, and safety outcomes over a 12-week period (see Table 3.31 for safety results).

Table 3.31 Results for safety outcomes relating to UME/VIL vs TIO+IND

	UME/VIL 62.5/25 (N=482)	TIO 18 + IND 150 (N=479)
AEs, n (%)	202 (42)	186 (39)
Drug-related AEs, n (%)	30 (6)	37 (8)
AE leading to study withdrawal/ discontinuation of medication, n (%)	12 (2)	8 (2)
Non-fatal SAE, n (%)	17 (4)	15 (3)
Fatal SAE, n (%)	4 (<1)[a]	1 (<1)
COPD exacerbation[b], n (%)	48 (10)	49 (10)
CV events of special interest[c], n (%)	11 (2)	9 (2)

Source: Kalberg (2016), Table 4.
Note: Based on ITT population.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; IND, indacaterol; SAE, serious adverse events; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.
a The three deaths relating to ventricular fibrillation, cardiac arrest, and pneumonia in the UME/VIL treatment group occurred ≥14 days after the last dose of the study medication, as recorded in the electronic case report forms. The cardiac arrest was reported by the investigator as being related to the study medication. No other deaths were deemed to be related to the study medication.
b Exacerbations were defined as worsening of COPD symptoms, requiring use of additional treatment other than the prescribed bronchodilator and/or emergency treatment or hospitalisation.
c Included cardiac arrhythmias, cardiac failure, ischaemic heart disease, central nervous system haemorrhages, and cerebrovascular conditions.

Indacaterol/ glycopyrronium versus tiotropium + eformoterol

QUANTIFY

The authors stated that indacaterol/glycopyrronium has previously been investigated in comparison with indacaterol and glycopyrronium; however, this non-inferiority trial is the first to evaluate the FDC in comparison with another combination of a LAMA and LABA (i.e. tiotropium and eformoterol at PBS-listed doses, in separate inhalers).

In both treatment groups, the patients had moderate or severe risk of exacerbations (GOLD II and GOLD III groups as defined by GOLD 2010) with 57.7% and 55.7% of patients in the indacaterol/glycopyrronium and tiotropium plus eformoterol groups, respectively, being classified as moderate COPD. Over 86% of patients in both treatment groups had no COPD exacerbation history at baseline.

The non-inferiority margin was predefined as 4 units, which has been reported in the literature as an appropriate definition for the limit for a clinically relevant effect for the SGRQ-C (refer to ToR 2). Secondary endpoints included TDI scores, symptoms of SGRQ-C, spirometry (FEV_1 and FVC), rate of moderate and severe COPD exacerbations requiring hospitalisation, and time to first moderate/severe exacerbation during the treatment period. The authors acknowledged that a limitation of the study, was that only the incidence of at least one exacerbation was considered, rather than the number of exacerbations experienced.

All the 934 randomised patients were included in the full analysis set (FAS). Non-inferiority was met for indacaterol/glycopyrronium compared with tiotropium plus eformoterol (difference: –0.69 units; 95% CI–2.31 to 0.92; p=0.399) at week 26. Compared with tiotropium plus eformoterol, patients receiving indacaterol/glycopyrronium showed a significantly increased pre-dose FEV_1 (+68 mL, 95% CI 37 mL to 100 mL; p<0.001) and FVC (+74 mL, 95% CI 24 mL to 125 mL; p=0.004) in the FAS at week 26. Post-dose FEV_1 and post-

dose FVC showed no significant differences between the treatment groups. The authors pointed out that concomitant drugs did not influence efficacy parameters.

The authors highlighted that indacaterol/glycopyrronium and tiotropium plus eformoterol were comparable across safety outcomes over a 26-week period (see Table 3.32 for safety results).

Table 3.32 Results for safety outcomes relating to IND/GLY vs TIO+EFO

	IND/GLY 110/50 (N=476)	TIO 18 + EFO 112 (N=479)
AEs, n (%)	208 (43.7)	195 (42.6)
Drug-related AEs, n (%)	32 (6.7)	24 (5.2)
AE leading to study withdrawal/ discontinuation of medication, n (%)	20 (4.2)	14 (3.1)
Non-fatal SAE, n (%)	30 (6.3)	24 (5.2)
Drug-related SAEs, n (%)	3 (0.6)	3 (0.2)
SAE leading to study withdrawal/ discontinuation of medication, n (%)	8 (1.7)	6 (1.3)
Fatal SAE, n (%)	3 (0.6)	3 (0.7)

Source: Buhl (2015a), Table 3.
Note: Based on ITT population.
Abbreviations: AE, adverse event; eformoterol (EFO), GLY, glycopyrronium IND, indacaterol; SAE, serious adverse events; TIO, tiotropium

Summary of findings

- Kalberg et al (2016; good quality) compared the efficacy and safety of umeclidinium/vilanterol versus tiotropium plus indacaterol and demonstrated non-inferiority of the two treatment combinations based on trough FEV_1. Both umeclidinium/vilanterol and tiotropium plus indacaterol were well tolerated.
- The PBAC has previously considered the same comparison, as umeclidinium/vilanterol was the first LAMA/LABA FDC approved for COPD and therefore the most appropriate comparator at the time was tiotropium plus indacaterol (in separate inhalers). The newly available evidence is consistent with the previous evidence considered by the PBAC.
- QUANTIFY (2015: good quality) compared the efficacy and safey of indacaterol/glycopyrronium versus tiotropium plus eformoterol and demonstrated non-inferiority of the two treatment combinations based on SGRQ-C. Observed differences in lung function require further investigation because the trial was not designed to detect a minimally important difference in FEV_1 or FVC. Both indacaterol/glycopyrronium and tiotropium plus eformoterol were well tolerated.

1.4.4 LAMA/LABA versus LAMA monotherapy

As discussed in Section 2, clinical practice guidelines indicate that combining bronchodilators of different pharmacological classes may improve efficacy in COPD patients; however, the availability of combination products raises questions regarding the timing of their initiation during the course of COPD (Ferguson et al, 2015). As such, this PBS review seeks to clarify whether there is additional benefit of moving from monotherapy to dual therapy, and in which patients this may be appropriate.

The five trials listed in Table 3.33 contribute towards the evidence base for this question and are discussed in detail below.

Table 3.33 List of RCTs comparing LAMA/LABA dual therapy with LAMA monotherapy

Trial ID	Citation	Description
BRIGHT	Beeh KM, Korn S, Beier J, Jadayel D, Henley M, D'Andrea P, et al (2014). Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study. Respiratory Medicine 108 (4):584-592.	Key publication
Maleki-Yazdi (2014)	Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M and Church A (2014). Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: Results of a 24-week, randomized, controlled trial. Respiratory Medicine 108 (12):1752-1760.	Key publication
Maltais (2014)	Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH, et al (2014). Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. Therapeutic Advances in Respiratory Disease 8(6):169-181.	Key publication
TONADO 1 and 2	Ferguson GT, Flezar M, Korn S, Korducki L, Gronke L, Abrahams R, et al (2015). Efficacy of Tiotropium + Olodaterol in Patients with Chronic Obstructive Pulmonary Disease by Initial Disease Severity and Treatment Intensity: A Post Hoc Analysis. Advances in Therapy 32 (6):523-536.	Post hoc analysis based on disease severity and treatment intensity[21]
OTEMTO 1 and 2	Singh D, Ferguson GT, Bolitschek J, Gronke L, Hallmann C, Bennett N, et al (2015b). Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. Respiratory Medicine 109 (10):1312-1319.	Key publication
	Singh D, Gaga M, Schmidt O, Bjermer L, Gronke L, Voss F, et al (2016). Effects of tiotropium + olodaterol versus tiotropium or placebo by COPD disease severity and previous treatment history in the OTEMTO studies. Respiratory Research 17 (1) (73).	Poc hoc analysis based on disease severity and treatment history

Abbreviations: LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; RCT, randomised controlled trial.

The study characteristics of the five relevant RCTs, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.34.

[21] The overall results from the TONADO 1 and TONADO 2 trials were presented in the original tiotropium/olodaterol submission (Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al (2015). Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). European Respiratory Journal 45 (4):969-979).

Table 3.34 Details of RCTs comparing LABA/LABA dual therapy with LAMA monotherapy in patients with COPD

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
GLY/IND vs TIO						
BRIGHT 1. Beeh (2014) 2. Fair quality 3. Germany, Spain 4. Novartis	85	Superiority. Double-blind,[22] double-dummy, three-period cross-over.	GLY/IND 50/110 µg qd (n=77) TIO 18 µg qd (n=83) PBO (n=77) Number in each treatment arm is based on the full analysis set.	Inclusion (1) Age ≥40 years, (2) moderate-to-severe COPD (stage II or III – GOLD 2008), (3) post-bronchodilator FEV_1 of ≥40% and <70% of predicted normal, (4) post-bronchodilator FEV_1/FVC ratio of <0.70 at screening. Exclusion (1) Any history of asthma, (2) patients requiring long-term oxygen therapy, (3) COPD exacerbation (requiring antibiotics, systemic steroids or hospitalisation) in the 6 weeks prior to Visit 1, (4) respiratory tract infection within 4 weeks prior to Visit 1, (5) lung lobectomy, lung volume reduction, or lung transplantation. Other (1) Salbutamol/albuterol were provided for rescue use throughout the study, but not permitted within 6 hrs of each visit, (2) concomitant COPD medications and significant non-drug therapies were continued during the study.[23]	3 weeks per treatment arm; 3-week washout between treatments.	Primary Physiological response to exercise during SMETT after 3 weeks. Secondary Isotime IC during SMETT; trough IC; trough FEV_1 at 3 weeks; other spirometry measures; pulmonary function (via body plethysmography); rescue medication; safety (physical examination, vital signs, AEs).
TIO/OLO vs TIO						
TONADO 1 and 2 1. Ferguson (2015) 2. Fair quality 3. Various, including three Australian sites 4. Boehringer Ingelheim	5,163	Two replicate superiority studies. Double-blind.	TIO/OLO 5/5 µg qd (n=1,029) TIO/OLO 2.5/5 µg qd (n=1,030)[24] TIO 5 µg qd (n=1,033) TIO 2.5 µg qd (n=1,032)[25] OLO 5 µg qd (n=1,038)[25] All treatments were delivered via the Respimat inhaler.	Inclusion (1) Age ≥40 years, (2) history of moderate to very severe COPD (GOLD 2-4), (3) post-bronchodilator FEV_1 <80% of predicted normal, (4) post-bronchodilator FEV_1/FVC <70%. Exclusion (1) History of asthma, (2) significant disease other than asthma, (3) myocardial infarction within 1 year of screening, (3) known active tuberculosis, clinically evidence bronchiectasis, cystic fibrosis or life-threatening pulmonary obstruction, (4) previous thoracotomy with pulmonary resection, (5) regular use of daytime oxygen. Other (1) Patients receiving ICS at baseline could continue with their medication, (2) all patients were provided with salbutamol/albuterol as rescue medication as required, (3) patients receiving LAMA or LABA prior to the study were required to discontinue these during screening.	52 weeks	Primary FEV_1 AUC from 0 to 3 hrs; trough FEV_1 response (i.e. change from baseline); SGRQ – all measured at 24 weeks. Secondary FEV_1 AUC from 0 to 3 hrs and trough FEV_1 response (i.e. change from baseline) on Day 1 and Weeks 2, 6, 12, 18, 24, 32, 40 and 52; SGRQ on Day 1 and Weeks 12, 24 and 52.

[22] Investigator-blinded only for tiotropium.
[23] The most common medications taken were inhaled corticosteroids, especially budesonide (26.0% of patients in the glycopyrronium/indacaterol group), tiotropium (24.1%) and placebo (26.0%).
[24] Results for this arm was not shown as the medicine and/or dose is not PBS listed.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
OTEMTO 1 and 2 1. Singh (2015b), Singh (2016) 2. Fair quality 3. US, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, South Africa, Spain, UK 4. Boehringer Ingelheim	1,623	Two replicate superiority studies. Double-blind.	TIO/OLO 5/5 µg qd (n=204) TIO/OLO 2.5/5 µg qd (n=202)[25] TIO 5 µg qd (n=204) PBO (n=204) All treatments were delivered via the Respimat inhaler.	Inclusion (1) Age ≥40 years, (2) moderate-to-severe COPD (stage II or III – GOLD), (3) post-bronchodilator FEV_1 of ≥30% and <80% of predicted normal, (4) FEV_1/FVC ratio of <0.70 predicted. Exclusion (1) Any history of asthma, (2) another significant disease, (3) COPD exacerbation or symptoms of lower respiratory tract infection within the previous 3 months, (4) unstable or life-threatening cardiac arrhythmia. Other (1) Allowed to continue ICS therapy (if they were on a stable dose for 6 weeks prior to screening), (2) LABA or LAMAs other than study medication were prohibited during the screening or treatment periods, (3) open-label salbutamol provided as rescue medication throughout the study.	12 weeks; final follow up was 3 weeks after the final dose of study medication.	Primary SGRQ total score; FEV_1 AUC from 0 to 3 hrs; trough FEV_1.[26] Secondary TDI focal score; trough FVC and FVC AUC (0 to 3 hrs); safety (AEs, SAEs, vital signs).
UME/VIL vs TIO						
Maleki-Yazdi (2014) 1. N/A 2. Good quality 3. US, Bulgaria, Canada, Germany, Hungary, Romania, Russia, Spain 4. GlaxoSmithKline	905	Superiority. Double-blind, double-dummy.	UME/VIL 62.5/25 µg qd (n=454) TIO 18 µg qd (n=451)	Inclusion (1) Age ≥40 years, (2) moderate to very severe COPD, (3) pre- and post-albuterol FEV_1/FVC ratio of <70%, (4) pre- and post-albuterol/salbutamol FEV_1 of ≤70% of predicted normal at Visit 1, (5) a score of ≥2 on the mMRC scale at Visit 1. Exclusion (1) Current diagnosis of asthma or other respiratory disorders, (2) historical or current evidence of clinically significant, uncontrolled cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine or haematological abnormalities, (3) hospitalisation for COPD or pneumonia within 12 weeks prior to Visit 1, (4) long-term oxygen therapy. Other (1) Albuterol/salbutamol was provided as relief medication, (2) patients treated with ICS at screening were required to continue to the end of the treatment period unless there was a significant medical reason for discontinuation.	24 weeks	Primary Trough FEV_1 at Day 169.[27] Secondary Weighted mean FEV_1 from 0 to 6 hrs at Day 1, 84 and 168 (24 weeks); trough FEV_1 at Days 2, 28, 56, 84, 112, 140 and 168; time of onset of action; trough FVC; percentage of responders achieving an increase in trough FEV_1 of ≥0.100L above baseline at Day 169, peak FEV_1 at Day 168; SGRQ; time to first COPD exacerbation; rescue medication; incidence of AEs.

[25] Results for the TIO/OLO 2.5/5 µg arm are not shown as the dose is not PBS listed.
[26] Defined as mean of the FEV_1 values at 23 hr and 23 hr 50 min post-dose.
[27] Defined as mean of FEV_1 values obtained 23 and 24 hours after the previous day's dosing.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
UME/VIL vs UME						
Maltais (2014) 1. N/A 2. Fair quality 3. US, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Germany, Russia, South Africa, Ukraine, UK. 4. GlaxoSmithKline	349 (Study 417); 308 (Study 418)	Two double-blind, incomplete block cross-over studies.	Study 417 UME/VIL 125/25 µg[28] (n=144) UME/VIL 62.5/25 µg (n=152) VIL 25 µg[29] (n=76) UME 62.5 µg (n=49) UME 125 µg[29] (n=50) PBO (n=170) Study 418 UME/VIL 125/25 µg[29] (n=128) UME/VIL 62.5/25 µg (n=130) VIL 25 µg[29] (n=64) UME 62.5 µg (n=40) UME 125 µg[29] (n=41) PBO (n=151)	Inclusion: (1) Age ≥40 years, (2) clinical diagnosis of moderate-to-severe COPD, (3) post-bronchodilator FEV_1/FVC <70% and FEV_1 ≥35% and ≤70% predicted, (4) a score of ≥2 on the mMRC Dyspnea Scale at Visit 1. Exclusion (1) Comorbid respiratory conditions or a current diagnosis of asthma, (2) hospitalisation for an acute COPD exacerbation or pneumonia within 12 weeks of study start, (3) oxygen therapy for >12 hrs per day. Other (1) Patients were required to discontinue the use of LAMA or LABA therapies alone or in combination, (2) all medication (including short-acting bronchodilators) were required to be withheld for a 4 hrs period prior to spirometry testing, (3) patients using ICS were required to have maintained regular use of a stable dose of ICS during the run-in period at a dose ≤1000 mcg/day fluticasone propionate or equivalent, (4) patients were provided with salbutamol for use on an as-needed basis through the run-in, washout, and treatment periods.	12 weeks per treatment group. Patients received two of six treatments.	Primary Trough FEV_1 and exercise endurance time at Week 12. Secondary Measures of lung volume at Week 12; use of rescue medication; ease of inhaler use; safety (AEs, exacerbations, vital signs, clinical chemistry tests, haematology tests, 12-lead ECG).

Note: N refers to number randomised unless otherwise specified.

Abbreviations: AE, adverse event; AUC, area under the curve; BDI, Basline Dyspnea Index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; OLO, olodaterol; PBO, placebo; qd, once daily; SGRQ, St George's Respiratory Questionnaire; SMETT, sub-maximal constant-load cycle ergometry exercise tolerance test; TDI, Transition Dyspnea Index; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

[28] Results not presented for this treatment group, as the dose is not PBS listed.

Glycopyrronium/indacaterol versus tiotropium

BRIGHT study

This study compared treatment with glycopyrronium/indacaterol 50/110 µg with tiotropium 18 µg, and placebo in a three-way cross-over study. The primary outcome was exercise endurance time at Day 21, but the study also measured lung function outcomes using spirometry at baseline and Day 21 of each treatment period.

As shown in Table 3.35, glycopyrronium/indacaterol significantly improved trough FEV_1 compared with tiotropium on Day 21; however, the study was only powered to detect a difference between glycopyrronium/indacaterol and placebo. Therefore, while the results indicate that dual LAMA/LABA therapy was superior to tiotropium monotherapy, the statistical significance of the results must be interpreted with caution.

It should be noted that 31% of patients were on ICS therapy at baseline; therefore, a subset of patients were on triple therapy, while others were on dual LAMA plus ICS therapy during the treatment period. Insufficient data were available to undertake a subgroup analysis of those patients who were on ICS therapy versus those who were not.

Table 3.35 Least squares mean difference in trough FEV_1 – GLY/IND vs TIO

	Treatment difference GLY/IND vs TIO	p-value
LS mean difference in trough FEV_1 at 3 weeks, L	0.10 (0.05, 0.15)	<0.001

Source: Beeh (2014), Table 2.
Note: Treatment effects for each of the three cross-over periods were not reported separately.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; GLY, glycopyrronium; IND, indacaterol; LS, least squares; TIO, tiotropium.

No clinically relevant differences were observed between glycopyrronium/indacaterol and tiotropium (or placebo) with respect to safety and tolerability (see Table 3.36).

Table 3.36 Safety outcomes relating to GLY/IND vs TIO

Safety outcome	GLY/IND 50/110 (N=77) n (%)	TIO 18 (N=83) n (%)	PBO (N=77) n (%)
AE incidence	29 (37.7)	23 (27.7)	28 (36.4)
Severe AE	1 (1.3)	1 (1.2)	3 (3.9)
COPD worsening[a]	7 (9.1)	5 (6.0)	3 (3.9)

Source: Beeh (2014), Table 5.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; IND, indacaterol; PBO, placebo; TIO, tiotropium.
a Data on incidence of COPD exacerbations were combined with AE data and reported under the preferred term of "COPD worsening" together with all other events with the same preferred term.

Tiotropium/olodaterol versus tiotropium

TONADO study

TONADO 1 and 2 were large, 52-week RCTs in patients with moderate to very severe COPD. The studies demonstrated that tiotropium/olodaterol significantly improved lung function and symptoms compared with the individual components. The PBAC has previously considered overall efficacy and safety data from these studies (Buhl et al, 2015); however, a post hoc analysis, that examined the effects of prior LAMA or LABA treatment and initial

disease severity on lung function, has not previously been considered by the PBAC and may provide useful information for this review.

Ferguson et al (2015) conducted several post hoc analyses of pooled data from TONADO 1 and 2, including analyses according to sex and age, as well as the following subgroups:

- prior maintenance treatment with LAMA or LABA
- GOLD 2 (predicted FEV_1 50% to <80%), 3 (30% to <50%) and 4 (<30%)
- prior use of ICS.

Table 3.37 shows treatment differences in adjusted mean trough FEV_1 after 24 weeks of treatment, according to treatment history and GOLD severity classification. Tiotropium/olodaterol once-daily improved lung function over tiotropium monotherapy in patients with GOLD 2 and 3-4 disease, and there were no notable differences in lung function responses according to whether patients were naïve or experienced to LAMA or LABA therapy at baseline.

Table 3.37 Adjusted mean trough FEV_1 after 24 weeks of treatment according to treatment history and GOLD classification – TIO/OLO vs TIO

	Adjusted mean (SE) FEV_1, mL				Treatment difference, mL, (SE)	95% CI	p-value
Treatment-naïve	**n**	**TIO/OLO**	**n**	**TIO**			
GOLD 2	226	146 (14)	237	68 (14)	79 (20)	40, 118	<0.0001
GOLD 3-4	193	148 (14)	206	79 (13)	69 (19)	32, 106	0.0002
Treatment-experienced	**n**	**TIO/OLO**	**n**	**TIO**			
GOLD 2	270	156 (13)	275	95 (13)	61 (18)	26, 97	0.0007
GOLD 3-4	328	118 (9)	299	76 (10)	41 (14)	15, 68	0.0023

Source: Ferguson (2015), Tables 3 and 4; Table S1 and S2 in online supplementary materials.
Note: Adjusted mean (SE) obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; OLO, olodaterol; SE, standard error; TIO, tiotropium.

