

Supplementary material

Figure S1. Literature search flow diagram of relevant studies

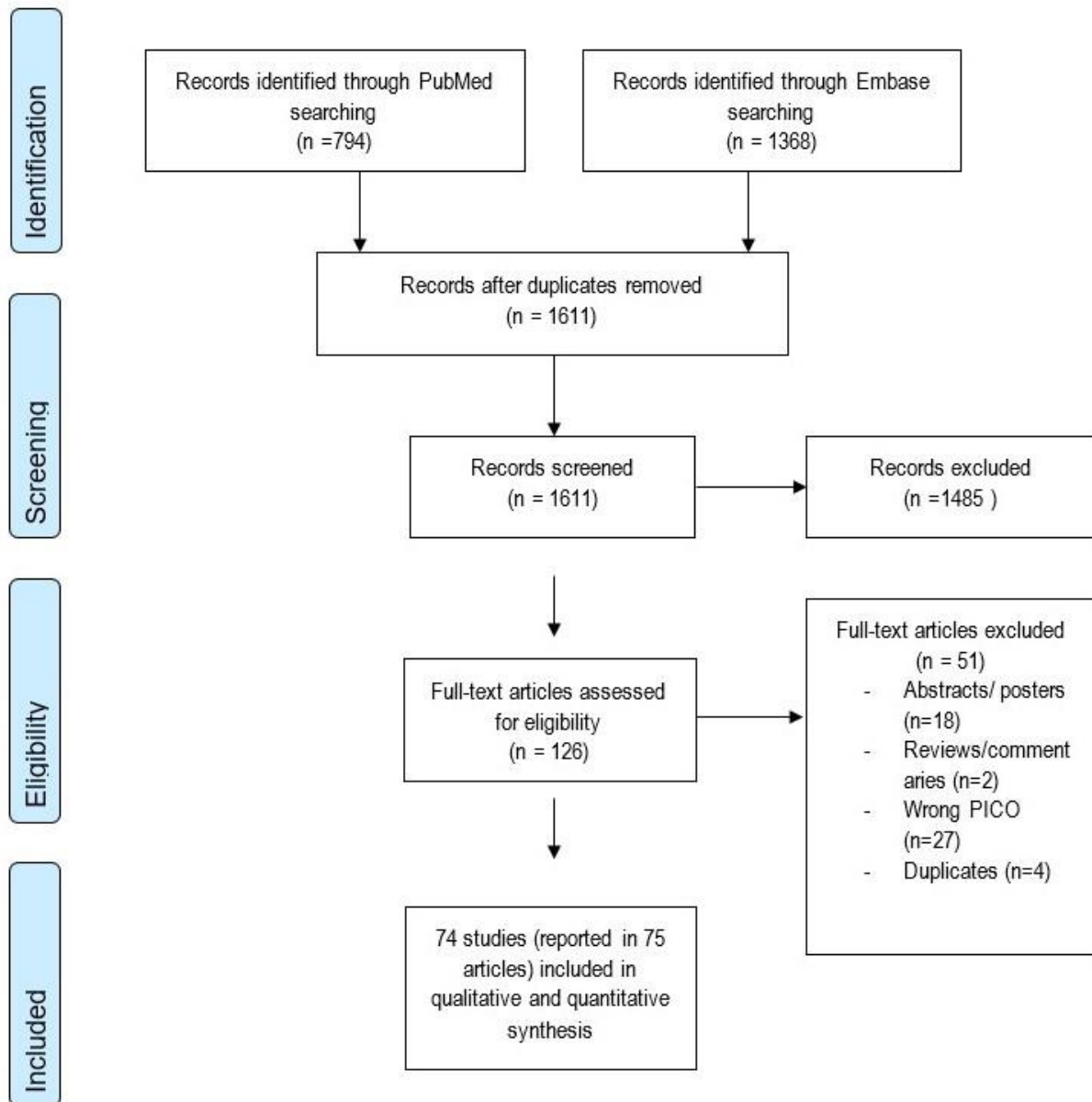


Table S1 Pubmed and Embase search strategies

Pubmed search strategy
<p>((((((((((((((("Tiotropium Bromide"[Mesh] OR ("tiotropium bromide"[MeSH Terms] OR ("tiotropium"[All Fields] AND "bromide"[All Fields]) OR "tiotropium bromide"[All Fields] OR "tiotropium"[All Fields]) OR ("tiotropium bromide"[MeSH Terms] OR ("tiotropium"[All Fields] AND "bromide"[All Fields]) OR "tiotropium bromide"[All Fields] OR "spiriva"[All Fields])) OR ("GSK573719"[Supplementary Concept] OR ("GSK573719"[Supplementary Concept] OR "GSK573719"[All Fields] OR "umeclidinium"[All Fields]) OR INCRUSE[All Fields])) OR ("Glycopyrrolate"[Mesh] OR glycopyrronium[All Fields] OR SEEBRI[All Fields])) OR ("Muscarinic Antagonists"[Mesh] OR LAMA[All Fields])) OR ("aclidinium bromide"[Supplementary Concept] OR aclidinium[All Fields] OR EKLIRA[All Fields])) OR ("indacaterol"[Supplementary Concept] OR ("indacaterol"[Supplementary Concept] OR "indacaterol"[All Fields])) OR ("olodaterol"[Supplementary Concept] OR ("olodaterol"[Supplementary Concept] OR "olodaterol"[All Fields])) OR ("vilanterol"[Supplementary Concept] OR ("vilanterol"[Supplementary Concept] OR "vilanterol"[All Fields])) OR ("Formoterol Fumarate"[Mesh] OR ("formoterol fumarate"[MeSH Terms] OR ("formoterol"[All Fields] AND "fumarate"[All Fields]) OR "formoterol fumarate"[All Fields] OR "formoterol"[All Fields])) OR ("Ipratropium"[Mesh] OR ("ipratropium"[MeSH Terms] OR "ipratropium"[All Fields]) OR ("ipratropium"[MeSH Terms] OR "ipratropium"[All Fields] OR "atrovent"[All Fields])) OR ("fluticasone-salmeterol drug combination"[MeSH Terms] OR ("fluticasone-salmeterol"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "fluticasone-salmeterol drug combination"[All Fields] OR "seretide"[All Fields])) OR ("Budesonide, Formoterol Fumarate Drug Combination"[Mesh] OR ("budesonide, formoterol fumarate drug combination"[MeSH Terms] OR ("budesonide"[All Fields] AND "formoterol"[All Fields] AND "fumarate"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "formoterol fumarate drug combination budesonide"[All Fields] OR "symbicort"[All Fields])) OR ("fluticasone furoate-vilanterol trifenate"[Supplementary Concept] OR BREO[All Fields] OR RELVAR[All Fields] OR REVINTY[All Fields])) OR ("QVA149"[Supplementary Concept] OR ULTIBRO[All Fields])) OR ("tiotropium-olodaterol"[Supplementary Concept] OR SPIOLTO[All Fields])) OR ANORO[All Fields] OR DUAKLIR[All Fields] AND ("Pulmonary Disease, Chronic Obstructive"[Mesh] OR ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]) OR ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields]))</p>