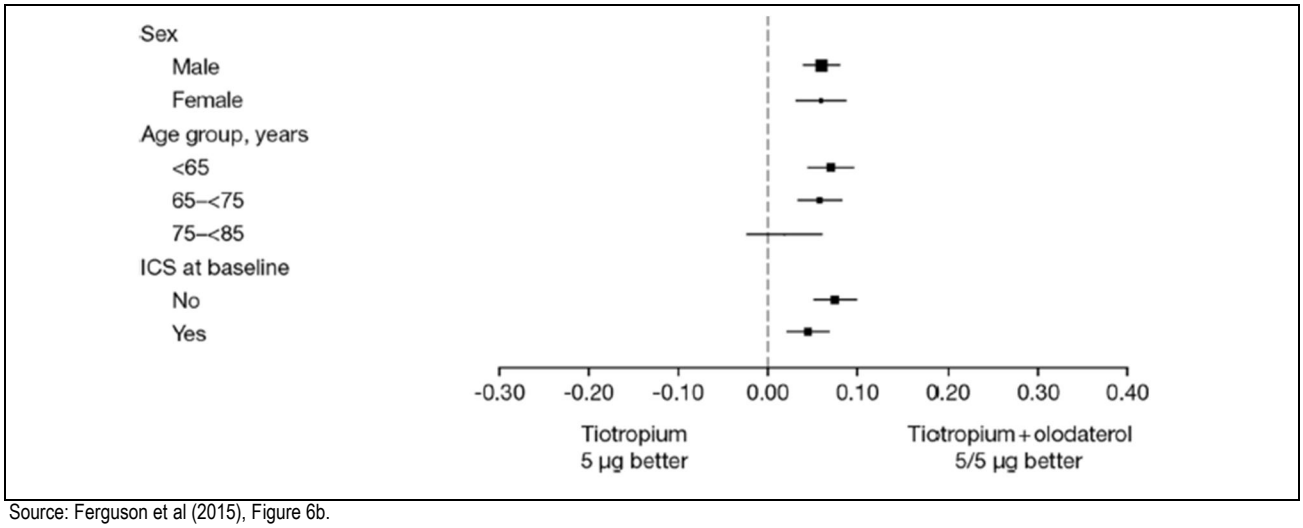
The authors emphasised that despite the absence of statistical comparisons between subgroups, it was apparent that trough FEV_1 responses were, in general, greater in patients with less severe disease (GOLD 2). They concluded that these results add support for the use of combination bronchodilation earlier in the course of COPD.

Importantly, the results are potentially confounded by the fact that patients were permitted to continue ICS use throughout the study; however, the proportion of patients in each GOLD category who were treated with ICS at baseline (and throughout the study) is unknown. Therefore, in treatment-experienced patients, the comparison may often represent a comparison of dual therapy (ICS + LAMA) versus triple therapy, rather than single versus dual (LAMA/LABA) therapy. This would more likely be the case in GOLD 3-4 than GOLD 2 patients. The original TONADO publication indicated that 466 (45.1%) of patients randomised to tiotropium and 506 (49.2%) of patients randomised to tiotropium/olodaterol were on ICS

medication at baseline.[29]

The forest plot depicted in Figure 3.2 shows that, with respect to trough FEV_1, dual therapy with tiotropium/olodaterol was more effective than tiotropium alone across all of the subgroups analysed, with the exception of one age group (patients aged 75-85 years). The results, while not shown by GOLD subgroups or long-acting bronchodilator treatment history, indicate that the magnitude of the difference between dual and monotherapy may be greater than triple to dual therapy.

Figure 3.2 Forest plot for trough FEV1 response at 24 weeks – TIO/OLO vs TIO (Respimat)



Source: Ferguson et al (2015), Figure 6b.
Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; OLO, olodaterol; TIO, triotropium.

Overall, this post hoc analysis demonstrated that tiotropium/olodaterol significantly improved trough FEV_1 in all GOLD severity groups compared to tiotropium alone, irrespective of whether patients had received prior long-acting bronchodilators at baseline. Improvements from baseline in lung function were generally greater in patients with less severe disease.

OTEMTO study

The OTEMTO study comprised two replicate RCTs (OTEMTO 1 and 2); however, unlike TONADO, the OTEMTO study included a placebo arm, which was possible due to the shorter trial duration (12 weeks) and the exclusion of GOLD 4 patients. The placebo arm enabled the study to evaluate the effect of tiotropium/olodaterol on PROs, where the MCIDs are generally set in the context of an active drug versus placebo comparison.

The study was designed and powered to test tiotropium/olodaterol versus placebo for all primary end points, which included SGRQ total score, FEV_1 AUC from 0 to 3 hours (FEV_1 AUC_{0-3}), and trough FEV_1 at Week 12. Comparisons of tiotropium/olodaterol and tiotropium (Respimat) were also presented.

Across all treatment arms and both OTEMTO studies, between 60% and 69% of participants were GOLD Grade II; between 34% and 42% of patients were on ICS medication at baseline; and between 29% and 40% of patients were on LAMA therapy at baseline.

[29] Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al (2015). Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). European Respiratory Journal 45 (4):969-979.

As shown in Table 3.38, combination therapy with tiotropium/olodaterol resulted in a better improvement in trough FEV_1 at Week 12 than tiotropium in OTEMTO 2, but not OTEMTO 1.

Table 3.38 Trough FEV_1 in OTEMTO 1 and 2 after 12 weeks – ITT on full analysis set[a]

Difference in trough FEV_1, L	TIO/OLO vs TIO	TIO/OLO vs PBO	TIO vs PBO
	Mean (SE) [95% CI]	Mean (SE) [95% CI]	Mean (SE) [95% CI]
OTEMTO 1	0.028 (0.019) [–0.009, 0.066]	0.162 (0.019) [0.124, 0.200][b]	0.134 (0.019) [0.096, 0.172][b]
OTEMTO 2	0.039 (0.019) [0.002, 0.076][c]	0.166 (0.019) [0.129, 0.203][b]	0.127 (0.019) [0.090, 0.165][b]

Source: Singh (2015b), pg 1314 and Supplementary Table S2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; OLO, olodaterol; SE, standard error; TIO, triotropium.
Note: OTEMTO 1: placebo n=198; TIO n=200; TIO/OLO n=200. OTEMTO 2: placebo n=193; TIO n=197; TIO/OLO n=199.
a All patients who received at least one dose of study medication and had baseline and at least one post-baseline measurement for any of the primary endpoints.
b p<0.0001.
c p=0.0395.

The trough FEV_1 results from the OTEMTO study do not provide convincing evidence to confirm the superiority of tiotropium/olodaterol over tiotropium. It should be acknowledged that not all outcomes assessed in the study were reported in this review. Based on the overall findings of the study, the authors concluded that treatment with tiotropium/olodaterol led to improvements in lung function over placebo and tiotropium that "were translated into clinically significant improvements in symptoms and health-related quality of life".

As shown in Table 3.39, overall incidence of adverse events was similar for tiotropium/olodateral (43-44%) and tiotropium Respimat (44-45%).

Table 3.39 Safety outcomes relating to TIO/OLO vs TIO or PBO

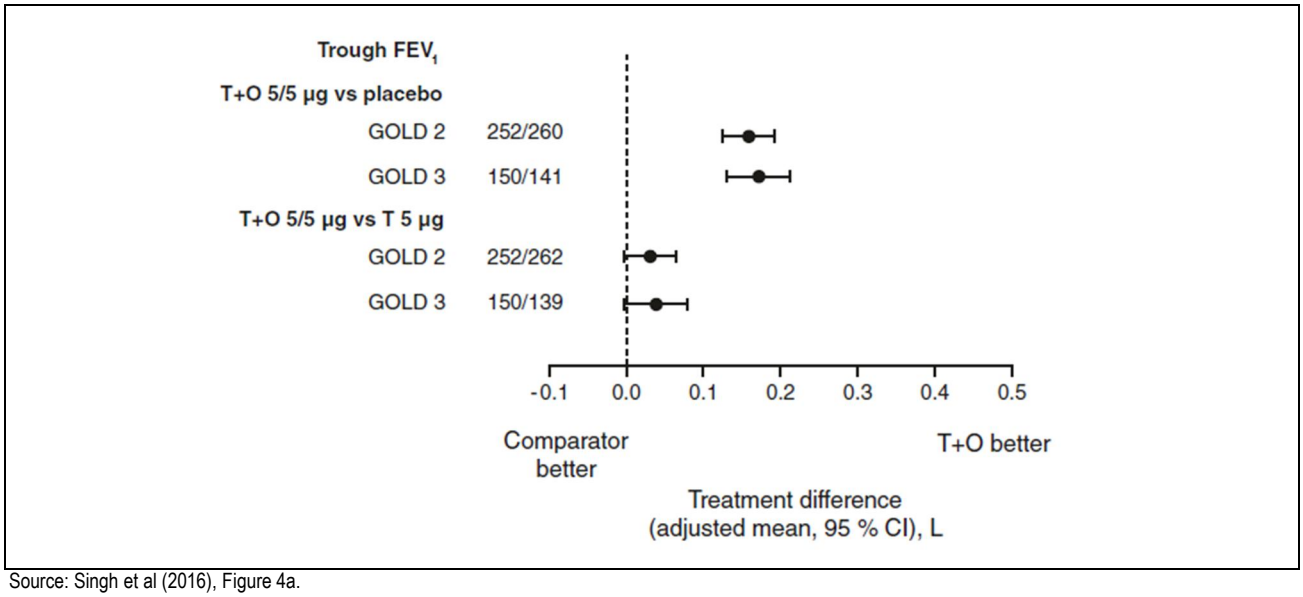
Safety outcome	TIO/OLO 5/5 n/N (%)	TIO 5 n/N (%)	PBO n/N (%)
All AEs	-	-	-
OTEMTO 1	91/203 (44.8)	90/203 (44.3)	105/204 (51.5)
OTEMTO 2	87/202 (43.1)	93/203 (45.8)	93/202 (46.0)
Treatment-related[a] AEs	-	-	-
OTEMTO 1	8/203 (3.9)	8/203 (3.9)	12/203 (5.9)
OTEMTO 2	10/202 (5.0)	5/202 (2.5)	10/202 (5.0)
AEs leading to discontinuation	-	-	-
OTEMTO 1	3/203 (1.5)	3/203 (1.5)	11/203 (5.4)
OTEMTO 2	1/202 (0.5)	7/202 (3.4)	10/202 (5.0)
SAEs	-	-	-
OTEMTO 1	10/203 (4.9)	6/203 (3.0)	11/203 (5.4)
OTEMTO 2	6/202 (3.0)	12/202 (5.9)	4/202 (2.0)
Vascular disorders	-	-	-
OTEMTO 1	4 (2.0)	4 (2.0)	11 (5.4)
OTEMTO 2	6 (3.0)	6 (3.0)	5 (2.5)

Source: Singh (2015b), Supplementary Table S6.
Abbreviations: AE, adverse event; OLO, olodaterol; PBO, placebo; SAE, serious adverse event; TIO, triotropium.
a Investigator-defined

Singh et al (2016) undertook a post hoc analysis of the OTEMTO studies to evaluate the efficacy of tiotropium/olodaterol compared to placebo and tiotropium in various subgroups of patients. Four main subgroup analyses were performed that compared GOLD 2 and GOLD 3 patients (see Figure 3.3); GOLD A-D patients[30] (see Figure 3.4); treatment history (see Figure 3.5) and baseline use of ICS (see Figure 3.6).

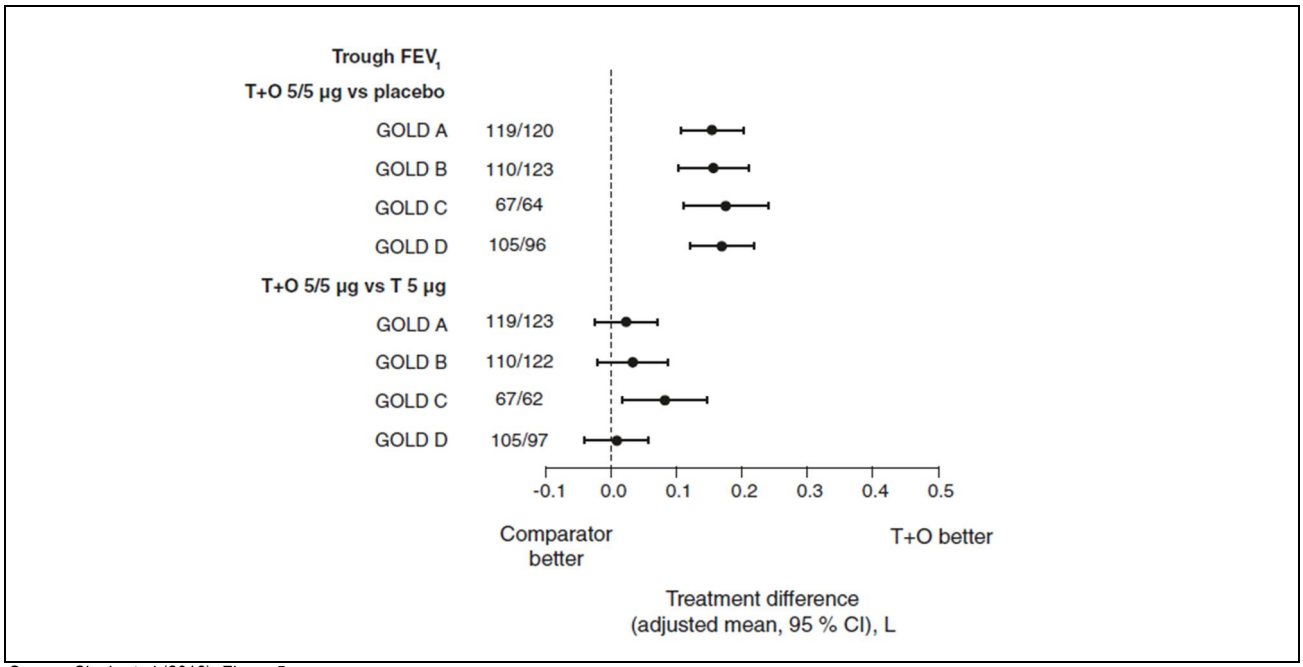
[30] Based on the mMRC dyspnoea scale.

Figure 3.3 Forest plot for trough FEV_1 response in patients with GOLD 2 or 3 disease – TIO/OLO vs PBO and TIO/OLO vs TIO



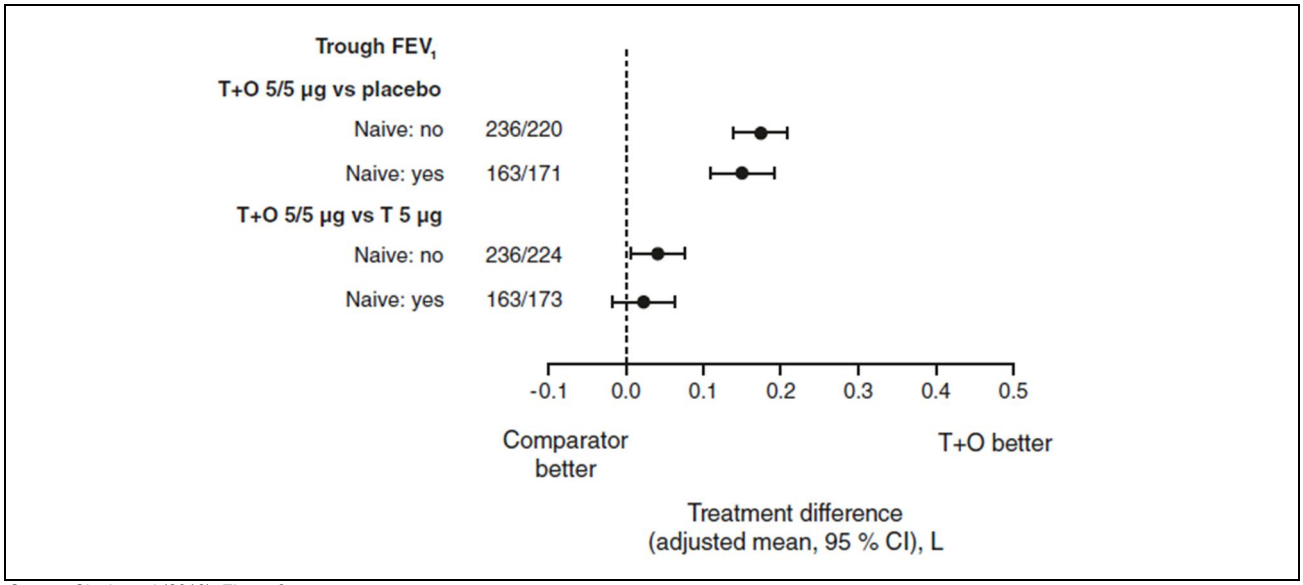
Source: Singh et al (2016), Figure 4a.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; O, olodaterol; OLO, olodaterol; PBO, placebo; T, tiotropium; TIO, triotropium.

Figure 3.4 Forest plot for trough FEV_1 response in patients with GOLD A-D disease – TIO/OLO vs PBO and TIO/OLO vs TIO



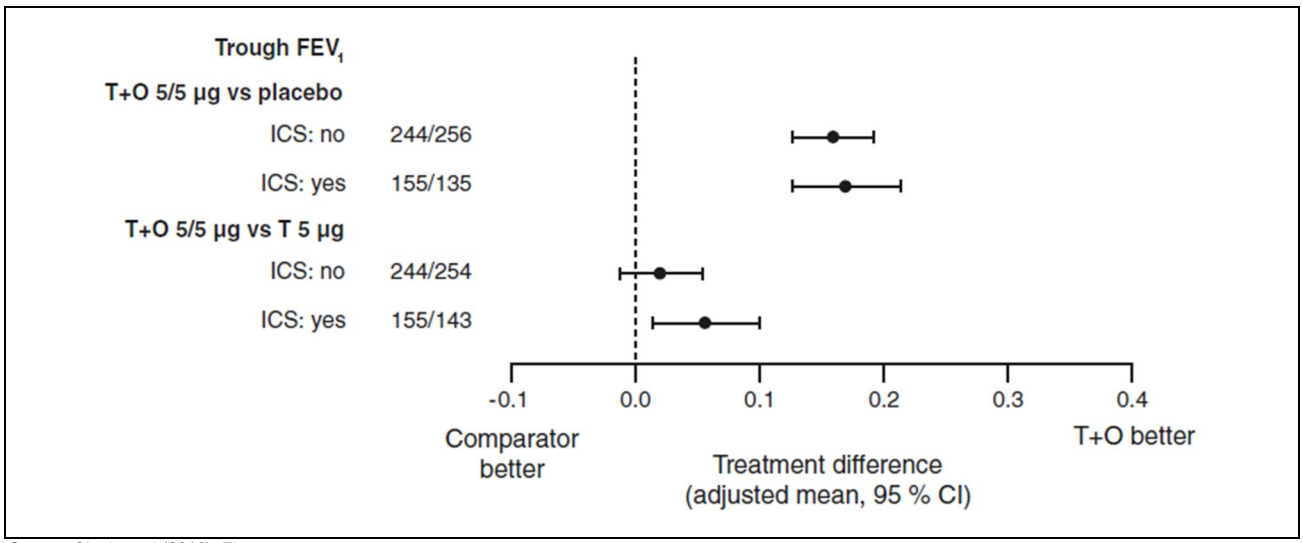
Source: Singh et al (2016), Figure 5a.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; O, olodaterol; OLO, olodaterol; PBO, placebo; T, tiotropium; TIO, triotropium.

Figure 3.5 Forest plot for trough FEV_1 response in patients who were treatment naïve or experienced at baseline – TIO/OLO vs PBO and TIO/OLO vs TIO



Source: Singh et al (2016), Figure 6a.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; O, olodaterol; OLO, olodaterol; PBO, placebo; T, tiotropium; TIO, triotropium.

Figure 3.6 Forest plot for trough FEV_1 response in patients who were or were not taking ICS at baseline – TIO/OLO vs PBO and TIO/OLO vs TIO



Source: Singh et al (2016), Figure 7a.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; O, olodaterol; OLO, olodaterol; PBO, placebo; T, tiotropium; TIO, triotropium.

Across most subgroup analyses, treatment with tiotropium/olodaterol resulted in numerically better results than tiotropium monotherapy for trough FEV_1, although in most cases the 95% CI crossed zero, indicating that the differences were not statistically significant. The exceptions were in patients classified as GOLD C; patients who had experience with LAMA, LABA and/or ICS at baseline; and patients who were receiving ICS at baseline. However, the study was not sufficiently powered for statistical comparison between subgroups and the apparent superiority of tiotropium/olodaterol over tiotropium in some subgroups may be an erroneous finding.

The authors concluded that the added benefits of tiotropium/olodaterol compared to tiotropium monotherapy in treatment-naive patients suggest that tiotropium/olodaterol should be considered as an option for patients at the point where there is a need to initiate maintenance therapy (as well as in patients with more severe disease). However, the authors' conclusions took into account a wider range of outcomes (including FEV_1 AUC_{0-3}, SGRQ, and TDI focal score) than those that are considered in this review of the evidence. Importantly, for trough FEV_1, the 95% CI crossed zero for the comparison of tiotropium/olodaterol and tiotropium in treatment-naïve individuals.

Umeclidinium/vilanterol versus tiotropium

Maleki-Yazdi (2014)

This study was briefly mentioned in a minor resubmission for umeclidinium/vilanterol (Anoro) in which, amongst other things, the manufacturer was clarifying the incremental benefit of the LAMA/LABA combination therapy versus monotherapy. The minor resubmission referred to the study as ZEP117115, but provided minimal information about the study and results. Therefore, it is included in this review of new evidence.

The results for the primary outcome are shown in Table 3.40. The authors indicated that the observed improvement in trough FEV_1 of 0.112 L for umeclidinium/vilanterol compared to tiotropium was both statistically significant and clinically meaningful. Furthermore, the authors noted that the statistically significant improvement was observed early and maintained at other clinic visits throughout the treatment period.

Table 3.40 Treatment differences in least squares mean change from baseline – Trough FEV_1

LS mean change from baseline	UME/VIL 62.5/25		TIO 18		Treatment difference, L, (95% CI)	p-value
	n	Mean (SE)	n	Mean (SE)		
Trough FEV_1 at Day 84, L[a]	453	0.189 (0.0111)	449	0.081 (0.0113)	0.109 (0.078, 0.140)	<0.001
Trough FEV_1 at Day 169, L[b]	454	0.205 (0.0114)	451	0.093 (0.0115)	0.112 (0.081, 0.144)	<0.001

Source: Maleki-Yazdi (2014), Table 2 and Supplementary file 7.
Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 and 5 min pre-dose on Day 1), smoking status, center group, Day, Day by baseline, and Day by treatment interactions.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ITT, intention-to-treat; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.
a Based on patients with analysable data for one or more visits.
b Primary outcome; ITT population.

The study also demonstrated that after 24 weeks of treatment, a significantly higher proportion of patients treated with umeclidinium/vilanterol achieved an increase in trough FEV_1 of ≥0.100 L above baseline than patients treated with tiotropium (see Table 3.41).

Table 3.41 Patients achieving an increase in trough FEV_1 of ≥0.100L above baseline at Day 169 – ITT population

Trough FEV1 ≥0.100L above baseline	UME/VIL (N=454)	TIO (N=451)	OR (95% CI)	p-value
Proportion of patients at Day 169, n (%)	275 (61)	192 (43)	2.1 (1.6, 2.7)	<0.001

Source: Maleki-Yazdi (2014), Table 2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ITT, intention-to-treat; OR, odds ratio; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

Table 3.42 shows the time to first on-treatment exacerbation also favoured dual therapy; however, the difference between dual- and monotherapy was less pronounced for this outcome.

Table 3.42 On-treatment exacerbations – ITT population

	UME/VIL (N=454)	TIO (N=451)	Time to first on-treatment exacerbation, days
Subjects with on-treatment exacerbation, n (%)	16 (4)	29 (6)	-
Number of these subjects receiving ICS, n (%)	12 (75)	20 (69)	-
Time to first on-treatment exacerbation, HR (95% CI), p-value	-	-	0.5 (0.3, 1.0) 0.044

Source: Maleki-Yazdi (2014), Supplementary file 11.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICS, inhaled corticosteroid; ITT, intention-to-treat; OR, odds ratio; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

The analysis of safety outcomes indicated that there were no major safety concerns, with an equal and relatively low proportion of SAEs and on-treatment fatalities in both treatment groups (see Table 3.43).

Table 3.43 Results for safety outcomes relating to UME/VIL vs TIO – ITT population

Safety outcome	UME/VIL (N=454)	TIO (N=451)
Any AE, n (%)	202 (44)	190 (42)
Any SAE, n (%)	16 (4)	17 (4)
Drug-related AE, n (%)	19 (4)	17 (4)
AE-s leading to permanent discontinuation of medication or withdrawal, n (%)	18 (4)	14 (3)
Fatal AEs, n (%) On-treatment Post-treatment	- 2 (<1) 0	- 2 (<1) 3 (<1)
Cardiovascular AEs	9 (2)	7 (2)
Pneumonia[a]	1 (<1)	3 (<1)

Source: Maleki-Yazdi (2014), Table 4.
Abbreviations: AE, adverse event; ITT, intention-to-treat; SAE, serious adverse event; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.
a The subject in the UMEC/VI 62.5/25 group with an on-treatment pneumonia event had entered screening on an ICS. Of the three TIO subjects that had an on-treatment pneumonia event, one subject was receiving an ICS.

It should be noted that at screening a comparable number of patients in each treatment arm were using ICS therapies: 247 (54%) and 237 (53%) patients in the umeclidinium/vilanterol and tiotropium arms, respectively. An exploratory analysis of the impact of ICS use on outcomes in this study demonstrated that it did not impact the treatment effect on trough FEV_1 after 24 weeks; however, the authors acknowledged that the study was insufficiently powered to detect such interactions.

Umeclidinium/vilanterol versus umeclidinium

Maltais (2014)

The publication by Maltais et al (2014) summarised results from two similar RCTs (referred to as Study 417 and 418) that were conducted by the same sponsor. While the major focus of the study was on exercise endurance, trough FEV_1 was included as a co-primary outcome, enabling the assessment of umeclidinium/vilanterol with its mono-components. As shown in Table 3.34, the studies included six treatment arms, including a placebo arm; however, only

two of the active arms were PBS-listed doses (umeclidinium/vilanterol 62.5/25 µg and umeclidinium 62.5 µg) and are therefore the sole focus of this summary.

The analysis of the primary outcome is shown in Table 3.44. In Study 418, both umeclidinium/vilanterol and umeclidinium monotherapy were associated with significant improvements in trough FEV_1 compared with placebo. In Study 417, while p-values were reported, the authors stated that statistical significance could not be inferred because the prior comparison in the testing hierarchy (exercise endurance time) failed to demonstrate significance.

Importantly, Maltais et al (2014) reported that umeclidinium/vilanterol demonstrated greater least squares mean changes from baseline in trough FEV_1 compared with umeclidinium (see Table 3.44); however, no statistical comparisons of the groups were undertaken and the authors acknowledged that these studies were not powered to detect treatment differences between dual and monotherapy. It should be noted that 39% of patients in Study 418 were on ICS at baseline, as were 28% of patients in Study 417.

Table 3.44 Trough FEV_1 change from baseline and difference from placebo – UME/VIL, UME monotherapy and PBO

Trough FEV_1, L	UME/VIL 62.5/25		UME 62.5		PBO	
Study 417	**n**		**n**		**n**	
LS mean (SE) change from baseline, L	130	0.178 (0.0156)	43	0.054 (0.0264)	148	–0.032 (0.0149)
Difference from placebo (95% CI), L	130	0.211 (0.172, 0.249) p<0.001	43	0.087 (0.030, 0.143) p<0.01	-	-
Study 418						
LS mean (SE) change from baseline, L	117	0.200 (0.0156)	38	0.101 (0.0267)	119	–0.043 (0.0156)
Difference from placebo (95% CI), L	117	0.243 (0.202, 0.284) p<0.001	38	0.144 (0.086, 0.203) p<0.001	-	-
Post hoc combined						
LS mean (SE) change from baseline, L	247	0.189 (0.0110)	NR	NR	267	–0.035 (0.0108)
Difference from placebo (95% CI), L	247	0.224 (0.196, 0.252)	NR	NR	-	-

Source: Maltais et al (2014), Table 2 and Supplementary Table 2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; LS, least squares; NR, not reported; PBO, placebo; SAE, serious adverse event; SE, standard error; UME, umeclidinium; VIL, vilanterol.
Note: n is the number of patients with analysable data at Week 12.
Analysis performed using a repeated measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit by period walking speed, visit by mean walking speed, and visit by treatment interactions. For FEV_1, walking speed is replaced by baseline.

Table 3.45 shows the safety outcomes for Studies 417 and 418. In both studies, umeclidinium monotherapy was associated with a lower incidence of on-treatment adverse events. Nevertheless, no significant safety concerns were identified.

Table 3.45 Results for safety outcomes relating to UME/VIL, UME monotherapy[a] and PBO

Safety outcome	UME/VIL 62.5/25	UME 62.5	PBO
Study 417	**n=152**	**n=49**	**n=170**
Any AE, n (%)	-	-	-
On-treatment	35 (23)	6 (12)	46 (27)
Post-treatment	6 (4)	2 (4)	10 (6)
Drug-related AE, n (%)	4 (3)	0	7 (4)

Safety outcome	UME/VIL 62.5/25	UME 62.5	PBO
AE-s leading to permanent discontinuation of study treatment, n (%)	6 (4)	2 (4)	9 (5)
Any SAE, n (%)	-	-	-
On-treatment	4 (3)	0	6 (4)
Post-treatment	1 (<1)	0	1 (<1)
Drug-related SAE, n (%)	0	0	0
Fatal AEs, n (%)	-	-	-
On-treatment	0	0	0
Post-treatment	0	0	0
Study 418	**n=130**	**n=40**	**n=151**
Any AE, n (%)	-	-	-
On-treatment	57 (44)	12 (30)	59 (39)
Post-treatment	10 (8)	2 (5)	7 (5)
Drug-related AE, n (%)	8 (6)	1 (3)	7 (5)
AE-s leading to permanent discontinuation of study treatment, n (%)	5 (4)	1 (3)	8 (5)
Any SAE, n (%)	-	-	-
On-treatment	3 (2)	1 (3)	4 (3)
Post-treatment	0	0	1 (<1)
Drug-related SAE, n (%)	0	0	0
Fatal AEs, n (%)	-	-	-
On-treatment	1 (<1)	0	0
Post-treatment	0	0	0

Source: Maltais et al (2014).
Abbreviations: AE, adverse event; PBO, placebo; SAE, serious adverse event; UME, umeclidinium; VIL, vilanterol.
a Patients were allowed to remain on ICS so there is a chance some of these people were effectively on dual therapy and the others were on triple.

Summary of findings

- Overall, there is evidence of modest benefit of moving from LAMA monotherapy to LAMA/LABA dual therapy. All dual therapies were well tolerated.
- The BRIGHT study (2014; fair quality) was a cross-over study that assessed the efficacy and safety of glycopyrronium/indacaterol versus tiotropium monotherapy. After three weeks of treatment, the least squares mean difference in trough FEV_1 favoured dual therapy over monotherapy with a treatment difference of 100 mL. However, the results should be interpreted with caution, given that the study was only powered to detect a difference between glycopyrronium/indacaterol and placebo.
- Results from the TONADO study (fair quality) were considered at the July 2015 PBAC meeting; however, subsequent post hoc analyses of the TONADO study based on treatment history and severity of COPD may also be of interest to the PBAC. The 52-week study demonstrated that tiotropium/olodaterol treatment resulted in a statistically significantly improvement in trough FEV_1 in all GOLD severity groups compared to tiotropium alone, irrespective of whether patients had received prior long-acting bronchodilators at baseline. The magnitude of the treatment difference between monotherapy and dual therapy ranged from 41 mL in GOLD 3-4, treatment-experienced patients, to 79 mL in GOLD 2, treatment-naïve patients. The results indicate that the magnitude of the treatment difference may be more pronounced in

patients with less severe disease (GOLD 2), and provide support for the adoption of dual therapy early in COPD.

- The OTEMTO studies (fair quality) were two shorter-term RCTs that also assessed the comparative effectiveness of tiotropium/olodaterol versus tiotropium. At 12 weeks, the results favoured tiotropium/olodaterol over tiotropium, with treatment differences of 28 mL and 39 mL in OTEMTO 1 and 2, respectively. The difference was statistically significant in OTEMTO 2, but overall the OTEMTO studies did not provide convincing evidence to confirm the superiority of dual therapy over monotherapy.
- An RCT by Maleki-Yazdi (2014; good quality) examined treatment differences between umeclidinium/vilanterol and tiotropium. The study was briefly dicussed in the minor resubmission for umeclindium/vilanterol (Anoro), but the results were not taken into account in the meta-analysis that was used to determine the relative pricing of dual therapy and monotherapy (discussed below). Umeclidinium/vilanterol demonstrated statistically significant and clinically meaningful improvements in trough FEV_1 over tiotropium monotherapy, with a treatment difference of 112 mL at 24 weeks, and a difference in on-treatment exacerbations that favoured umeclidinium/vilanterol.
- A publication by Maltais et al (2014; fair quality) reported results from two incomplete block, cross-over studies that compared the efficacy and safety of umeclidinium/vilanterol with placebo, vilanterol, and umeclidinium. In terms of the change from baseline in trough $FEV_{1,}$ the results numerically favoured the umeclidinium/vilanterol group over umeclidinium monotherapy, with treatment differences of 243 mL and 144 mL versus placebo, respectively. However, the studies were not powered for that treatment comparison and should therefore be interpreted with caution.

The recent study findings outlined above should be interpreted in the context of previous PBAC decision making with respect to monotherapy versus dual therapy. The major submission for umeclidinium/vilanterol (Anoro), considered at the March 2014 PBAC meeting, included a meta-analysis of two pivotal studies (DB2113360 and DB2113374) that compared umeclindium/vilanterol and tiotropium. [redacted]

To determine the relative pricing of the two products, [redacted]

1.4.5 LAMA/LABA versus LABA monotherapy

No studies were identified that compared a LAMA/LABA FDC with a PBS-listed LABA monotherapy (i.e. indacaterol).

1.4.6 LAMA/LABA versus ICS/LABA

As outlined in Section 2, treatment with ICS/LABA combinations is recommended specifically in COPD patients who are at an increased risk of exacerbations, as these patients are generally thought to receive the greatest benefit from ICS therapy. However, several recent publications indicate that combination therapies containing an ICS are often prescribed earlier in the course of disease to less severe COPD patients. According to Beeh et al (2016), ICS/LABA combinations are commonly prescribed as maintenance treatment for individuals with low exacerbation risk who have less severe COPD, despite the fact that LAMA/LABA combinations may have a better risk-benefit profile in that patient population. In addition, for patient populations in which ICS/LABA medicines are currently indicated, there is interest in determining the comparative efficacy of LAMA/LABA combination therapies, due to ICS-related safety concerns.

The five studies listed in Table 3.46 contribute towards the evidence base for this question and are discussed in detail throughout this section.

Table 3.46 List of RCTs comparing dual LAMA/LABA therapy with dual ICS/LABA therapy

Trial ID	Citation	Description
ENERGITO	Beeh KM, Derom E, Echave-Sustaeta J, Gronke L, Hamilton A, Zhai D, et al (2016). The lung function profile of once-daily tiotropium and olodaterol via respimat is superior to that of twice-daily salmeterol and fluticasone propionate via a accuhaler (Energito study). International Journal of COPD 11:193-205.	Key publication
FLAME	Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al (2016). Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. The New England journal of medicine 374 (23):2222-2234.	Key publication
ILLUMINATE	Vogelmeier CF, Bateman ED, Pallante J, Alagappan VKT, D'Andrea P, Chen H, et al (2013). 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. The Lancet Respiratory Medicine 1 (1):51-60.	Key publication
LANTERN	Zhong N, Wang C, Zhou X, Zhang N, Humphries M, Wang L, et al (2015). LANTERN: A randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. International Journal of COPD 10:1015-1026.	Key publication
Singh (2015a)	Singh D, Worsley S, Zhu CQ, Hardaker L and Church A (2015a). Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: A randomised trial. BMC Pulmonary Medicine 15 (1) (no pagination)(91).	Key publication

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; RCT, randomised controlled trial.

The study characteristics of the five relevant studies, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.47.

Table 3.47 Details of RCTs comparing dual therapy with LABA/LAMA versus ICS/LABA in patients with COPD

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
TIO/OLO vs FLU/SAL						
ENERGITO 1. Beeh (2016) 2. Fair quality 3. Belgium, Czech Republic, Denmark, Germany, Hungary, Netherlands, Spain, Sweden 4. Boehringer Ingelheim	229	Superiority. Double-blind, double-dummy, cross-over.	TIO/OLO 5/5 µg qd (n=221) TIO/OLO 2.5/5 µg qd (n=215)[31] FLU/SAL 500/50 µg bid (n=219) FLU/SAL 250/50 µg bid (n=212)[32]	Inclusion (1) Age ≥40 years, (2) moderate to severe COPD (GOLD 2 or 3 – 2010 version), (3) post-bronchodilator FEV_1 ≥30% and <80% predicted normal, (4) post-bronchodilator FEV_1/FVC <70% at screening visit. Exclusion (1) Significant disease other than COPD including asthma, (2) any COPD exacerbation requiring treatment with antibiotics, systemic steroids, or hospitalisation in the past 3 months, (3) abnormal laboratory tests according to the investigator. Other (1) Patients entered a 4-week screening period during which inhaled and oral corticosteroids, β-adrenergics, and LAMAs were discontinued, (2) open-label salbutamol was provided for use during the screening and washout periods.	6 weeks per treatment arm. Treatment periods were separated by a 21-day washout.	Primary Change from baseline in FEV_1 AUC from 0-12 hrs at 6 weeks. Secondary Change from baseline in FEV_1 AUC from 0-24 hrs and 12-24 hrs; peak FEV_1 from 0-3 hrs; trough FEV_1 response; trough FVC; peak FVC; safety (AEs).
UME/VIL vs FLU/SAL						
Singh (2015a) 1. N/A 2. Good quality 3. Czech Republic, Denmark, Germany, Hungary, The Netherlands, Poland, Russia, Spain 4. GlaxoSmithKline	716	Superiority. Double-blind, double-dummy.	UME/VIL 62.5/25 µg qd (n=358) FLU/SAL 500/50 µg bid (n=358)	Inclusion (1) Age ≥40 years, (2) established COPD clinical history (patients classified as GOLD Stage B or D only); (3) post-salbutamol FEV_1/FVC ratio <0.70 and a post-salbutamol FEV_1 of ≥30% and ≤70% of predicted normal values, (4) dyspnoea score of ≥2 on mMRC. Exclusion (1) Asthma or other respiratory disorders, (2) a documented history of ≥1 COPD exacerbation requiring oral corticosteroids, antibiotics and/or hospitalisation in the 12 months prior to screening, (3) hospitalisation for pneumonia within 12 weeks of screening. Other (1) Salbutamol was permitted for as-needed symptom relief throughout the study, except 4 hrs prior to spirometry testing, (2) patients were permitted to use mucolytics such as acetylcysteine throughout the study, and oxygen for intermittent use or as-needed therapy ≤12 hrs per day, (3) patients were not permitted to use depot corticosteroids; systemic, oral or parenteral corticosteroids; antibiotics; cytochrome P450 SA4 strong inhibitors; inhaled LABA, LAMA, ICS or ICS/LABA combination products; PDE4 inhibitors; or xanthines.	12 weeks	Primary Change from baseline in weighted mean FEV_1 over 0-24 hrs on Day 84.[32] Secondary Trough FEV_1 on Day 85;[33] peak FEV_1 over 0-6 hrs post-dose (days 1 and 84); time to onset; increase in FEV_1 ≥12% and ≥0.200L above baseline at any time during 0-6 hrs post-dose (Day 1); weighted mean FVC 0-24 hrs; trough FVC; rescue medication use; BDI; TDI on Days 28, 56 and 84; SGRQ; EQ-5D; CAT score; safety (AEs, vital signs).

[31] Results for this treatment arm are not shown as the dose is not PBS listed.
[32] Calculated from pre-dose FEV_1 and post-dose FEV_1 evaluations at 5 and 15 minutes and 1, 3, 6, 9, 12 (pre-evening dose), 13, 15, 18, 23 and 24 hours after the morning dose.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
GLY/IND vs FLU/SAL						
ILLUMINATE 1. Vogelmeier (2013) 2. Good quality 3. Belgium, Czech Republic, Estonia, Germany, Hungary, Republic of Korea, Lithuania, Norway, Spain 4. Novartis	523	Superiority. Double-blind, double-dummy. Subjects were stratified at randomisation for smoking status.	GLY/IND 50/110 µg qd (n=258)[34] FLU/SAL 500/50 µg bid (n=264)	Inclusion (1) Age ≥40 years, (2) moderate-to-severe COPD (GOLD stages II and III), (3) no exacerbations in previous year, (4) post-bronchodilator FEV_1 between 40% and 80% of predicted value, and post-bronchodilator FEV_1/FVC ratio <0.70, (5) symptomatic patients, according to daily electronic diary data between visit 2 (–14) and visit 3 (Day 1), with a total score of 1 or more on at least 4 of the last 7 days. Exclusion (1) Any history of asthma or onset of symptoms prior to 40 years, (2) COPD exacerbation that required treatment with antibiotics, systemic steroids or hospitalisation in the last year up to and including visit 3, (3) respiratory tract infection with 4 weeks prior to visit 1, (4) concomitant pulmonary disease, (5) long-term oxygen therapy on a daily basis. Other (1) Patients discontinued their long-acting COPD maintenance therapy before the 14-day run-in period for at least 7 days prior for LAMAs and the LABA indacaterol, and for 48 hrs for other LABAs and ICS/LABA combinations, (2) during run-in patients were provided with ipratropium bromide (SAMA) four times a day and salbutamol (SABA) as needed, (3) Salbutamol was permotted for use as rescue medication throughout the study.	26 weeks; final follow up 30 days post-treatment.	Primary Standardised AUC from 0 to 12 hrs post-dose for FEV_1 at 26 weeks. Secondary Trough FEV_1;[35] peak FEV_1; trough FVC; serial spirometry; TDI focal scores; SGRQ total scores; rescue medication use; daily patient-reported clinical symptoms (recorded morning and evening with an electronic diary); safety (AEs, vital signs, laboratory analyses).

[33] The mean of the FEV_1 values recorded 23 and 24 hours after morning dosing on day 84. Trough FEV_1 on Day 85 was analysed using a mixed model for repeated measures analysis with covariates of baseline FEV_1, smoking status, day, treatment, day by baseline interaction and day by treatment interaction, where day is nominal.
[34] One patient was randomised in error and did not receive any study medication, and was excluded.
[35] Average of the values taken at –45 and –15 mins pre-dose.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
LANTERN 1. Zhong (2015) 2. Good quality 3. China, Taiwan, Argentina, Chile 4. Novartis	744	Non-inferiority. Double-blind, double-dummy.	GLY/IND 50/110 µg qd (n=372) FLU/SAL 500/50 µg bid (n=372)	Inclusion (1) Age ≥40 years, (2) moderate-to-severe COPD (GOLD (2010) stages II and III), (3) mMRC ≥2 at screening, (4) post-bronchodilator FEV_1 ≥30% and <80% of predicted normal, (5) post-bronchodilator FEV_1/FVC <0.7 at Visit 2. Exclusion (1) ≥1 COPD exacerbation (requiring antibiotics and/or oral corticosteroids and/or hospitalisation) in the year before screening, (2) any history of asthma or onset of respiratory symptoms prior to the age 40 years, (3) long-term oxygen therapy, (4) patients who experience FEV_1 decrease ≥20% between the run-in period and randomisation visit, (5) patients with concomitant pulmonary disease (e.g. lung fibrosis, primary bronchiectasis, pulmonary hypertension). Other (1) Study population was predominantly Chinese patients (80%), (2) patients were permitted to use selective serotonin reuptake inhibitors, intra-nasal corticosteroids, or H1-antagonists alongside study medication, (3) only 16.4% of GLY/IND and 25.2% of FLU/SAL patients had a history of exacerbation in the past year.	26 weeks; final follow up 30 days post-treatment.	Primary[36] Trough FEV_1 at Week 26. Secondary[37] FEV_1 AUC from 0 to 4 hours post-dose at Week 26; peak FEV_1 and FVC; trough FVC; TDI focal score; SGRQ at Week 12 and 26; use of rescue medication, exacerbations[38], and other symptoms recorded in patient e-diaries; CAT score; safety (AEs, vital signs, laboratory analyses).

[36] Mean trough FEV_1 after 26 weeks (imputed with the last observation carried forward), was analysed using a mixed model. The model included treatment, smoking status (current/ex-smoker), COPD exacerbation history (yes/no), baseline ICS use (yes/no), and region as fixed effects; baseline FEV_1 measurement and FEV_1 reversibility as covariates; and center nested within region as a random effect. The estimated adjusted treatment difference for QVA149 to SFC was displayed along with the associated two-sided 95% CI.

[37] Moderate or severe COPD exacerbation was analyzed as an exacerbation rate by a negative binomial model, and time to first exacerbation by a Kaplan–Meier curve and Cox proportional hazard model. The negative binomial model and Cox proportional hazard model included treatment, baseline ICS use (yes/no), baseline total symptom score, baseline COPD exacerbation history (the number of COPD exacerbations in the year prior to screening), FEV_1 reversibility components, smoking history (current/ex-smoker), and region.

[38] Exacerbations were defined as worsening of symptoms that were captured via the ediary. Moderate and severe exacerbations were also captured in the case report form (CRF). Quality control and reconciliation of the exacerbation data contained within the e-diary and CRF was carried out. The Anthonisen criteria were used to define the symptoms of an exacerbation. A COPD exacerbation was considered moderate, if patients were treated with systemic corticosteroids or antibiotics or both, and were considered severe, if patients were hospitalized or experienced an emergency room (ER) visit longer than 24 hours.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
FLAME 1. Wedzicha (2016) 2. Good quality 3. 356 sites in 43 countries (no Australian sites) 4. Novartis	3,362	Non-inferiority. Double-blind, double-dummy.	GLY/IND 50/110 µg qd (n=1,680) FLU/SAL 500/50 µg bid (n=1,682)	Inclusion (1) Age ≥40 years, (2) COPD with a documented history of ≥1 exacerbation during the previous year for which they received treatment with systemic glucocorticoids, antibiotics, or both, (3) COPD grade of 2 or higher on the mMRC scale, (4) post-bronchodilator FEV_1 ≥25% and <60% of the predicted value and a post-bronchodilator FEV_1/FVC ratio <0.70. Exclusion (1) History of asthma, (2) onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years, (3) clinically significant renal, cardiovascular, arrhythmia, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or haematological abnormalities, (4) COPD exacerbation that resulted in treatment with antibiotics and/or systemic corticosteroids and/or hospitalisation in the 6 weeks prior to Visit 1, (5) long-term oxygen therapy (>12 hrs per day). Other (1) Patients were treated with tiotropium 18 µg qd for a 4-week run-in period, after which tiotropium was discontinued, (2) open-label salbutamol was provided as rescue medication, (3) pre-existing LABA, LAMA, ICS and ICS/LABA therapies were discontinued prior to run-in and, apart from study medications, were not permitted throughout the treatment periods.	52 weeks; final follow up 30 days post-treatment.	Primary Annual rate of all COPD exacerbations (mild, moderate, severe).[39] Secondary Time to first exacerbation of any severity; time to first moderate or severe exacerbation; time to first severe exacerbation; annual rates of moderate or severe exacerbations and of severe exacerbations; trough FEV_1; standardised AUC for FEV_1 from 0-12 hours; SGRQ total score; use of rescue medication; safety (AE, SAE).

Note: N refers to number randomised unless otherwise specified.
Abbreviations: AE, adverse event; AUC, area under the curve; BDI, Baseline Dyspnea Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FLU, fluticasone; FVC, forced vital capacity; GLY, glycopyrronium; GOLD, Global initiative for chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; mMRC, modified Medical Research Council; OLO, olodaterol; PBO, placebo; qd, once daily; SAE, serious adverse event; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; SMETT, sub-maximal constant-load cycle ergometry exercise tolerance test; TDI, Transition Dyspnea Index; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol; FLU/SAL fluticasone propionate/salmeterol; FLU/VIL, fluticasone furoate/vilanterol.

[39] An important secondary objective, if non-inferiority could be established, was to show whether glycopyrronium/indacaterol would be superior to fluticasone propionate/salmeterol in reducing the annual rate of all COPD exacerbations.

Tiotropium/olodaterol versus fluticasone/salmeterol

ENERGITO study

This cross-over study assessed the short-term effect on lung function of tiotropium/olodaterol and fluticasone/salmeterol in COPD patients classified as GOLD 2 (72%) or 3 (28%). A large proportion of patients were treatment-experienced at baseline, with 54% on LAMAs, 38% on ICS therapies, and 53% taking short-acting β-agonists.

Although the primary outcome was change from baseline in FEV_1 AUC from 0 to 12 hours (FEV_1 AUC_{0-12}), the comparative efficacy was also assessed via trough FEV_1 at 6 weeks. The adjusted mean difference between the treatments in terms of trough FEV_1 is shown in Table 3.48. Tiotropium/olodaterol was associated with improvements over fluticasone propionate/salmeterol that reached statistical significance for this outcome, as well as other lung function outcomes including FEV_1 AUC_{0-12}, FEV_1 AUC_{0-24}, and FEV_1 AUC_{12-24} (data not shown).

Table 3.48 Difference between treatments at 6 weeks, full analysis set – TIO/OLO versus FLU/SAL

Trough FEV_1 (mL)	Treatment difference – TIO/OLO (n=221) vs FLU/SAL (n=219)	95% CI	p-value
Adjusted mean (SE)	58 (12)	34, 82	<0.0001

Source: Beeh et al (2016), Table 5.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; FLU, fluticasone propionate; OLO, olodaterol; SAL, salmeterol; SE, standard error; TIO, tiotropium.
Note: Based on the full analysis set: all participants who received at least one dose of trial medication and had both baseline and post-baseline measurements for the primary end point. Results were not reported by treatment period.

There were no unexpected safety findings in either treatment group and both dual therapies were generally well tolerated (see Table 3.49).

Table 3.49 Results for safety outcomes relating to TIO/OLO vs FLU/SAL – Treated population

Safety outcome	TIO/OLO (N=221)	FLU/SAL (N=219)
Any AE, n (%)	75 (33.9)	81 (37.0)
COPD worsening	20 (9.0)	19 (8.7)
Pneumonia	1 (0.5)	1 (0.5)
Drug-related AE, n (%)	6 (2.7)	9 (4.1)
Severe AEs	6 (2.7)	11 (5.0)
AEs leading to discontinuation, n (%)	6 (2.7)	3 (1.4)
Any SAE, n (%)	7 (3.2)	9 (4.1)
Requiring hospitalisation	5 (2.3)	9 (4.1)
Fatal AEs, n (%)	2 (0.9)[a]	0

Source: Beeh et al (2016), Table 6.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; OLO, olodaterol; SAE, serious adverse event; SAL, salmeterol; TIO, tiotropium.
a One was cerebral haemorrhage in a predisposed patient and the other occurred 19 days after the last dose of study treatment, with unknown cause.

The authors acknowledged that recent changes in GOLD patient groups have limited the generalisability of these study results. Namely, the inclusion criteria for the ENERGITO study was based on an earlier version of GOLD, where patients were categorised as GOLD 2 or 3, based on spirometric assessment. In recent years, GOLD have adopted broader definitions to

categorise COPD patients (GOLD Groups A-D) that take into account airflow limitation, exacerbation risk, symptoms and breathlessness.

Umeclidinium/vilanterol versus fluticasone propionate/salmeterol

Singh (2015a)

As discussed earlier, ICS and ICS/LABA combination therapies are generally indicated in COPD patients with moderate-to-severe airflow limitation and a history of exacerbations (i.e. GOLD C and D patients). However, in clinical practice, patients without a history of exacerbations are often taking ICS combination therapies despite a paucity of evidence for the risk-benefit profile of corticosteroids in these patients. Singh et al (2015a) conducted an RCT in patients with no history of COPD exacerbations that required oral corticosteroids, antibiotics and/or hospitalisation in the previous year with the aim of determining the comparative efficacy and safety of a LAMA/LABA versus ICS/LAMA combination therapy in this lower risk population.

As shown in Table 3.50, 12 weeks of treatment with umeclidinium/vilanterol resulted in a statistically significantly greater improvement in trough FEV_1 from baseline, compared with fluticasone propionate/salmeterol. The magnitude of the between-group treatment difference was similar in GOLD Group B and D patients; however, statistical analyses of these subgroup comparisons were not undertaken.

Table 3.50 Treatment differences in least squares mean – Trough FEV_1

Trough FEV_1	UME/VIL (n=333)	FLU/SAL (n=338)	Treatment difference, L, (95% CI)	p-value
Least squares mean (SE)				
n	333	338	0.090 (0.055, 0.125)	<0.001
Day 85, L	1.600 (0.0126)	1.511 (0.0125)		
Change from baseline, L	0.151 (0.0126)	0.062 (0.0125)		
GOLD B subgroup[a]	**Mean (SD)**			
n	185	189	NR	NR
Change from baseline, L	0.162 (0.2661)	0.070 (0.2340)		
GOLD D subgroup[b]	**Mean (SD)**			
n	148	149	NR	NR
Change from baseline, L	0.143 (0.2067)	0.049 (0.2160)		

Source: Singh (2015a), Table 2.
Note: Results based on number of patients with analysable data at the time point of interest (i.e. Day 85)
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone propionate; GOLD, Global initiative for chronic Obstructive Lung Disease; NR, not reported; SAL, salmeterol; SD, standard deviation; SE, standard error; UME, umeclidinium; VIL, vilanterol.
a FEV_1 ≥50% to <80% predicted.
b FEV_1 ≥30% to <50% predicted.

Furthermore, patients treated with umeclidinium/vilanterol had statistically significantly greater odds than patients treated with fluticasone propionate/salmeterol of achieving an increase from baseline in trough FEV_1 ≥0.100 L on Day 85 (see Table 3.51).

Table 3.51 Proportion of patients achieving lung function improvements on Day 85 – UME/VIL vs FLU/SAL

Increase in trough FEV_1 ≥0.100L above baseline	UME/VIL (n=333)	FLU/SAL (n=338)	OR (95% CI)	p-value
Increase, n (%)	192 (58)	139 (41)	1.94 (1.42, 2.64)	<0.001
No increase, n (%)	141 (42)	199 (59)		

Source: Singh (2015a), Additional file 5.
Note (1): Results based on number of patients with analysable data at the time point of interest (i.e. Day 85).
Note (2): The odds ratio was recalculated for the ITT population, assuming that none of the dropouts experienced a trough FEV1 ≥0.100L above baseline on Day 85. The result remained significant (OR 1.82; 95% CI: 1.35, 2.45; p=0.0001) using this more conservative approach.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone propionate; OR, odds ratio; SAL, salmeterol; UME, umeclidinium; VIL, vilanterol.

Despite the significant differences demonstrated across various lung function outcomes, the trial did not demonstrate any differences between the treatment groups in relation to symptomatic and quality of life outcomes. The authors suggested that the study may have been too short to detect between-group differences in PROs, or the study may have been too small.

Overall, the frequency of AEs was similar between the treatment groups and no tolerability issues were identified (see Table 3.52). Interestingly, there were numerically fewer COPD exacerbations in the fluticasone propionate/salmeterol group; however, the statistical and clinical significance of this finding is unclear.

Table 3.52 Safety outcomes in the ITT population – UME/VIL vs FLU/SAL

Safety outcome	UME/VIL (N=358)	FLU/SAL (N=358)
Any AE, n (%)	99 (28)	105 (29)
COPD exacerbations	8 (2)	3 (<1)
Cardiac ischaemia	3 (<1)	0
Cardiac arrhythmias	3 (<1)	2 (<1)
Pneumonia	0	1 (<1)
LRTI (excluding pneumonia)	1 (<1)	0
Any SAE, n (%)	7 (2)	2 (<1)
Treatment-related AE, n (%)	7 (2)	14 (4)
AEs leading to permanent discontinuation or withdrawal, n (%)	6 (2)	5 (1)
Fatal AEs, n (%)	1 (<1)	0

Source: Singh (2015a), Table 4.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; ITT, intention-to-treat; LRTI, lower respiratory tract infection; SAE, serious adverse event; SAL, salmeterol; UME, umeclidinium; VIL, vilanterol.

A potential limitation is that patient recruitment was restricted to GOLD B and D patients, so that potential benefits of umeclidinium/vilanterol compared with fluticasone propionate/salmeterol are unknown in very severe COPD.

Glycopyrronium/indacaterol versus fluticasone propionate/salmeterol

ILLUMINATE study

ILLUMINATE was an earlier study with a similar purpose to the study by Singh et al (2015a); that is, to investigate the comparative benefits and safety of maintenance treatment with

combined LAMA/LABA therapies versus ICS/LABA therapy in low risk COPD patients who are symptomatic but have not experienced an exacerbation requiring treatment with antibiotics, systemic corticosteroids, or hospitalisation in the previous year.[40]

Despite the low risk, non-exacerbation population that was recruited in this study, approximately a third of patients were on ICS at baseline. Interestingly, the authors noted that neither patients who were not on ICS therapy at baseline, nor those who were, experienced a clinically meaningful deterioration in mean pre-bronchodilator FEV_1 during the run-in period, when ICSs were not permitted (–33 mL versus –35 mL, respectively).

The results for trough FEV_1 are shown in Table 3.53 and demonstrate that glycopyrronium/indacaterol provided significantly better and clinically relevant improvement[41] in lung function compared with fluticasone propionate/salmeterol by the end of the 26-week treatment period. It also provided improvements in important PROs such as dyspnoea and rescue medication use compared with fluticasone propionate/salmeterol.

Table 3.53 Result for trough FEV_1 at Weeks 12 and 26 – GLY/IND vs FLU/SAL

Trough FEV_1	GLY/IND (n=258) Mean (SE)	FLU/SAL (n=264) Mean (SE)	Treatment difference, L, (95% CI)	p-value
Trough FEV_1 at Week 12, L	1.612 (0.023)	1.520 (0.022)	0.092 (0.059, 0.125)	<0.0001
Trough FEV_1 at Week 26, L	1.601 (0.027)	1.498 (0.025)	0.103 (0.065, 0.141)	<0.0001

Source: Vogelmeier et al (2013), Table 2 and page 55 (in text0.
Note: Based on full analysis set; ITT.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone propionate; IND, indacaterol; GLY, glycopyrronium; SAL, salmeterol; SE, standard error.

There were numerically fewer AEs in the glycopyrronium/indacaterol group compared with the fluticasone propionate/salmeterol group, as well as fewer patients who experienced a worsening of COPD (see Table 3.54), although it is unlikely that these differences were statistically significant. The authors concluded that switching from ICS/LABA to dual bronchodilation with glycopyrronium/indacaterol would not result in deterioration in quality of life.

While this study demonstrated that treatment with two long-acting bronchodilators in patients at low risk of exacerbations may optimise lung function and symptom benefit, further studies are needed to assess LAMA/LABA FDCs in more severe, exacerbating patients where ICS are currently recommended.

Table 3.54 Results for safety outcomes relating to GLY/IND vs FLU/SAL – Safety population[a]

Safety outcome	GLY/IND (N=258)	FLU/SAL (N=264)
Any AE, n (%)	143 (55.4)	159 (60.2)
COPD worsening, including COPD exacerbations[b]	44 (17.1)	62 (23.5)
Pneumonia	0	4 (1.5)
LRTI	1 (0.4)	0

[40] Exacerbation was defined as the worsening of two or more major symptoms (dyspnoea, sputum volume, and sputum purulence) for at least two consecutive days; or worsening of one major symptom together with one minor symptoms (sore throat, colds, fever without other cause, increased cough, or increased wheeze) for at least two consecutive days.
[41] The MCID for trough FEV_1 was defined as 100 mL.

Safety outcome	GLY/IND (N=258)	FLU/SAL (N=264)
Cardiac disorders	2 (0.8)	2 (0.8)
Respiratory thoracic, and mediastinal disorders	19 (7.4)	20 (7.6)
AEs leading to discontinuation, n (%)	22 (8.5)	27 (10.2)
Any SAE, n (%)	13 (5.0)	14 (5.3)
Cardiac disorders	2 (0.8)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	3 (1.2)	4 (1.5)
SAE leading to discontinuation, n (%)	5 (1.9)	9 (3.4)
Deaths, n (%)	0	1 (0.4)

Source: Vogelmeier et al (2013), Table 4 and Table 5.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; IND, indacaterol; GLY, glycopyrronium; LRTI, lower respiratory tract infection; SAE, serious adverse event; SAL, salmeterol.
a All patients that received at least one dose of study drug.
b Exacerbations were considered to be moderate severity if they required treatment with systemic corticosteroids and/or antibiotic without leading to hospitalisation; and severe if they also required hospitalisation.

LANTERN study

Like several previously discussed studies, the LANTERN study compared the efficacy of glycopyrronium/indacaterol and fluticasone propionate/salmeterol in symptomatic patients with low exacerbation risk, where the use of ICS may be inappropriate or premature. The comparison was undertaken in the context of non-inferiority (of the LAMA/LABA to the ICS/LABA) based on trough FEV_1 at Week 26, with the non-inferiority margin defined as –60 mL.[42]

Approximately 55% and 54% of patients were using ICS as baseline in the glycopyrronium/indacaterol and fluticasone propionate/salmeterol treatment arms, respectively.

Glycopyrronium/indacaterol was deemed to be non-inferior to fluticasone propionate/salmeterol by meeting the predefined non-inferiority margin of –60 mL in trough FEV_1 for the per protocol set. The LAMA/LABA FDC demonstrated statistically significant superiority to the ICS/LABA combination for trough FEV_1 for the full analysis set, see Table 3.55. Various subgroup analyses are also presented, including ICS use at baseline, severity of COPD, and exacerbation history with all comparisons favouring glycopyrronium/indacaterol over fluticasone propionate/salmeterol.

A greater proportion of patients in the glycopyrronium/indacaterol group achieved an improvement of ≥100 mL or ≥200 mL in trough FEV_1 from baseline to Week 26 compared with fluticasone propionate/salmeterol (see Table 3.56).

In addition to lung function outcomes, the LANTERN study also reported the total number of exacerbations per patient and rate of exacerbations per year. The results are shown in Table 3.57, according to exacerbation severity.

[42] The non-inferiority margin was based on the treatment difference between fluticasone propionate/salmeterol and placebo of 160 mL with a 95% confidence interval (CI) of 120–200 mL, as summarised in a Cochrane review (Nannini et al, 2007). The non-inferiority margin was set as one-half of the lower bound of the confidence interval.

Table 3.55 Change from baseline for trough FEV_1 (LOCF) – GLY/IND vs FLU/SAL

LS mean difference from baseline	GLY/IND 50/110		FLU/SAL 500/50		Treatment difference	p-value
Primary analysis	**n**	**Mean ±SE**	**n**	**Mean ±SE**	**Δ (95% CI)**	
Trough FEV_1 at Week 26, L *Per protocol analysis*[a]	NR	NR	NR	NR	0.072 (0.040, 0.104)	NR
Trough FEV_1 at Week 26, L	352	1.259 ±0.017	340	1.183 ±0.017	0.075 (0.044, 0.107)	<0.001
Subgroup – COPD severity						
Mild/moderate	184	NR	184	NR	0.079 (0.036, 0.122)	NR
Severe/very severe	168	NR	156	NR	0.071 (0.025, 0.117)	NR
Subgroup – baseline ICS use						
Yes	196	NR	184	NR	0.062 (0.019, 0.104)	NR
No	156	NR	156	NR	0.092 (0.044, 0.139)	NR
Subgroup – COPD exacerbation						
Yes	58	NR	80	NR	0.062 (–0.009, 0.134)	NR
No	294	NR	260	NR	0.078 (0.043, 0.114)	NR

Source: Zhong et al (2015), pg 1018; Figure 3; Table 2; Figure 4.
Note: Results based on the full analysis set (all randomised patients who received at least one dose of study drug), unless otherwise specified.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; LOCF, last observation carried forward; LS, least squares; NR, not reported; SAL, salmeterol; SE, standard error.
a All patients in the full analysis set without any major protocol deviations.

Table 3.56 Analysis of responders of post-dose trough FEV_1 after 26 weeks of treatment

	GLY/IND 50/110 (N=372)	FLU/SAL 500/50 (N=369)	OR (95% CI)	p-value
≥100 mL improvement, n/N[a] (%)	215/336 (60.6)	152/344 (44.2)	1.88 (1.38, 2.56)	<0.001
≥200 mL improvement, n/N[a] (%)	155/355 (43.7)	85/344 (24.7)	2.38 (1.70, 3.33)	<0.001

Source: Zhong et al (2015), Table S3 (Supplementary material).
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OR, odds ratio; SAL, salmeterol.
Note: Odds ratio, 95% CI, and p-value are from a logistic regression model: Logit(proportion)=treatment + baseline FEV_1 + baseline ICS + FEV_1 reversibility components + smoking status + COPD exacerbation history + region + centre (region). Centre is included as a random effect nested within region.
a n= number of patients who achieved a clinically important improvement of change from baseline on trough FEV_1; N= number of patients with a trough FEV_1 value at both baseline and post-baseline (included in the analysis).

Table 3.57 Total number and rate of exacerbations – GLY/IND vs FLU/SAL

Moderate or severe exacerbations	GLY/IND 50/110 (n=372)	FLU/SAL 500/50 (n=369)
All COPD exacerbations		
Exacerbations per patient, n (%)	-	-
0	297 (79.8)	272 (73.7)
1	53 (14.2)	73 (19.8)
2	17 (4.6)	18 (4.9)
3	3 (0.8)	3 (0.8)
≥4	2 (0.5)	3 (0.8)
Total number of exacerbations	105	131
Total number of treatment years	179.2	174.9
Rate of exacerbations per year	0.59	0.75
Moderate or severe exacerbations		
Exacerbations per patient, n (%)	-	-
0	328 (88.2)	301 (81.6)
1	35 (9.4)	55 (14.9)
2	9 (2.4)	13 (3.5)
3	0	0
≥4	0	0
Total number of exacerbations	53	81
Total number of treatment years	179.2	174.9
Rate of exacerbations per year	0.30	0.46

Moderate or severe exacerbations	GLY/IND 50/110 (n=372)	FLU/SAL 500/50 (n=369)
Severe exacerbations[a]		
Exacerbations per patient, n (%)	-	-
0	366 (98.4)	353 (95.7)
1	6 (1.6)	15 (4.1)
2	0	1 (0.3)
3	0	0
≥4	0	0
Total number of exacerbations	6	17
Total number of treatment years	179.2	174.9
Rate of exacerbations per year	0.03	0.09

Source: Zhong et al (2015), Table 3.
Note: Results based on the full analysis set (all randomised patients who received at least one dose of study drug).
Abbreviations: COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; SAL, salmeterol.
a Exacerbation that resulted in hospitalisation.

A Kaplan-Meier plot of the time to first moderate or severe COPD exacerbation over 26 weeks of treatment (full analysis set) showed a hazard ratio of 0.65 (95% CI: 0.44, 0.95; p=0.028), in favour of glycopyrronium/indacaterol. Furthermore, the annualised rate of moderate to severe COPD exacerbations was significantly lower in the glycopyrronium/indacaterol treatment arm compared with fluticasone propionate/salmeterol, indicating a risk reduction of 31% (see Table 3.58). The overall annualised exacerbation rates were also stratified according to exacerbation history, due to unintended differences between the treatment groups for this risk factor at baseline (16.4% for glycopyrronium/indacaterol; 25.2% for fluticasone propionate/salmeterol). Importantly, while the annualised rate of COPD exacerbations (all, moderate to severe, severe) was lower for glycopyrronium/indacaterol in all of the exacerbation history subgroups, the differences were generally not statistically significant, and the subgroups were not sufficiently powered for hypothesis testing.

Both treatments were well tolerated, but adverse events occurred less frequently in the patients treated with glycopyrronium/indacaterol, including fewer cases of pneumonia (see Table 3.59).

Overall, glycopyrronium/indacaterol demonstrated non-inferiority to fluticasone propionate/salmeterol on the primary endpoint (trough FEV_1 at 26 weeks), and it also demonstrated superiority for this outcome. While not reported in this review, the study assessed several PROs that failed to show a significant difference between treatments. The authors speculated that the PROs may not be sensitive enough to differentiate between two highly active treatments.

Despite the lack of superiority on PROs, the authors concluded that for patients with infrequent exacerbations that are classified as GOLD Group D because of airflow limitation, results from LANTERN suggest that these patients should be receiving a LAMA/LABA instead of ICS/LABA.

Table 3.58 Analysis of COPD exacerbations over 26 weeks by treatment group – GLY/IND vs FLU/SAL

	GLY/IND	50/110	FLU/SAL	500/50	Comparative estimate (95% CI)	p-value
	n/N (%)	Rate (95% CI)	n/N (%)	Rate (95% CI)	Rate ratio (95% CI)	
Annualised rate of any COPD exacerbation	-	-	-	-	-	-
Overall	372	-	369	-	0.79 (0.58, 1.07)	NR
With COPD exacerbation history at baseline	15/61 (24.6)	0.78 (0.47, 1.31)	43/93 (46.2)	1.81 (1.31, 2.52)	0.43 (0.25, 0.76)	0.003
Without COPD exacerbation history at baseline	60/311 (19.3)	0.66 (0.49, 0.87)	54/276 (19.6)	0.67 (0.49, 0.92)	0.98 (0.67, 1.43)	0.916
Annualised rate of moderate or severe exacerbations	-	-	-	-	-	-
Overall	372	0.30 (NR)	369	0.46 (NR)	0.69 (0.48, 1.00)	0.048
With COPD exacerbation history at baseline	12/61 (19.7)	0.49 (0.29, 0.82)	32/93 (34.4)	0.81 (0.56, 1.19)	0.60 (0.33, 1.08)	0.086
Without COPD exacerbation history at baseline	32/311 (10.3)	0.23 (0.16, 0.33)	36/276 (13.0)	0.30 (0.21, 0.43)	0.76 (0.46, 1.24)	0.266
Annualised rate of severe COPD	-	-	-	-	-	-
Overall	372	-	369	-	0.31 (0.11, 0.85)	<0.05
With COPD exacerbation history at baseline	0/61 (0)	-	7/93 (7.5)	-	-	-
Without COPD exacerbation history at baseline	6/311 (1.9)	-	9/276 (3.3)	-	-	-
	N	-	N	-	Hazard ratio (95% CI)	
Time to first moderate or severe exacerbation	372	-	369	-	0.65 (0.44, 0.95)	0.028
Time to first severe exacerbation	372	-	369	-	0.32 (0.12, 0.88)	0.027

Source: Zhong et al (2015), Table 3 and Figure 5; Table S6, Figure S1 and Figure S3 (Supplementary material).
Note: Rate ratio, its 95% CI, and p-value are from a negative binomial regression model: log (exacerbation rate) = treatment + smoking status + baseline ICS use (yes/no) + baseline total symptom score + FEV_1 reversibility components + region. Log (length of time in the study) is included in the model as an offset term.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; GLY, glycopyrronium; HR, hazard ratio; IND, indacaterol; SAL, salmeterol.

Table 3.59 Results for safety outcomes relating to GLY/IND vs FLU/SAL – Safety set[a]

Safety outcome	GLY/IND (N=372)	FLU/SAL (N=369)
Any AE, n (%)	149 (40.1)	175 (47.4)
COPD worsening[b]	75 (20.2)	97 (26.3)
Upper respiratory tract infection	13 (3.5)	26 (7.0)
Bronchitis	7 (1.9)	4 (1.1)
Pneumonia	3 (0.8)	10 (2.7)
AEs leading to discontinuation, n (%)	12 (3.2)	17 (4.6)
AEs leading to hospitalisation, n (%)	16 (4.3)	31 (8.4)
Hospitalised for COPD exacerbation, n (%)	6 (1.6)	16 (4.3)
Hospitalised for pneumonia, n (%)	2 (0.5)	4 (1.1)
Any SAE, n (%)	20 (5.4)	35 (9.5)
SAE leading to discontinuation, n (%)	9 (2.4)	11 (3.0)
Deaths, n (%)	2 (0.5)	0

Source: Zhong et al (2015), Table 5 and Figure S2 (Supplementary material).
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; SAE, serious adverse event; SAL, salmeterol.
a Safety set refers to all patients who received at least one dose of the study drug, regardless of whether the patient was randomised.
b Including COPD exacerbations.

FLAME study

The FLAME study was the only new evidence comparing LAMA/LABA versus ICS/LABA combination therapies that examined annual rates of COPD exacerbations as a primary outcome. As outlined in Table 3.47, FLAME was a non-inferiority study that randomised over 3,000 patients with a documented history of one or more exacerbations in the previous year. The non-inferiority margin was 15% (i.e. a rate ratio for exacerbations with glycopyrronium/indacaterol versus fluticasone propionate/salmeterol of 1.15).

At baseline, the treatment groups were balanced in terms of COPD severity and use of ICS. In patients randomised to glycopyrronium/indacaterol, 75% were classified as GOLD Group D and 24% were GOLD Group B; with the corresponding proportions in the fluticasone propionate/salmeterol group of 74% and 25%.

Over half of the patients in both groups were ICS users at baseline (57% and 56% in glycopyrronium/indacaterol and fluticasone propionate/salmeterol groups, respectively).

Analysis of the primary outcome was based on the per protocol population. As demonstrated in Table 3.60, the annual rate of all COPD exacerbations was 11% lower in the glycopyrronium/indacaterol group than the fluticasone propionate/salmeterol group; thus the criteria for non-inferiority was achieved.[43] Importantly, the annual rate of moderate-to-severe exacerbations (i.e. exacerbations associated with a cost to the health care system) was 17% lower in the glycopyrronium/indacaterol group than in the fluticasone propionate/salmeterol group.

[43] A supportive analysis undertaken using the modified ITT population also established non-inferiority.

Table 3.60 Analysis of COPD exacerbations over 52 weeks – GLY/IND vs FLU/SAL

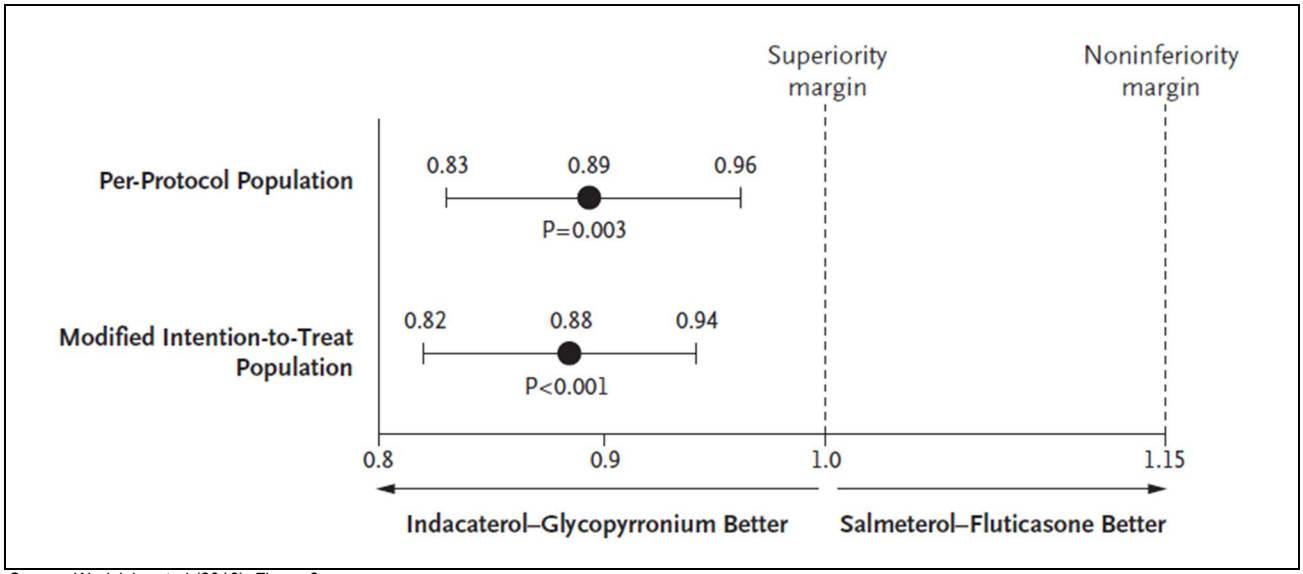
Annual rate of exacerbations	GLY/IND		FLU/SAL		Rate ratio (95% CI)	p-value
Primary analysis	**n**	**Rate (95% CI)**	**n**	**Rate (95% CI)**		
All exacerbations (mild to severe) *Per protocol population*	1,518	3.59 (3.28, 3.94)	1,544	4.03 (3.68, 4.41)	0.89 (0.83, 0.96)	0.003
All exacerbations (mild to severe)	1,651	3.59 (3.29, 3.92)	1,656	4.09 (3.75, 4.46)	0.88 (0.82, 0.94)	<0.001
Mild exacerbations[a]	1,651	2.46 (2.20, 2.74)	1,656	2.72 (2.43, 3.03)	0.91 (0.83, 0.99)	0.030
Moderate exacerbations[b]	1,651	0.81 (0.72, 0.91)	1,656	0.98 (0.87, 1.10)	0.83 (0.74, 0.92)	<0.001
Moderate or severe exacerbations	1,651	0.98 (0.88, 1.10)	1,656	1.19 (1.07, 1.32)	0.83 (0.75, 0.91)	<0.001
Severe exacerbations[c]	1,651	0.15 (0.11, 0.19)	1,656	0.17 (0.13, 0.22)	0.87 (0.69, 1.09)	0.23

Source: Wedzicha et al (2016), p 2229 (in text); Figure 2; Figure S5A; Table S5 (Supplementary material).
Note (1): Analyses based on the modified ITT population unless otherwise specified. The modified ITT population was all patients who underwent randomisation, received at least one dose of a drug during the treatment period, and did not have major violations of compliance with Good Clinical Practice guidelines before unblinding occurred.
Note (2): Annualised rate estimates are from a generalised linear model assuming a negative binomial distribution with fixed effects of treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. The offset variable log(exposure time in years) was used.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; SAL, salmeterol.
a Exacerbations involving worsening of symptoms for more than two consecutive days but not leading to treatment with systemic glucocorticoids or antibiotics.
b Exacerbations leading to treatment with systematic glucocorticoids, antibiotics, or both.
c Exacerbations leading to hospital admission or a visit to the emergency department that lasted more than 24 hours in addition to treatment with systemic glucocorticoids, antibiotics, or both.

The robustness of the results were tested in several sensitivity analyses using both on- and off-treatment data from patients who discontinued treatment early. The sensitivity analyses were consistent with the primary analysis, indicating that glycopyrronium/indacaterol was more effective than fluticasone propionate/salmeterol at preventing exacerbations.

Figure 3.7 shows the results of a secondary analysis in which the primary outcome was adjusted for multiple testing. Glycopyrronium/indacaterol achieved superiority over fluticasone propionate/salmeterol in reducing the annual rate of all COPD exacerbations in both the per protocol and modified ITT populations.

Figure 3.7 Rate ratio for all exacerbations (mild, moderate, and severe) – GLY/IND vs FLU/SAL



Source: Wedzicha et al (2016), Figure 2a.
Abbreviations: FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; SAL, salmeterol.

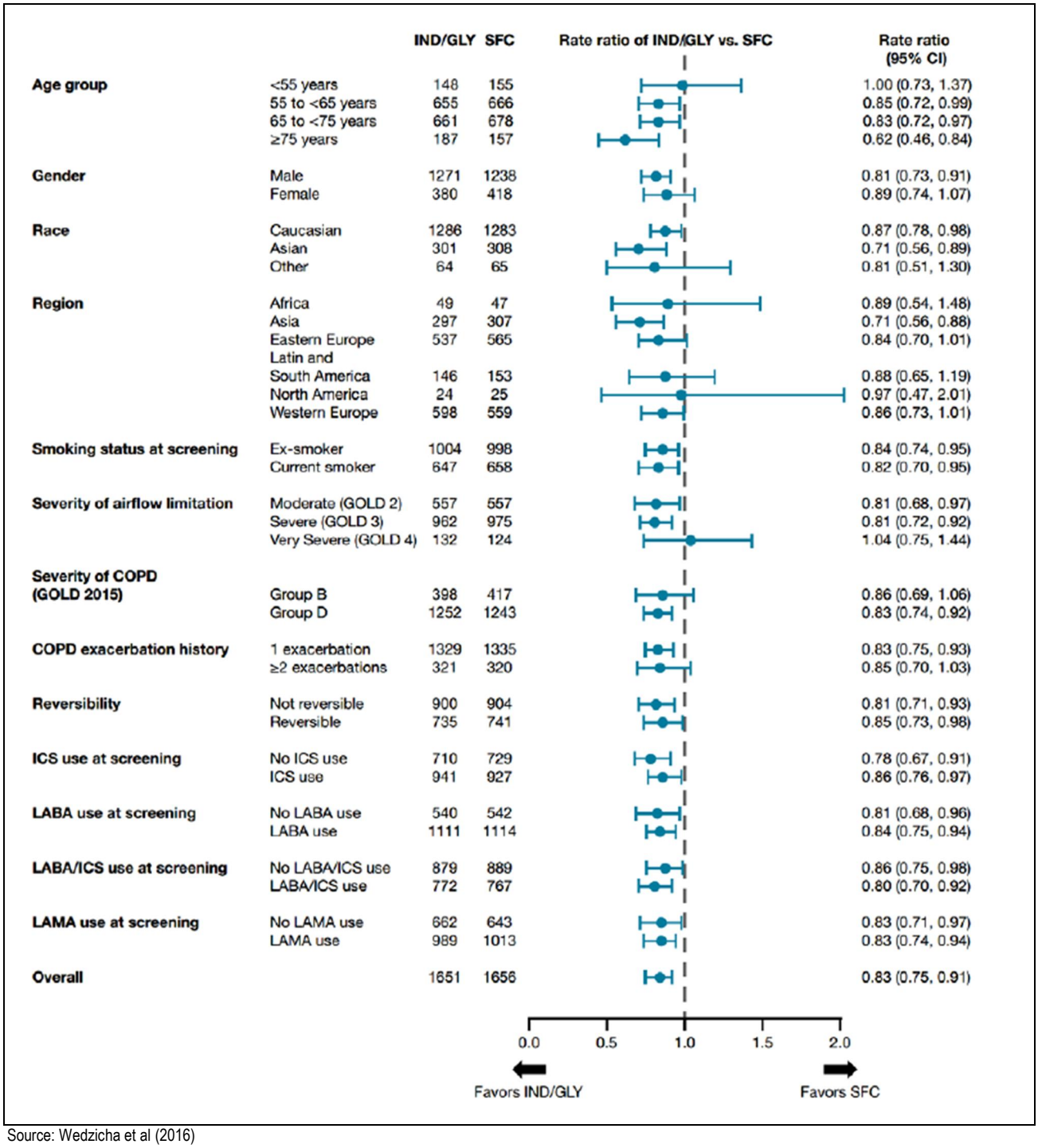
Subgroup analyses were undertaken to assess the impact that other factors, such as severity of COPD and prior use of maintenance therapies would have on the treatment effect. Table 3.61 demonstrates that, across all analysed subgroups, the results favoured glycopyrronium/indacaterol. The forest plot in Figure 3.8 shows similar results; however, those sub-analyses focused specifically on moderate or severe exacerbations.

Table 3.61 Subgroup analyses of COPD exacerbations (all severities) over 52 weeks – GLY/IND vs FLU/SAL

	GLY/IND (n=1,651)	FLU/SAL (n=1,656)	Rate ratio (95% CI)
Severity of airflow limitation			
Moderate	557	557	0.93 (0.82, 1.06)
Severe	962	975	0.84 (0.76, 0.92)
Very severe	132	124	0.94 (0.72, 1.22)
Severity of COPD			
Group B	398	417	0.98 (0.85, 1.14)
Group D	1,252	1,243	0.85 (0.78, 0.92)
COPD exacerbations in previous year			
1	1,329	1,335	0.87 (0.81, 0.95)
≥2	321	320	0.89 (0.76, 1.05)
ICS use at screening			
No	710	729	0.88 (0.79, 0.98)
Yes	941	927	0.88 (0.80, 0.97)
LABA use at screening			
No	540	542	0.91 (0.81, 1.04)
Yes	1,111	1,114	0.86 (0.79, 0.94)
ICS/LABA use at screening			
No	879	889	0.88 (0.80, 0.97)
Yes	772	767	0.88 (0.79, 0.97)
LAMA use at screening			
No	662	643	0.91 (0.81, 1.02)
Yes	989	1,013	0.86 (0.78, 0.94)

Source: Wedzicha et al (2016), Figure 2, Figure 3.
Note: Analyses based on the modified ITT population.
Note: Based on a negative binomial model that included terms for treatment, baseline smoking status, use of inhaled glucocorticoids at the time of screening, severity of airflow limitation, and geographic region as fixed effects and baseline total symptom score (on a scale ranging from 0 to 18, with higher total scores indicating worse symptoms) and 1-year history of COPD exacerbations as covariates.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting bete agonist; LAMA, long-acting muscarinic antagonist; SAL, salmeterol.

Figure 3.8 Forest plot of estimated moderate or severe COPD exacerbation rate ratio by demographic and disease characteristics

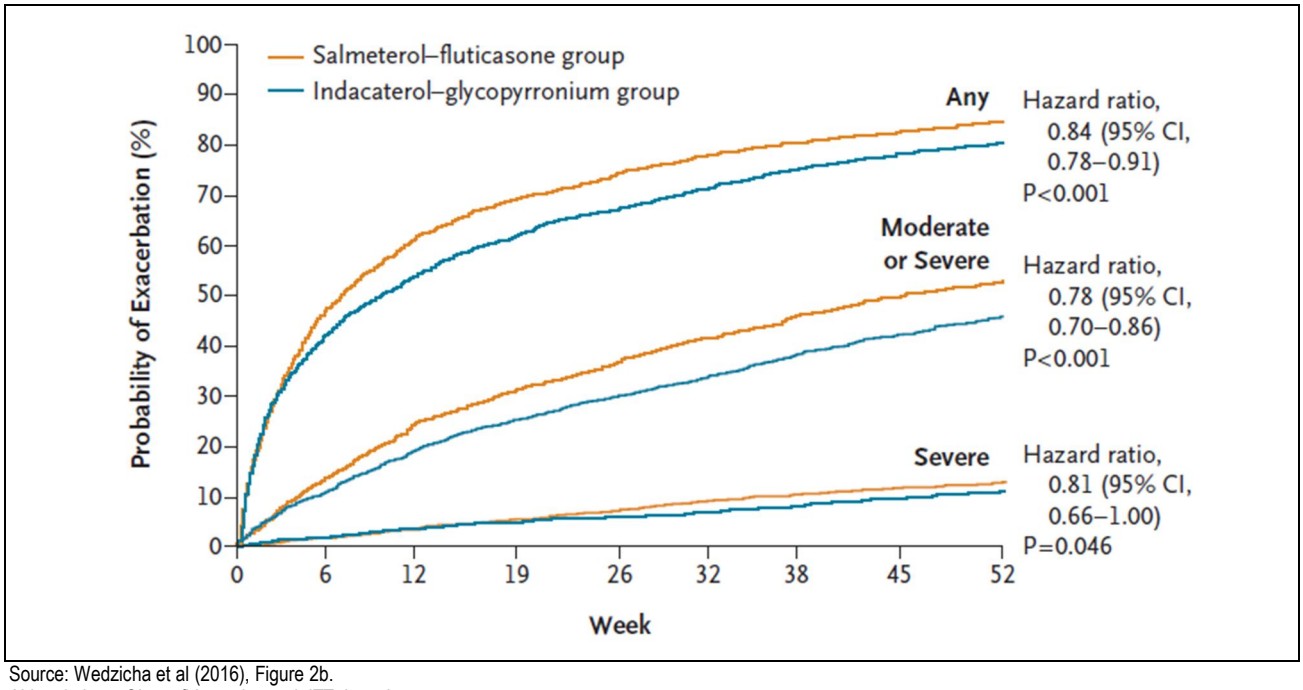


Source: Wedzicha et al (2016)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SFC, salmeterol/fluticasone combination.

Time to first exacerbation favoured glycopyrronium/indacaterol (71 days; 95% CI 60, 82) over fluticasone propionate/salmeterol group (median time to first exacerbation: 51 days; 95% CI 46, 57), representing a 16% lower risk. The risk difference was even greater with respect to moderate or severe exacerbations (22%), with a median time to moderate or severe exacerbation of 127 days and 87 days in the glycopyrronium/indacaterol and fluticasone propionate/salmeterol groups, respectively (see Figure 3.9).

Figure 3.9 Time to first exacerbation (any severity, moderate or severe, or severe) – modified ITT



Source: Wedzicha et al (2016), Figure 2b.
Abbreviations: CI, confidence interval; ITT, intention-to-treat.
Note (1): Analysis based on the modified ITT population.
Note (2): Analysed using a Cox regression model that included terms for treatment, baseline smoking status, use of inhaled glucocorticoids at the time of screening, severity of airflow limitation, and geographic region as fixed effects and baseline total symptom score (on a scale ranging from 0 to 18, with higher total scores indicating worse symptoms) and 1-year history of COPD exacerbations as covariates.

The change from baseline in trough FEV_1 was examined as a secondary outcome. Table 3.62 shows that treatment with glycopyrronium/indacaterol resulted in a statistically significantly greater improvement in trough FEV_1 than fluticasone propionate/salmeterol.

Table 3.62 Adjusted mean change from baseline in trough FEV_1 – GLY/IND vs FLU/SAL

LS mean change from baseline, L	GLY/IND (n=1,597)	FLU/SAL (n=1,595)	Treatment difference Δ (95% CI)	p-value
Trough FEV_1 – Day 28	0.079	0.006	0.073 (0.061, 0.085)	<0.001
Trough FEV_1 – Day 85	0.070	–0.008	0.078 (0.066, 0.091)	<0.001
Trough FEV_1 – Day 183	0.049	–0.037	0.086 (0.073, 0.100)	<0.001
Trough FEV_1 – Day 267	0.034	–0.039	0.073 (0.059, 0.087)	<0.001
Trough FEV_1 – Day 365 (Week 52)	0.015	–0.048	0.062 (0.048, 0.077)	<0.001

Source: Wedzicha et al (2016), p 2229; Figure S7A; Table S6 (Supplementary appendix).
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; LS, least squares; SAL, salmeterol.
Note (1): Analysis was based on the full analysis set. Number of patients included in the analysis: GLY/IND n=1,597; FLU/SAL n=1,595.
Note (2): Change from baseline in trough FEV_1 was analysed using a mixed model for repeated measures. The model included terms of treatment, baseline measurements (FEV_1/FVC as appropriate), smoking status at baseline, baseline ICS use, COPD severity (using GOLD 2011 classification), region, visit (as a factor), baseline-by-visit interaction and treatment-by-visit interaction, and an unstructured variance–covariance structure.
Abbreviations:

There were no unexpected safety findings and although there were more cases of pneumonia in the fluticasone propionate/salmeterol group, the statistical and clinical significance of the result was unclear (see Table 3.63).

Table 3.63 Safety outcomes relating to the comparison of GLY/IND vs FLU/SAL – Safety set[a]

Safety outcome	GLY/IND (N=1,678)	FLU/SAL (N=1,680)
Patients with ≥1 AE, n (%)	1,459 (86.9)	1,498 (89.2)
AEs, n (%)	-	-
COPD worsening	1,299 (77.4)	1,374 (81.8)
LRTI	82 (4.9)	98 (5.8)
Pneumonia	53 (3.2)	80 (4.8)
Any SAE, n (%)	308 (18.4)	334 (19.9)
Deaths, n (%)	24 (1.4)	24 (1.4)
Cardiovascular	9 (0.5)	11 (0.7)
Respiratory	5 (0.3)	2 (0.1)
AEs leading to discontinuation, n (%)	126 (7.5)	143 (8.5)
SAE leading to discontinuation, n (%)	85 (5.1)	87 (5.2)

Source: Wedzicha et al (2016), Table 2; Table S8 (Supplementary appendix).
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; LRTI, lower respiratory tract infection; SAE, serious adverse event; SAL, salmeterol.
a The safety analysis included patients who received a drug during the treatment period. Patients were included in the analysis for the treatment they received; one patient who had been assigned to the fluticasone propionate/salmeterol group had mistakenly received glycopyrronium/indacaterol.

The authors acknowledged that the overall rate of exacerbations reported in the FLAME study was relatively high; however, they noted that this may have resulted from the use of electronic diaries to flag exacerbations and emphasised that the higher rate of exacerbations would not bias the results in favour of one treatment over another.

LAMA/LABA versus ICS/LABA

Horita 2017

The RG also considered the results of a recent Cochrane review published after the search period for the systematic review. The review meta-analysed the results of 11 studies (n=9,839) that compared LAMA plus LABA to LABA plus ICS treatment, predominantly in patients with moderate to severe COPD without recent exacerbations. Follow up ranged from 6 to 52 weeks.

The authors found that compared to LABA plus ICS, LAMA plus LABA treatment was associated with:

- greater improvements in trough FEV_1 change from baseline (MD 0.08 L; 95% CI 0.06 to 0.09, P < 0.0001, I^2 = 50%, moderate quality evidence)
- fewer exacerbations (OR 0.82; 95% CI 0.70 to 0.96, P = 0.01, I^2 = 17%, low quality evidence)
- more frequent improvement in QoL, measured by a SGRQ total score change from baseline of four points or greater (the MCID) (OR 1.25; 95% CI 1.09 to 1.44, P = 0.002, I^2 = 0%, moderate quality evidence)
- lower risk of pneumonia (OR 0.57; 95% CI 0.42 to 0.79, P = 0.0006, I^2 = 0%, low quality evidence).

No statistically significant differences between LAMA plus LABA and LABA plus ICS treatment were found on the following outcomes:

- serious adverse events

- SGRQ total score change from baseline
- all-cause death.

The authors concluded that the findings supported recent GOLD Strategy Report (2017) recommendations favouring LAMA/LABA therapy over ICS/LABA, in patients where dual therapy is appropriate.

Summary of findings

- Due to safety concerns relating to ICS therapies, some recent studies have examined the comparative efficacy of LAMA/LABA and ICS/LABA dual therapies in patients whose exacerbation history may, according to clinical guidance, warrant the use of ICS therapy.
- The FLAME study (good quality) compared the efficacy and safety of glycopyrronium/indacaterol and fluticasone propionate/salmeterol. Of the studies discussed in this section, the FLAME study is most relevant to this review, as the patients recruited into the study were required to have had at least one exacerbation that required healthcare resources in the previous year. Based on exacerbation and lung function outcomes, glycopyrronium/indacaterol consistently achieved non-inferiority compared with fluticasone propionate/salmeterol. In a secondary analysis, glycopyrronium/indacaterol achieved superiority over fluticasone propionate/salmeterol in reducing the annual rate of COPD exacerbations.
- In light of the aforementioned discordance between clinical guidance and clinical practice, several studies have recently been undertaken to compare the efficacy and safety of FDCs of LAMA/LABA and ICS/LABA, in patients who rarely experience exacerbations and in whom the clinical need for the ICS component is, therefore, less compelling.
- Singh et al (2015a; good quality) demonstrated that umeclidinium/vilanterol may represent a superior treatment option to fluticasone propionate/salmeterol in symptomatic COPD patients who do not experience frequent exacerbations.
- The ENERGITO study (fair quality) found that patients with moderate-to-severe COPD who received tiotropium/olodaterol achieved statistically significant improvements in lung function (including trough FEV_1) over patients who received fluticasone propionate/salmeterol.
- The ILLUMINATE study (good quality) and the LANTERN study (good quality) also focused on patients who had not experienced an exacerbation requiring treatment with antibiotics, systemic corticosteroids, or hospitalisation in the previous year. In both studies, glycopyrronium/indacaterol was found to be both non-inferior and, in secondary analyses, superior to fluticasone propionate/salmeterol at 26 weeks, based on trough FEV_1.
- Horito et al (2017) meta-analysed the results of 11 studies comparing LAMA plus LABA to LABA plus ICS, and found LAMA plus LABA treatment associated with fewer exacerbations, greater improvements in FEV_1, lower risk of pneumonia, and more frequent clinically meaningful QoL improvements (measured by SGRQ improvement of 4 or more units). The evidence was considered of low or moderate quality. Study

patients predominantly had moderate to severe COPD without recent exacerbations. This study was published after the search period for the review, but was considered by the RG.

1.4.7 ICS/LABA versus LAMA monotherapy

This section seeks to add to the evidence base relating to the additional benefit that may be gained by moving from LAMA monotherapy to dual ICS/LABA therapy, and in which patients this may be appropriate. Three studies, not previously considered by the PBAC, were identified and the citation details are listed in Table 3.64.

Table 3.64 List of RCTs comparing an ICS/LABA combination therapy with LAMA monotherapy

Trial ID	Citation	Description
Covelli (2016)	Covelli H, Pek B, Schenkenberger I, Scott-Wilson C, Emmett A and Crim C (2016). Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. International Journal of COPD 11:1-12.	Key publication
INSPIRE	Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z and Stockley RA (2008). The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. American Journal of Respiratory and Critical Care Medicine 177 (1):19-26.	Key publication
Sarac (2016)	Sarac P and Sayiner A (2016). Compare the efficacy and safety of long-acting anticholinergic and a combination of inhaled steroids and long-acting beta-2 agonist in moderate chronic obstructive pulmonary disease. Tuberkuloz ve Toraks 64 (2):112-118.	Key publication

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; RCT, randomised controlled trial.

The study characteristics of the three relevant studies, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.65. The results reported in each study that are of relevance to this review are then outlined in subsections according the specific treatment comparisons.

Table 3.65 Details of RCTs comparing dual therapy with ICS/LABA with LAMA monotherapy in patients with COPD

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
FLU/SAL vs TIO						
INSPIRE 1. Wedzicha (2008) 2. Good quality 3. Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Greece, Italy, Latvia, Lithuania, Netherlands, Norway, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Ukraine, UK. 4. GlaxoSmithKline	1,323	Superiority. Double-blind, double-dummy.[44]	FLU/SAL 500/50 µg bid (n=658) TIO 18 µg qd (n=655)	Inclusion (1) Age 40-80 years, (2) clinical history of exacerbations, (3) post-bronchodilator FEV_1 of less than 50% predicted, (3) reversibility to 400 µg salbutamol 10% or less of predicted FEV_1, (4) score of ≥2 on mMRC Dyspnea Scale. Exclusion (1) Any respiratory disorder other than COPD, (2) long-term oxygen therapy (≥12 hours per day). Other (1) All patients discontinued existing COPD maintenance medications and received oral prednisolone 30 mg/day ad inhaled salmeterol 50 µg bid during a 2-week run-in period prior to randomisation, (2) during the trial patients were allowed SABA medications for relief therapy and standardised short courses of oral systemic corticosteroids and/or antibiotics where indicated for treatment of COPD exacerbations.	2 years	Primary Healthcare utilisation exacerbation rate.[45,46] Secondary SGRQ; post-dose FEV_1 (measured 2 hrs after inhalation of study medication); all-cause mortality; safety (AEs, study withdrawal).
Sarac (2016) 1. N/A 2. Poor quality 3. Turkey 4. NR	44	Superiority. Open-label.	FLU/SAL 500/50 µg bid (n=22) TIO 18 µg qd (n=22)	Inclusion (1) Age 35-80 years, (2) FEV_1 between 50% and 80% predicted, (3) ≥1 exacerbations in preceding year. Exclusion (1) History of asthma, (2) previous documentation of bronchial hyperreactivity, (3) history of allergy and/or atopy, (4) presence of congestive heart failure, (5) any cardiopulmonary disease that might interfere with the patient's follow up. Other (1) Two-week washout period during which all long-acting bronchodilators and inhaled steroids were stopped, (2) patients were permitted to use short-acting bronchodilators as needed, (3) in the event of an exacerbation, patients could be treated with antibiotics and/or systemic steroids.	1 year	All outcomes[47] Exacerbation[48] within the preceding three months (measured at 3, 6, 9 and 12 months);[49] time to first exacerbation; pulmonary function tests (FEV_1, FVC); arterial blood gases; 6-minute walk test; CAT score; Borg Dyspnoea Score; adverse events.

[44] Treatment allocation was stratified by centre and smoking status on a 1:1 basis.
[45] Defined as exacerbations that required treatment with oral corticosteroids and/or antibiotics or required hospitalisation.
[46] Exacerbation rates were analysed using a generalized linear model (assuming the negative binomial distribution) with number of exacerbations as the outcome and the log of time on treatment as an offset variable, with covariates of baseline smoking status, disease severity (% predicted FEV_1 at baseline), body mass index, number of exacerbations reported in the 12 months before screening, age, gender, and country. Adjusted mean rates per year and pairwise treatment ratios with P values and confidence intervals (CIs) were calculated. The incidence of exacerbations requiring hospitalization was compared between treatments using Fisher's exact test.
[47] Primary and secondary outcomes not specified.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
FLU/VIL vs TIO						
Covelli (2016) 1. N/A 2. Good quality 3. US, Canada, Czech Republic, Germany, Poland, Romania 4. GlaxoSmithKline	623	Superiority. Double-blind, double-dummy.[50] Subjects were stratified at randomisation for COPD exacerbation history[51] and for reversibility status.[52]	FLU/VIL 100/25 µg qd (n=310) TIO 18 µg qd (n=313)	Inclusion (1) Age ≥40 years, (2) clinical diagnosis of COPD, (3) post-bronchodilator FEV_1 between 30% and 70% of predicted normal and an FEV_1/FVC ratio ≤70% at screening, (4) a history of CVD/a CVD event or, in addition to being a current/former smoker, had at least one current CV risk factor (hypertension, hypercholesterolemia, or treated diabetes). Exclusion (1) History of asthma or respiratory disorders other than COPD, (2) recent (≤12 months) lung resection, (3) clinically significant abnormal chest X-ray, laboratory, Holter or electrocardiogram finding at screening, (4) recent (≤12 weeks) hospitalisation for COPD, (5) recent (≤6 weeks) acute worsening of COPD requiring treatment with corticosteroids or antibiotics, (6) noncompliance, COPD exacerbation, or LRTI during the run-in period, (7) long-term oxygen therapy (>12 hr/day). Other (1) Patients were required to discontinue COPD medications for a run-in period (systemic/oral/parenteral corticosteroids for 6 weeks prior; ICS or ICS/LABA combinations for 4 weeks prior; long-acting anticholinergics 1 week prior; and LABAs within 48 hours prior to screening), (2) albuterol was provided a rescue medication and was permitted for use throughout the study.	12 weeks; final (safety) follow up was performed 7 days after last treatment visit.	Primary Change from baseline in 24 hr weighted mean FEV_1 on Day 84. Secondary Time to onset of bronchodilation; trough FEV_1; other spirometry measures; use of rescue medication; symptoms; SGRQ; CAT score; inflammatory biomarkers (exploratory endpoint); safety (cardiovascular monitoring, cortisol excretion, COPD exacerbations, AEs).

Note: N refers to number randomised unless otherwise specified.

Abbreviations: AE, adverse event; AUC, area under the curve; BDI, Basline Dyspnea Index; bid, twice daily; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV_1, forced expiratory volume in one second; FLU, fluticasone furoate; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LRTI, lower respiratory tract infection; mMRC, modified Medical Research Council; N/A, not applicable; NR, not reported; OLO, olodaterol; PBO, placebo; qd, once daily; SGRQ, St George's Respiratory Questionnaire; SMETT, sub-maximal constant-load cycle ergometry exercise tolerance test; TDI, Transition Dyspnea Index; TIO, tiotropium; UK, United Kingdom; US, United States; VIL, vilanterol.

[48] Defined as any worsening of respiratory symptoms for three or more days that necessitated increased use of bronchodilators or additional administration of antibiotics and/or systemic steroids or that resulted in a visit to the emergency department and/or admission to hospital.

[49] Chi-square and Fisher's Exact test were performed for categorical variables. Student's t-test was done for variables which showed a normal distribution, and Mann-Whitney U test was done for variables that did not.

[50] Tiotropium and placebo capsules were closely matched in colour, but tiotropium capsules had trade markings that were not present on the placebo capsules. Whether subjects would notice and correctly or incorrectly interpret this difference is unclear. Both the tiotropium and placebo blister packages were covered with opaque overlabels that hide the information on the tiotropium packaging. HandiHalers were covered with labels to mask identifying marks.

[51] Either did or did not have ≥1 COPD exacerbation requiring oral corticosteroid and/or antibiotic treatment and/or hospitalisation in the 3 years prior to screening.

[52] Either reversible (defined as an increase in FEV_1 of ≥12% and ≥200 mL) or non-reversible (defined as an increase in FEV_1 <200 mL or ≥200 mL and <12% after albuterol administration at screening).

Fluticasone propionate/salmeterol versus tiotropium

INSPIRE study

The purpose of the INSPIRE study was to examine exacerbation rates and mortality over an extended period of time. As dictated by the inclusion criteria (see Table 3.65) the patient population in INSIRE had relatively severe COPD with a mean post-bronchodilator FEV_1 (percent predicted) at baseline of 39%. Exacerbations were also relatively frequent in this population, with 85% of patients randomised to fluticasone propionate/salmeterol and 88% of patients randomised to tiotropium reporting at least one exacerbation in the previous year.

The use of maintenance therapy was therefore high at baseline, with 48% of patients in the fluticasone propionate/salmeterol group and 51% in the tiotropium arm on ICS at study entry. In addition, 43% and 46% were on LABA maintenance therapy, respectively, and 13% and 14% were using a LAMA. All pre-existing COPD therapies were required to be discontinued prior to a two-week run-in period before baseline.

The comparative rate of exacerbations between the treatment groups is shown in Table 3.66. Based on the differences observed in the use of oral corticosteroids and antibiotics to treat exacerbations, the authors suggested that treatment with fluticasone propionate/salmeterol and tiotropium achieved similar exacerbation rates via different mechanisms.

Table 3.66 Number of exacerbations and rate of exacerbations per year – FLU/SAL vs TIO

Exacerbations	FLU/SAL (n=658)	TIO (n=665)	Rate ratio (95% CI)	p-value
HCU exacerbations, mean no. per year	1.28	1.32	0.97 (0.84, 1.12)	0.656
Requiring oral corticosteroids	0.69	0.85	0.81 (0.67, 0.99)	0.039
Requiring antibiotics	0.97	0.82	1.19 (1.02, 1.38)	0.028
≥1 exacerbation requiring therapeutic intervention, %	62	59	-	-
Exacerbations requiring hospitalisation, %	16	13	-	0.085

Source: Wedzicha et al (2008), Table 3.
Abbreviations: CI, confidence interval; FLU, fluticasone propionate; HCU, healthcare utilisation; SAL, salmeterol; TIO, tiotropium.

Overall mortality was relatively high in this study compared to the COPD literature in general; however, this is likely to be attributable to a relatively severe patient population and the long length of follow up. The risk of all-cause mortality was 52% lower in the fluticasone propionate/salmeterol treatment group, as represented by the statistically significant hazard ratio in Table 3.67.

Table 3.67 Mortality during the study period – FLU/SAL versus TIO

Exacerbations	FLU/SAL (n=658)	TIO (n=665)	HR (95% CI)	p-value
Mortality, n (%)	21 (3)	38 (6)	0.48 (0.27, 0.85)	0.012

Source: Wedzicha et al (2008), p 22.
Note: Time to death on treatment was analysed using the Cox proportional hazards model.
Abbreviations: CI, confidence interval; FLU, fluticasone propionate; HR, hazard ratio; SAL, salmeterol; TIO, tiotropium.

As shown in Table 3.68, the overall incidence of AEs was similar for fluticasone propionate/salmeterol (66%) and tiotropium (62%). Importantly, pneumonia was reported during treatment in 8% and 4% of patients, respectively, and the hazard ratio for time to

reported pneumonia (1.94; 95% CI: 1.19, 3.17) indicated a significant benefit of tiotropium in terms of pneumonia risk.

Table 3.68 Summary of mortality and safety outcomes in the ITT population – FLU/SAL vs TIO

Safety outcome	FLU/SAL (N=658)	TIO (N=665)
All-cause mortality, n (%)	21 (3)	38 (6)
During treatment	18 (3)	34 (5)
Event associated with death[a], n (%)	-	-
Cardiac disorders	9 (1)	19 (3)
Respiratory, thoracic and mediastinal disorders	5 (<1)	6 (<1)
Neoplasms benign, malignant and unspecified	2 (<1)	7 (1)
General disorders and administration site conditions	5 (<1)	2 (<1)
Infections and infestations	4 (<1)	0
Nervous system disorders	1 (<1)	2 (<1)
Vascular disorders	2 (<1)	0
Gastrointestinal disorders	0	1 (<1)
Hepatobiliary disorders	1 (<1)	0
Any AE, n (%)	435 (66)	414 (62)
COPD exacerbation	122 (19)	104 (16)
Pneumonia (including lobar pneumonia and bronchopneumonia)	50 (8)	24 (4)
Any SAE, n (%)	199 (30)	162 (24)

Source: Wedzicha et al (2008), Table 4.
Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; FLU, fluticasone propionate; SAE, serious adverse event; SAL, salmeterol; TIO, tiotropium.
a Deaths can be associated with more than one event.

Finally, it should be noted that patients randomised to tiotropium were significantly more likely to withdraw from the study than those randomised to fluticasone propionate/salmeterol (HR: 1.29; 95% CI 1.08, 1.54); however, the likelihood of withdrawal was comparable in those who had and had not been on ICS therapy prior to baseline.

Sarac (2016)

This study was a small, investigator-initiated RCT study (n=44) that also assessed the efficacy of fluticasone propionate/salmeterol versus tiotropium with respect to exacerbation risk. Exacerbation history at baseline was similar between the two treatment groups. Patients who were randomised to fluticasone/salmeterol experienced a mean of 2.2 ±2.1 exacerbations in the previous year, compared with 1.9 ±1.4 in patients randomised to tiotropium.

Overall, the mean number of exacerbations experienced during the year of this study was numerically lower in the fluticasone propionate/salmeterol treatment group; however, the difference was not statistically significant. The number of severe exacerbations was similar between the groups, though numerically lower in the fluticasone propionate/salmeterol group.

Table 3.69 Number of exacerbations during the follow-up period – FLU/SAL vs TIO

	FLU/SAL (n=22)	TIO (n=22)	p-value
Number of exacerbations, mean (SD)	1.2 ±1.7	2.1 ±2.2	0.070
Number of severe exacerbations,[a] mean (SD)	0.6 ±1.0	1.1 ±1.4	0.245
Time to first exacerbation in months, mean (SD)	4.2 ±4.0	4.2 ±3.3	0.697

Source: Sarac et al (2016), pg 114.
Abbreviations: FLU, fluticasone propionate; SAL, salmeterol; SD, standard deviation; TIO, tiotropium.
a Exacerbations that resulted in admission to the emergency department or hospital.

Furthermore, Sarac et al (2016) indicated that there was no difference in the rate of exacerbations between patients who reported frequent (two or more) exacerbations in the preceding year compared with those who reported one or fewer exacerbations.

However, it should be noted that the main weakness of the study was the small sample size and resulting high chance of type II error. Although the results numerically favoured fluticasone propionate/salmeterol, a statistically significant difference in exacerbations would have been difficult to observe, given the small number of patients who received each of the treatments.

Fluticasone furoate/vilanterol versus tiotropium

Covelli (2016)

The efficacy and safety of fluticasone furoate/vilanterol and tiotropium were compared in patients with or at risk of cardiovascular disease (CVD). Covelli et al (2016) highlighted the fact that concerns have previously been raised about the cardiovascular safety of both tiotropium and LABA therapies. While the patients recruited into this study had cardiovascular risk factors such as hypertension and hypercholesterolemia, nearly half had not experienced a COPD exacerbation in the three years before baseline.

The primary outcome was change from baseline in 24 hour weighted mean FEV_1 on Day 84; however, the study also reported other spirometry measures, including trough FEV_1. As shown in Table 3.70, the difference between treatment arms in terms of least squares mean change from baseline in trough FEV_1 amounted to only 5 mL and did not represent a statistically or clinically meaningful difference.

Table 3.70 Treatment differences in least squares mean for trough FEV_1 – FLU/VIL vs TIO

Trough FEV_1 (L)	FLU/VIL (n=268)	TIO (n=249)	LS mean change difference (95% CI)
Baseline, mean (SD)	1.35 (0.47)	1.35 (0.50)	-
Day 84, mean (SD)	1.43 (0.50)	1.43 (0.51)	-
LS mean change from baseline (SE)	0.098 (0.013)	0.093 (0.014)	0.005 (–0.029, 0.039)

Source: Covelli et al (2016), Table 3.
Abbreviations: CI, confidence interval; FLU, fluticasone furoate; LS, least squares; SE, standard error; SD, standard deviation; TIO, tiotropium; VIL, vilanterol.
Note: Secondary endpoints including change from baseline in trough FEV_1 were nested under the primary endpoint; however, the primary endpoint difference did not reach statistical significance and statistical inference cannot be made for trough FEV_1.
Abbreviations:

The safety profiles of fluticasone furoate/vilanterol and tiotropium in this study were comparable, despite minor differences in rates of pneumonia and COPD exacerbations (see Table 3.71). While more patients in the tiotropium arm experienced an exacerbation, the

study found that three of the eight exacerbations in the fluticasone furoate/vilanterol arm resulted in hospitalisation versus one of 11 in the tiotropium treatment group.

Table 3.71 Summary of safety outcomes – FLU/VIL versus TIO

Safety outcome	FLU/VIL (N=310)	TIO (N=313)
AEs during treatment, n (%)	113 (36)	99 (32)
Cardiovascular effects	13 (4)	15 (5)
Local steroid effects/candidiasis	17 (5)	11 (4)
LRTI excluding pneumonia	3 (<1)	4 (1)
Bone disorders/fractures	3 (<1)	1 (<1)
Pneumonia	3 (<1)	0
COPD exacerbation	7 (2)	11 (4)
Drug-related AE, n (%)	21 (7)	12 (4)
Any SAE, n (%)	10 (3)	10 (3)
AE leading to withdrawal, n (%)	6 (2)	14 (4)
Fatal AE, n (%)	0	2 (<1)[a]

Source: Covelli et al (2016), Table 4 and pg 9 (in text).
Abbreviations: AE, adverse event; FLU, fluticasone furoate; SAE, serious adverse event; LRTI, lower respiratory tract infection; TIO, tiotropium; VIL, vilanterol.
Note: Subjects who experienced a COPD exacerbation or pneumonia were withdrawn from the study. One patient in the fluticasone/vilanterol arm was withdrawn only after their second exacerbation.
a One due to cardiopulmonary arrest and the other due to cardiorespiratory arrest and cardiac failure.

Overall, the study indicated that the cardiovascular safety of both fluticasone furoate/vilanterol and tiotropium were acceptable; however, due to the short duration of the study (12 weeks) it is difficult to draw any firm conclusions about infrequent outcomes such as the incidence of CVD, pneumonia or risk of mortality.

Summary of findings:

- Wedzicha et al (2008; good quality) conducted an RCT over a two-year period to compare the effect of treatment with fluticasone propionate/salmeterol or tiotropium on the risk of exacerbations and mortality in patients with relatively severe COPD. The rate of exacerbations was similar in the two treatment groups; however, the nature of those exacerbations differed, with fluticasone propionate/salmeterol patients being significantly more likely to receive treatment with oral corticosteroids and tiotropium patients being treated significantly more often with antibiotics. While there was a significantly higher incidence of pneumonia with fluticasone propionate/salmeterol treatment, it was also associated with significant improvements in overall survival. More recent and larger studies examining the effect of ICS treatment on survival have subsequently become available and are discussed in Section 5 (ToR 4).
- Sarac et al (2016; poor quality) also compared exacerbation rates in patients treated with fluticasone propionate/salmeterol versus tiotropium. While the results numerically favoured the ICS/LABA combination, statistical significance was not achieved; however, the study may not have been sufficiently powered to detect a difference between the treatments.
- Covelli et al (2016; good quality) investigated the comparative efficacy and safety of fluticasone furoate/vilanterol and tiotropium in patients with CVD or at risk of a cardiovascular event. Both treatment groups demonstrated a similar magnitude of

improvement from baseline in terms of trough FEV_1. While fluticasone furoate/vilanterol and tiotropium were generally comparable with respect to safety, longer-term follow up may clarify the significance of some minor differences between the groups relating to pneumonia, exacerbations and withdrawals.

1.4.8 ICS/LABA versus LABA monotherapy

No studies were identified that directly compared the comparative efficacy of an ICS/LABA FDC with a PBS-listed LABA monotherapy (i.e. indacaterol).

One withdrawel RCT was identified that assessed the effect of switching patients who are at low risk of COPD exacerbations from fluticasone propionate/salmeterol to indacaterol monotherapy. The citation details are listed in Table 3.72 and study characteristics, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.73.

Table 3.72 List of RCTs comparing an ICS/LABA combination therapy with a LABA monotherapy

Trial ID	Citation	Description
INSTEAD	Rossi A, Van Der Molen T, Del Olmo R, Papi A, Wehbe L, Quinn M, et al (2014). INSTEAD: A randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. European Respiratory Journal 44 (6):1548-1556.	Key publication

Abbreviations: ICS, inhaled corticosteroid; LABA, long-actin g beta-agonist; RCT, randomised controlled trial.

Table 3.73 Details of RCTs comparing dual therapy with ICS/LABA with LABA monotherapy in patients with COPD

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
FLU/SAL vs IND						
INSTEAD 1. Rossi (2014) 2. Good quality 3. Argentina, Colombia, Italy, Malaysia, Mexico, Netherlands, Spain, Switzerland, UK 4. Novartis	581	Non-inferiority. Double-blind, double-dummy.	FLU/SAL 500/50 µg bid (n=288) IND 150 µg qd (n=293)	Inclusion (1) Age ≥40 years, (2), moderate COPD (Stage II – GOLD 2010), (3) receiving FLU/SAL 500/50 µg for ≥3 months, with no COPD exacerbations for more than a year before the study (patients for whom ICS is not recommended), (4) post-bronchodilator FEV_1 ≥50% and <80% of predicted normal, (5) post-bronchodilator FEV_1/FVC <0.7 at screening. Exclusion (1) COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalisation in the year before screening visit or during the run-in period, (2) history of asthma, (3) receiving any other maintenance treatment for COPD on entry to study (no washout of maintenance COPD medication was permitted), (4) long-term oxygen therapy, (5) respiratory tract infection within 4 weeks prior to the screening visit. Other (1) All patients received unblinded FLU/SAL for a 14-day run-in period, (2) salbutamol was provided as rescue medication.	26 weeks	Primary Trough FEV_1 at 12 weeks.[53] Secondary Trough FEV_1 at other visits; TDI total score; SGRQ total score at weeks 12 and 26; use of rescue medication; COPD exacerbations over 26 weeks;[54] trough inspiratory capacity (exploratory endpoint).

Note: N refers to number randomised unless otherwise specified.

Abbreviations: bid, twice daily; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FLU, fluticasone propionate; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; qd, once daily; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

[53] Mean of the FEV_1 measurements at 23 hr 10 min and 23 hr 45 mins after the morning dose on Day 84.

[54] COPD exacerbations were defined as worsening for at least two consecutive days of two or more of the major symptoms (dyspnoea, sputum volume or sputum purulence) or worsening of any one major symptom together with any one minor symptom (sore throat, colds (nasal discharge or nasal congestion), fever without other cause, cough or wheeze). Moderate exacerbations were those managed with antibiotics and/or oral corticosteroids; severe exacerbations were those that resulted in hospitalisation.

Fluticasone propionate/salmeterol versus indacaterol

INSTEAD study

This 26-week RCT assessed the effect of switching patients who are at low risk of COPD exacerbations from fluticasone propionate/salmeterol to indacaterol monotherapy. Patients were considered to be at low risk of exacerbations if they had post-bronchodilator FEV_1 ≥50% predicted normal and had experienced no more than one exacerbation in the previous year. Eligibility criteria also required patients to have received fluticasone propionate/salmeterol for at least three months prior to enrolment.

Interestingly, the patients recruited in this study represent a patient population in which ICS/LABA combinations are generally not recommended in clinical practice guidelines. However, given the significant proportion of such patients who are prescribed ICS early in the course of COPD, the authors felt that it would be helpful to understand the consequences of withdrawal of ICS in such populations.

Table 3.74 shows the results of the primary efficacy outcome (trough FEV_1 based on the per protocol population). The least squares mean change from baseline with indacaterol was –9 mL compared with fluticasone propionate/salmeterol and the lower bound of the 95% CI (–45 mL) was higher that the predefined non-inferiority margin of –60 mL. A subsequent test for superiority in the full analysis set demonstrated that the treatments were not significantly different.

Table 3.74 Change from baseline to Week 12 for trough FEV_1 – IND vs FLU/SAL

LS mean difference from baseline	IND 150		FLU/SAL 500/50		Treatment difference
	n	Mean ±SE	n	Mean ±SE	Δ (95% CI)
Trough FEV_1 at Week 12, L *Per protocol analysis*	247	1.584 ±0.0294	249	1.593 ±0.0300	–0.009 (–0.045, 0.026)
Trough FEV_1 at Week 12, L *Full analysis set*	293	NR	288	NR	–0.014 (–0.046, 0.019)

Source: Rossi et al (2014), pg 1550.
Note: The per protocol analysis was the primary efficacy analysis. Analysed using a mixed model, with treatment as a fixed effect and baseline FEV_1 and components of the FEV_1 screening test as covariates. The model also used smoking status and country as fixed effects, and centre nested within country as a random effect. Similar models, analysed for superiority, were used for the secondary and exploratory variables, with the relevant baseline parameter used in place of baseline FEV_1.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; FLU, fluticasone propionate; IND, indacaterol; LS, least squares; SAL, salmeterol; SE, standard error.

COPD exacerbations were assessed according to severity (i.e. mild, moderate and severe) as shown in Table 3.75. Across each of the categories of severity, there were no statistically significant differences between the treatments, with the results numerically favouring indacaterol (risk ratio for all exacerbations: 0.86; 95% CI 0.62, 1.20; p=0.367). It should be noted that the study was powered for lung function outcomes and not COPD exacerbations.

Table 3.75 Number and rate of exacerbations – IND vs FLU/SAL

Exacerbations	IND (n=293)	FLU/SAL (n=288)	IND (n=293)	FLU/SAL (n=288)	IND (n=293)	FLU/SAL (n=288)	IND (n=293)	FLU/SAL (n=288)
	All		Mild		Moderate		Severe	
Exacerbations per patient, n (%)	-	-	-	-	-	-	-	-
0	233 (79.5)	215 (74.7)	273 (93.2)	269 (93.4)	246 (84.0)	231 (80.2)	292 (99.7)	286 (99.3)
1	47 (16.0)	57 (19.8)	19 (6.5)	14 (4.9)	40 (13.7)	51 (17.7)	1 (0.3)	2 (0.7)
≥2	13 (4.5)	16 (5.5)	1 (0.3)	5 (1.7)	7 (2.4)	6 (2.1)	0	0
Total number of exacerbations	75	90	21	25	54	63	1	2
Rate of exacerbations per year	0.57	0.67	0.16	0.19	0.41	0.47	0.01	0.01

Source: Rossi et al (2014), pg 1550.
Note (1): The study was powered for lung function outcomes, not for exacerbations.
Note (2): The number of COPD exacerbations during the 26-week treatment period was analysed using a generalised linear model assuming a negative binomial distribution, and the proportions of patients achieving clinically relevant improvements in TDI and SGRQ-C were analysed using logistic regression.
Abbreviations: FLU, fluticasone propionate; IND, indacaterol; SAL, salmeterol.

Similarly, there was no statistically significant difference between fluticasone propionate/salmeterol and indacaterol with respect to the time to first moderate-to-severe exacerbation. The event-free rate at 6 months was 82.3% with indacaterol and 78.7% with fluticasone propionate/salmeterol.

Although the incidence of AEs and SAEs was higher in the fluticasone propionate/salmeterol group, there were no marked differences in the overall adverse event profiles between treatments, refer to Table 3.76.

Table 3.76 Results for safety outcomes relating to IND vs FLU/SAL – ITT population

Safety outcome	IND (N=293)	FLU/SAL (N=288)
Any AE, n (%)	131 (44.7)	154 (53.5)
Any SAE, n (%) Atrial fibrillation Pneumonia	5 (1.7) 0 0[a]	17 (5.9) 2 (0.7) 2 (0.7)
Death, n (%)	0	2 (0.7)[b]
Discontinuation due to AEs, n (%)	14 (4.8)	15 (5.2)
Discontinuation due to SAEs, n (%)	3 (1.0)	7 (2.4)

Source: Rossi (2014), Table 3.
Abbreviations: AE, adverse event; FLU, fluticasone propionate; IND, indacaterol; ITT, intention-to-treat; SAE, serious adverse event; SAL, salmeterol.
a One person in the IND group experienced pneumonia SAE 5 days after completing the study.
b One listed as sudden death and another due to mesothelioma. Neither of the deaths were suspected to be related to study medication.

While not all results from the INSTEAD study were reproduced in this review, the authors noted that there were also no clinically relevant differences between fluticasone propionate/salmeterol and indacaterol for dyspnoea (TDI), health staus (SGRQ) and use of rescue medication. The study concluded that the results observed in INSTEAD across a range of outcomes provide "strong and reassuring evidence to physicians that this type of patient can be switched from ICS/LABA to indacaterol" with no loss of efficacy and without triggering exacerbations.

Summary of findings

- In relation to trough FEV_1, indacaterol monotherapy demonstrated non-inferiority to fluticasone propionate/salmeterol over a 12-week period in patients at low risk of exacerbations (Rossi et al, 2014; good quality). No statistically significant differences were observed between the two treatment groups with respect to

exacerbations of any severity. Overall, the study demonstrated that patients with moderate airflow limitation and a history of no exacerbations in the previous year can withdraw from fluticasone propionate/salmeterol to indacaterol without any loss in efficacy.

1.4.9 ICS/LABA + LAMA versus ICS/LABA

As discussed in Section 2, COPD patients generally initiate maintenance therapy with long-acting bronchodilator monotherapy before stepping up to dual and then triple therapy as the severity of COPD worsens. As such, the PBAC is interested in clarifying whether there is additional benefit of moving from dual therapy to triple therapy, and in which patients this may be appropriate.

The two studies listed in Table 3.77 contribute towards the evidence base for this question and are discussed in detail throughout this section.

Table 3.77 List of RCTs comparing an ICS/LABA (dual therapy) with an ICS/LABA plus LAMA (triple therapy)

Trial ID	Citation	Description
Siler (2015)	Siler TM, Kerwin E, Sousa AR, Donald A, Ali R and Church A (2015). Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. Respiratory Medicine 109 (9):1155-1163.	Key publication
Sousa (2016)	Sousa AR, Riley JH, Church A, Zhu CQ, Punekar YS and Fahy WA (2016). The effect of umeclidinium added to inhaled corticosteroid/long-acting beta-2-agonist in patients with symptomatic COPD: A randomised, double-blind, parallel-group study. NPJ Primary Care Respiratory Medicine 26 (no pagination)(16031).	Key publication

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; RCT, randomised controlled trial.

The characteristics of the two relevant studies, such as the patient eligibility criteria, length of follow up and outcomes assessed, are summarised in Table 3.78. The results reported in each study that are of relevance to this review are then outlined in subsections according the specific treatment comparisons.

Table 3.78 Details of RCTs comparing triple therapy (ICS/LABA + LAMA) with dual therapy (ICS/LABA) in patients with COPD

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
FLU/VIL+UME vs FLU/VIL+PBO						
Siler (2015) 1. N/A 2. Good quality 3. US, Argentina, Canada, Chile, Czech Republic, Germany, Republic of Korea, Romania 4. GlaxoSmithKline	619 (Study 1); 620 (Study 2)	Superiority. Two replicate studies. Double-blind, placebo-controlled.	Study 1 FLU/VIL 100/25 µg + UME 62.5 µg (n=206)[55] FLU/VIL 100/25 µg + UME 125 µg (n=207)[56] FLU/VIL 100/25 µg + PBO (n=206) Study 2 FLU/VIL 100/25 µg + UME 62.5 µg (n=206)[57] FLU/VIL 100/25 µg + UME 125 µg (n=207)[58] FLU/VIL 100/25 µg + PBO (n=206)	Inclusion (1) Age ≥40 years, (2) established clinical history of COPD, (3) pre- and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and pre- and post-albuterol/salbutamol FEV_1 of ≤70% of predicted normal values at screening, (4) a score of ≥2 on the mMRC Dyspnea Scale at screening. Exclusion (1) Current diagnosis of asthma, (2) other respiratory disorders, (3) history or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled and/or a previous history of cancer in remission for <5 years prior to screening, (4) hospitalisation for COPD or pneumonia within 12 weeks prior to screening or LRTI that required antibiotics within 6 weeks prior to screening, (5) use of long-term oxygen therapy. Other (1) Patients underwent 4 weeks' run-in treatment with open-label FLU/VIL 100/25 µg prior to the treatment period; (2) patients were required to discontinue most COPD medications for a run-in period (systemic/oral/parenteral corticosteroids for 16 weeks prior; ICS until Visit 1; ICS/LABA combinations for 48 hours prior; long-acting muscarinic antagonists 1 week prior; and LABAs olodaterol and indacaterol 10 days prior to Visit 1), (3) use of salbutamol as rescue medication was permitted throughout the study, except during the 4 hrs prior to spirometry testing.	12 weeks	Primary Trough FEV_1 on Day 85.[59] Secondary Weighted mean FEV_1 from 0-6 hrs on Day 84; proportion of patients achieving an increase of ≥0.100 L above baseline in trough FEV_1; proportion of patients achieving an increase in FEV_1 of ≥12% and ≥0.200 L above baseline; peak FEV_1 at days 1, 28 and 84; time to onset of treatment response; serial and trough FVC at each timepoint; CAT score; SGRQ; rescue-free days; safety (AEs, vital signs, COPD exacerbations).

[55] FLU/VIL treatment was open label; UME and PBO were double-blind.
[56] Results not reported for this treatment group because umeclidinium 125 µg is not a PBS-listed dose.
[57] FLU/VIL treatment was open label; UME and PBO were double-blind.
[58] Results not reported for this treatment group because umeclidinium 125 µg is not a PBS-listed dose.
[59] Defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on day 84.

Trial ID 1. Related publications 2. Study quality 3. Country 4. Sponsor	N	Study design	Tx (n)	Eligibility criteria	Treatment period	Outcomes reported
ICS/LABA+UME vs ICS LABA+PBO						
Sousa (2016) 1. N/A 2. Fair quality 3. Czech Republic, Germany, Greece, Netherlands 4. GlaxoSmithKline	236	Superiority. Double-blind. Note: ICS/LABA was open-label. Blinding refers to UME and PBO treatments.	ICS/LABA bid + PBO qd (n=117) ICS/LABA bid + UME 62.5 µg qd (n=119) ICS/LABAs included FLU/SAL 500/500 µg bid, BUD/EFO 200/6 or 400/12 µg bid, or other ICS/LABAs with the exception of FLU/SAL 250/50 µg bid and FLU/VIL 100/25 µg qd.[60]	Inclusion (1) Age ≥40 years, (2) established clinical history of COPD, (3) receiving ICS/LABA at doses and frequencies approved for COPD ≥30 days before the run-in period of 7 ±2 days, (4) pre- and post-albuterol/salmeterol FEV_1/FVC ratio of <0.7 and a pre- and post-albuterol/salbutamol FEV_1 ≤070% of the predicted normal values, (5) dyspnoea score of ≥2 on the mMRC Dyspnea Scale at Visit 1, (6) remained symptomatic after receiving one of the ICS/LABA combinations approved for COPD ≥30 days before screening. Exclusion (1) Current diagnosis of asthma, (2) hospitalisation for COPD or pneumonia within 12 weeks prior to Visit 1, (3) LRTI requiring antibiotic use within 6 weeks of Visit 1, (4) use of long-term oxygen therapy (>12 hrs per day), (5) evidence of concurrent respiratory disease or other clinically significant medical condition. Other (1) Patients were required to discontinue most COPD medications for a run-in period (systemic/oral/parenteral corticosteroids for 6 weeks prior; LAMAs 1 week prior; LABAs olodaterol and indacaterol 14 days prior to Visit 1 and LABAs salmeterol and formoterol 48 hrs prior to Visit 1.	12 weeks	Primary Trough FEV_1 on Day 85 (defined as the mean of FEV_1 values obtained at 23 and 24 hrs after dosing on Day 84). Secondary Weighed mean FEV_1 from 0-6 hrs on Day 84; trough FEV_1 and weighted mean FEV_1 at other time points; proportion of patients achieving an increase in FEV_1 of ≥12% and ≥200 mL above baseline at any time during 0-6 hrs post-dose on Day 1; peak FEV_1, trough and serial FVC; use of rescue medication; TDI focal score on Day 84; CAT score; SGRQ; safety (AEs, clinical laboratory tests, vital signs, COPD exacerbations).

Note: N refers to number randomised unless otherwise specified.

Abbreviations: AE, adverse event; AUC, area under the curve; BDI, Basline Dyspnea Index; bid, twice daily; BUD, budesonide; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EFO, eformoterol; FEV_1, forced expiratory volume in one second; FLU, fluticasone; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LRTI, lower respiratory tract infection; mMRC, modified Medical Research Council; N/A, not applicable; OLO, olodaterol; PBO, placebo; qd, once daily; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; SMETT, sub-maximal constant-load cycle ergometry exercise tolerance test; TDI, Transition Dyspnea Index; TIO, tiotropium; UK, United Kingdom; UME, umeclidinium; VIL, vilanterol; FLU/SAL, fluticasone propionate/salmeterol; FLU/VIL, fluticasone furoate/vilanterol.

[60] The authors stated that previous studies have investigated FLU/SAL 250/50 and FLU/VIL 100/25.

Fluticasone furoate/vilanterol with or without umeclidinium

Siler (2015)

Two replicate 12-week studies assessed whether the addition of umeclidinium to fluticasone furoate/vilanterol would lead to improvements in trough FEV_1 as well as other lung function outcomes or quality of life. The patient disease characteristics were similar between the studies and treatment groups, although Study 2 had a slightly higher proportion of GOLD Stage II patients (46-50% compared with 40-41%); whereas, Study 1 had more GOLD stage III patients (44-48% versus 40-42%). Across both studies 10–17% of patients were classified as having GOLD stage IV COPD based on measures of lung function (i.e. previous GOLD criteria).

Interestingly, despite only minor differences in disease severity, there were noticeable differences in existing COPD medication at baseline. In Study 1, 63% of patients were on ICS therapy compared with 46% in Study 2; whereas, a higher proportion of patients were receiving LAMA medications in Study 2, 46%, compared with 22% in Study 1. LABA therapy was similar at 61% and 62% in Study 1 and 2, respectively.

The primary endpoint was trough FEV_1 at Day 85 and the MCID was predefined as 0.100 L. As shown in Table 3.79, triple therapy with PBS-listed doses of fluticasone furoate/vilanterol (100/25 µg) plus umeclidinium (62.5 µg) was associated with clinically meaningful improvements in trough FEV_1 at Day 85 versus dual therapy with fluticasone furoate/vilanterol (plus placebo). Figure 3.10 demonstrates that the significant difference between triple and dual therapy was observed throughout the duration of the 12-week study.

Table 3.79 Results for change from baseline for trough FEV_1 for the ITT population – FLU/VIL+PBO vs FLU/VIL+UME

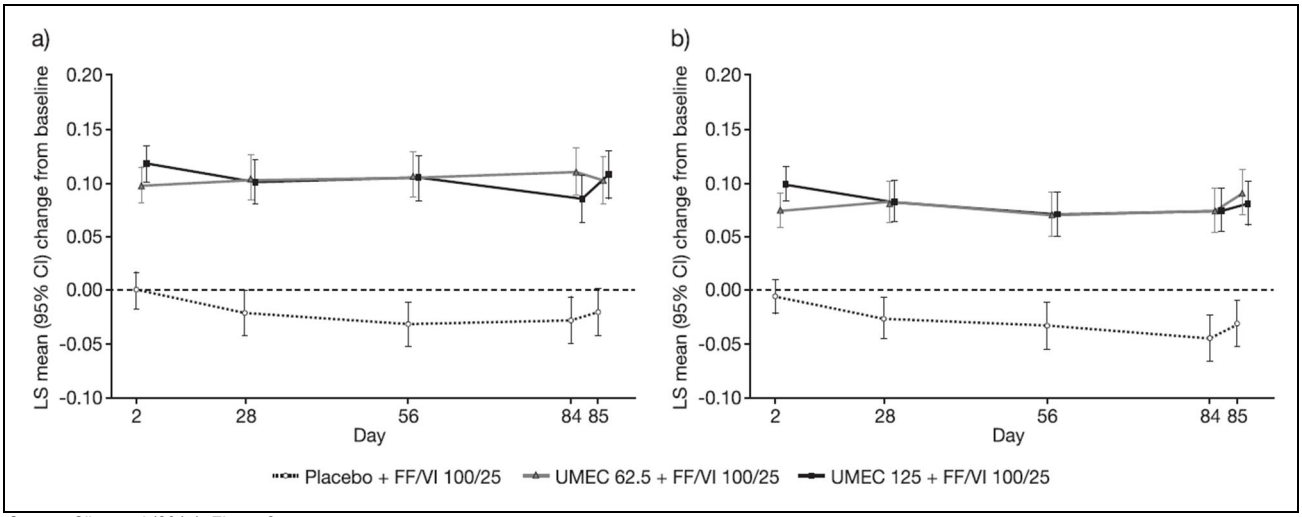
LS mean change from baseline	FLU/VIL + PBO (N=206)		FLU/VIL + UME (N=206)		Treatment difference	p-value
Trough FEV_1 at Day 85, L	n	Mean ±SE	n	Mean ±SE	Δ (95% CI)	
Study 1	190	–0.020 (0.011)	195	0.103 (0.011)	0.124 (0.093, 0.154)	≤0.001
Study 2	179	–0.030 (0.011)	195	0.092 (0.011)	0.122 (0.091, 0.152)	≤0.001

Source: Siler et al (2015), Table 2.

Note: Analysed using mixed models repeated measures analysis, with treatment, baseline FEV_1, smoking status, and day as covariates. Day-by-baseline and day-by-treatment were included as interactions. To account for multiplicity, a step-down closed testing hierarchy was employed. The fluticasone furoate/vilanterol plus umeclidinium combination with the higher (non-PBS) dose umeclidinium was tested for the primary endpoint, followed by the dose of interest to this review (i.e. fluticasone furoate/vilanterol 100/25 µg plus umeclidinium 62.5 µg).

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone; ITT, intention-to-treat; LS, least squares; PBO, placebo; SE, standard error; UME, umeclidinium; VIL, vilanterol; FLU/VIL, fluticasone furoate/vilanterol.

Figure 3.10 Least squares (95% CI) mean change from baseline in trough FEV_1 in Study 1 (a) and Study 2 (b) in the ITT population – FLU/VIL + UME vs FLU/VIL + PBO



Source: Siler et al (2015), Figure 2.
Note:). Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 min and 5 min pre-dose on Day 1), smoking status, Day, Day by baseline and Day by treatment interactions.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; ITT, intent-to-treat; FF/VI, fluticasone furoate/vilanterol combination; FLU, fluticasone; LS, least squares; PBO, placebo; UME or UMEC, umeclidinium; VIL, vilanterol.

The likelihood of achieving an increase in FEV_1 of ≥0.100 L above baseline was also substantially greater with fluticasone furoate/vilanterol plus umeclidinium therapy with odds ratios ranging between 4.8 and 5.6 in Study 1 and 2, respectively (see Table 3.80).

Table 3.80 Patients achieving an increase in trough FEV_1 of ≥0.100L above baseline at Day 85 – ITT population

Trough FEV_1 ≥0.100L above baseline	FLU/VIL+PBO (N=206)	FLU/VIL+UME (N=206)	OR (95% CI)	p-value
Proportion of patients at Day 85, n/N (%)	-	-	-	-
Study 1	27/205 (13)	94/206 (46)	5.6 (3.4, 9.1)	≤0.001
Study 2	28/205 (14)	88/206 (43)	4.8 (2.9, 7.8)	≤0.001

Source: Siler et al (2015), Table 2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; FLU, fluticasone; ITT, intent-to-treat; OR, odds ratio; PBO, placebo; UME, umeclidinium; VIL, vilanterol; FLU/VIL, fluticasone furoate/vilanterol.

Table 3.81 shows that both treatments were well tolerated with no unexpected safety findings, although the duration of treatment was relatively short.

It should be noted that the trial duration was insufficient to determine any comparative effects on COPD exacerbation rates. As such, exacerbations were considered as a safety outcome only. In addition, while HRQoL was measured in the studies, the results were inconsistent and the authors provided several explanations for this including: (i) noticeable improvements in HRQoL may have occurred during the 4-week run-in period when all patients received fluticasone furoate/vilanterol, before randomisation to umeclidinium or placebo, making further improvements difficult to detect; and (ii) existing PRO tools may lack adequate sensitivity to detect differences between two active treatments, where the magnitude of treatment difference would be expected to be lower.

These studies were only 12 weeks in duration, which is considered a sufficient period of time to observe sustained effects in lung function. However, longer studies with a patient

population with a history of exacerbations would be needed to assess the benefit of this triple therapy on COPD exacerbations compared with ICS/LABA therapy.

Table 3.81 Summary of safety results relating to FLU/VIL+PBO versus FLU/VIL+UME – ITT population

Safety outcome	FLU/VIL+PBO (N=206)		FLU/VIL+UME (N=206)	
	Study 1	Study 2	Study 1	Study 2
Any on-treatment AE, n (%)	72 (35)	81 (39)	75 (36)	67 (33)
COPD exacerbation	7 (3)	17 (8)	6 (3)	6 (3)
Pneumonia	3 (1)	1 (<1)	0	2 (<1)
LRTI excluding pneumonia	2 (<1)	0	2 (<1)	0
Cardiovascular AE	6 (3)	6 (3)	5 (2)	2 (<1)
Any on-treatment drug-related AE, n (%)	15 (7)	7 (3)	15 (7)	6 (3)
Any on-treatment SAE, n (%)	6 (3)	11 (5)	2 (<1)	8 (4)
AE leading to permanent discontinuation of medication/withdrawal, n (%)	5 (2)	9 (4)	3 (1)	7 (3)
Fatal AEs, n (%)	1 (<1)	4 (2)	0	1 (<1)

Source: Siler et al (2015), Table 3.
Abbreviations: AE, adverse events; COPD, chronic obstructive pulmonary disease; FLU, fluticasone; LRTI, lower respiratory tract infection; PBO, placebo; SAE, serious adverse events; UME, umeclidinium; VIL, vilanterol; FLU/VIL, fluticasone furoate/vilanterol.

Any ICS/LABA with or without umeclidinium

Sousa (2016)

The aim of this study was to assess the efficacy and safety of adding umeclidinium to ICS/LABAs in patients who were already receiving ICS/LABA therapy[61] for at least 30 days before enrolment, but remained symptomatic. In terms of baseline characteristics, there was a smaller proportion of high risk (GOLD D)[62] patients in the ICS/LABA plus umeclidinium group than the ICS/LABA plus placebo group. The umeclidinium group also experienced fewer exacerbations in the year before enrolment compared with the placebo group.

The primary outcome was change from baseline in trough FEV_1 at Day 85 and a post hoc sensitivity analysis was also conducted to test for differences between different ICS/LABA combinations.

As shown in Table 3.82, the addition of umeclidinium to an ICS/LABA produced statistically significant and clinically meaningful improvements in trough FEV_1, that were observed throughout the trial (see Figure 3.11).

In relation to the subgroup analysis, comparable improvements were observed in trough FEV_1 with fluticasone propionate/salmeterol and budesonide/eformoterol, suggesting that there is little difference between these background ICS/LABA therapies. The subgroup that included 'other' ICS/LABAs did not demonstrate significant differences between umeclidinium and placebo; however, this may have resulted from the small number of patients in the subgroup.

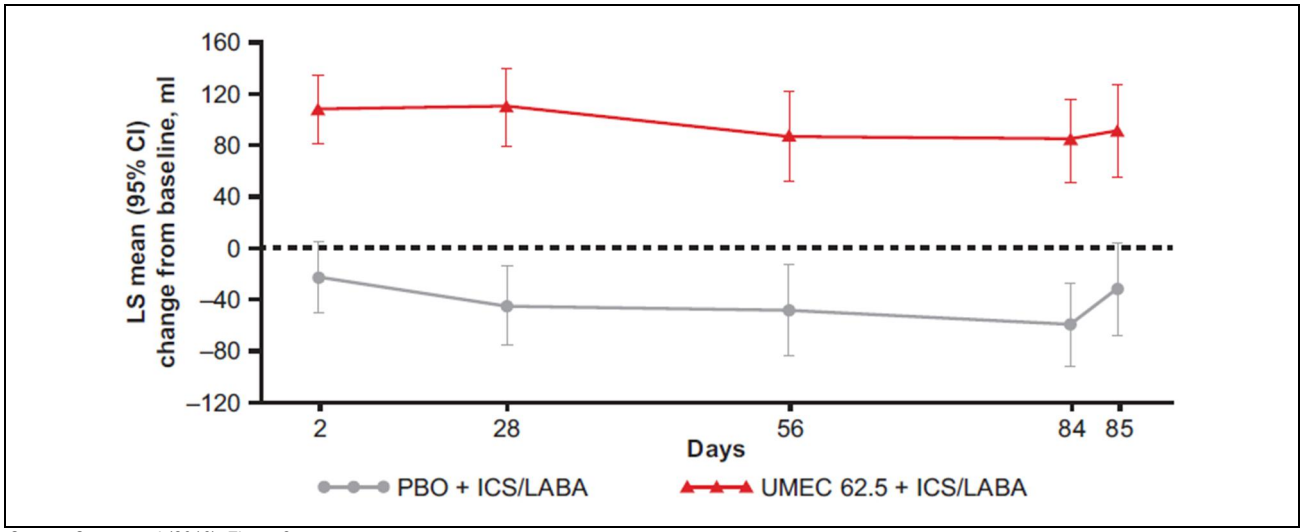
[61] Of the patients who were randomised to umeclidinium or placebo, 40% were taking fluticasone propionate/salmeterol, 43% were taking budesonide/eformoterol, and 17% were taking other ICS/LABA combinations including generics (but excluding fluticasone propionate/salmeterol 250/50 µg and fluticasone furoate/vilanterol 100/25 µg).
[62] Using the mMRC Dyspnea Scale.

Table 3.82 Results for change from baseline for trough FEV_1 at Day 85 – ICS/LABA+PBO vs ICS/LABA+UME

LS mean change from baseline	ICS/LABA + PBO (N=117)		ICS/LABA + UME (N=119)		Treatment difference	p-value
Overall	**n**	**Mean ±SE**	**n**	**Mean ±SE**	**Δ (95% CI)**	
Trough FEV_1 at Day 85, mL	110	–33 (18.4)	109	90 (18.3)	123 (71, 174)	<0.001
Post hoc analysis of trough FEV_1 by ICS/LABA subgroup[a]						
FLU/SAL	42	-	42	-	156 (77, 235)	<0.001
BUD/EFO	49	-	49	-	130 (55, 204)	<0.001
Other ICS/LABA combinations[b]	19	-	18	-	50 (–106, 207)	0.519

Source: Sousa et al (2016), Table 2.
Abbreviations: BUD, budesonide; CI, confidence interval; EFO, eformoterol; FEV_1, forced expiratory volume in one second; FLU, fluticasone; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LS, least squares; PBO, placebo; SAL, salmeterol; SE, standard error; UME, umeclidinium.
Note: Trough FEV_1 at Day 85 was analysed for the ITT population using a mixed model repeated measures analysis, including trough FEV_1 recorded at each of days 2, 28, 56, 84 and 85. The model included covariates of baseline FEV_1, type of ICS/LABA (FP/SAL, BD/FOR or other), smoking status, day, treatment and day-by-baseline interaction, where day is nominal. A day-by-treatment interaction term was also included to allow treatment effects to be estimated at each visit separately.
a The study was not powered to detect differences between ICS/LABA subgroups.
b Not including fluticasone propionate/salmeterol 250/50 µg or fluticasone furoate/vilanterol 100/25 µg.

Figure 3.11 LS mean (95% CI) change from baseline in trough FEV_1 – ITT population



Source: Sousa et al (2016), Figure 2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; ITT, intent-to-treat; LS, least squares; LABA, long-acting β2-agonist; PBO, placebo; UMEC, umeclidinium.

The proportion of patients that achieved an increase in trough FEV_1 of ≥0.100 L was also substantially higher with triple therapy compared with dual therapy (see Table 3.83).

Table 3.83 Patients achieving an increase in trough FEV_1 of ≥0.100L above baseline at Day 85 – ITT population

Trough FEV_1 ≥0.100L above baseline	ICS/LABA+PBO (N=117)	ICS/LABA+UME (N=119)	OR (95% CI)	p-value
Proportion of patients at Day 85, n/N (%)	19/117 (16)	55/119 (46)	4.8 (2.6, 9.1)	<0.001

Source: Sousa et al (2016), Table 2.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β2-agonist; OR, odds ratio; PBO, placebo; UME, umeclidinium.

On-treatment AEs were similar between the ICS/LABA plus umeclidinium and ICS/LABA plus placebo treatment groups, as were the number of SAEs. The number of patients who experienced COPD exacerbations was also balanced between the groups (see Table 3.84).

Table 3.84 Summary of safety results relating to ICS/LABA+PBO versus ICS/LABA+UME – ITT population

Safety outcome	ICS/LABA+PBO (N=117)	ICS/LABA+UME (N=119)
Any on-treatment AE, n (%)	49 (42)	45 (38)
COPD exacerbation	16 (14)	17 (14)
Pneumonia	2 (2)	3 (3)
Any on-treatment drug-related SAE, n (%)	0	0
Any on-treatment non-fatal SAE, n (%)	4 (3)	6 (5)
Any on-treatment fatal SAEs, n (%)	1 (<1)[a]	0
AE leading to permanent discontinuation of medication/withdrawal, n (%)	3 (3)	7 (6)

Source: Sousa et al (2016), Table 3.
Abbreviations: AE, adverse event; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β2-agonist; PBO, placebo; SAE, serious adverse event; UME, umeclidinium.
a Not drug-related (road traffic accident).

Summary of findings

- Siler et al (2015; good quality) reported the results from two replicate RCTs that demonstrated that the addition of umeclidinium to fluticasone furoate/vilanterol provided statistically significant and clinically meaningful improvements in lung function compared with fluticasone furoate/vilanterol plus placebo.
- Similarly, Sousa et al (2016; fair quality) observed statistically significant and clinically meaningful improvements in trough FEV_1 after 12 weeks when umeclidinium was added to ICS/LABAs, compared with ICS/LABA plus placebo, in a study where the patient population were already on ICS/LABA dual therapy, but remained symptomatic at baseline.
- Longer-term studies are needed to confirm the benefits of triple therapy with ICS/LABA plus a LAMA over ICS/LABA therapy alone. At least one ongoing study will assess the comparative efficacy of a fixed-dose triple combination of fluticasone furoate/umeclidinium/vilanterol with two fixed-dose dual combinations, fluticasone furoate/vilanterol and umeclindium/vilanterol (the IMPACT study, due for completion in 2017).
- The PBAC has previously seen evidence from the GLISTEN study that compared the efficacy of glycopyrronium plus fluticasone propionate/salmeterol versus fluticasone propionate/salmeterol alone (November 2015 PSD for glycopyrronium). Interim results from the study up to Week 12 indicated that triple therapy provided statistically significant improvements in trough FEV_1 compared to fluticasone propionate/salmeterol alone (Frith et al, 2015).

1.4.10 ICS/LABA + LAMA versus LAMA/LABA

No RCTs or large observational studies were identified that examined the comparative efficacy and safety of ICS/LABA + LAMA (or ICS + LAMA/LABA) versus LAMA/LABA. A recent Cochrane review also failed to identify any ongoing or completed RCTs comparing the treatment of stable COPD with ICS plus combination LAMA/LABA inhalers against combination LAMA/LABA inhalers alone (Tan et al, 2016).

This evidence gap is somewhat surprising, considering that the step up from LAMA/LABA to triple therapy (LAMA plus LABA plus ICS) is in keeping with recommendations from clinical practice guidelines for patients at high risk of exacerbations.