Embase search strategy
<p>('chronic obstructive lung disease'/exp OR 'chronic obstructive lung disease' OR 'copd'/exp OR copd OR 'chronic obstructive pulmonary disease'/exp OR 'chronic obstructive pulmonary disease') AND (('tiotropium bromide'/exp OR tiotropium OR spiriva) OR ('umeclidinium'/exp OR umeclidinium OR incuse) OR ('glycopyrronium'/exp OR glycopyrronium OR seebri) OR ('muscarinic receptor blocking agent'/exp OR lama) OR ('aclidinium bromide'/exp OR aclidinium OR eklira) OR ('indacaterol'/exp OR indacaterol) OR ('olodaterol'/exp OR olodaterol) OR ('vilanterol'/exp OR vilanterol) OR ('formoterol'/exp OR formoterol) OR ('ipratropium bromide'/exp OR ipratropium OR atrovent) OR ('fluticasone propionate plus salmeterol'/exp OR seretide) OR ('budesonide plus formoterol'/exp OR symbicort) OR ('fluticasone furoate plus vilanterol'/exp OR breo OR relvar) OR ('glycopyrronium bromide plus indacaterol'/exp OR ultibro) OR ('olodaterol plus tiotropium bromide'/exp OR spiolto) OR ('umeclidinium plus vilanterol'/exp OR anoro) OR ('aclidinium bromide plus formoterol fumarate'/exp OR duaklir)</p>

Table S2 Treatment effects on TDI score at weeks 12 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

		Direct evidence											
		Placebo	NA	NA	NA	-1.07 (-1.44,-0.69)	-1.63 (-2.46,-0.79)	-1.22 (-1.75,-0.69)	-0.93 (-1.34,-0.52)	-0.78 (-1.12,-0.43)	-0.99 (-0.16,-0.82)	-1.03 (-1.85,-0.21)	-0.78 (-1.04,-0.52)
NMA results (combining direct and indirect estimates)	-0.18 (-0.72,0.36)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.62 (-1.13,-0.11)
	-0.82 (-1.21,-0.43)	-0.64 (-1.28,0.00)	SFC250	NA	-0.30 (-0.62,0.02)	NA	NA	NA	NA	NA	NA	NA	NA
	-1.12 (-1.45,-0.79)	-0.94 (-1.55,-0.34)	-0.31 (-0.74,0.12)	SFC500	0.10 (-0.25,0.45)	NA	-0.36 (-0.66,-0.05)	NA	NA	NA	NA	NA	NA
	-1.12 (-1.34,-0.89)	-0.94 (-1.49,-0.38)	-0.30 (-0.62,0.02)	0.01 (-0.28,0.30)	UmecVil	NA	NA	0.33 (-0.07,0.72)	NA	NA	NA	NA	0.40 (0.11,0.70)
	-1.63 (-2.00,-1.25)	-1.44 (-2.10,-0.78)	-0.81 (-1.35,-0.27)	-0.50 (-1.00,-0.00)	-0.51 (-0.94,-0.07)	TioOlo	NA	NA	NA	NA	NA	0.60 (0.22,0.97)	NA
	-1.42 (-1.74,-1.09)	-1.24 (-1.83,-0.64)	-0.60 (-1.04,-0.15)	-0.29 (-0.54,-0.04)	-0.30 (-0.61,0.01)	0.21 (-0.29,0.70)	IndaGlyco	NA	0.41 (-0.03,0.85)	NA	NA	NA	0.63 (0.19,1.07)
	-0.88 (-1.13,-0.64)	-0.70 (-1.26,-0.14)	-0.07 (-0.48,0.34)	0.24 (-0.11,0.60)	0.23 (-0.02,0.49)	0.74 (0.30,1.19)	0.53 (0.18,0.88)	Umec	0.08 (-0.24,0.40)	NA	NA	NA	0.06 (-0.30,0.42)
	-0.84 (-1.08,-0.61)	-0.66 (-1.22,-0.11)	-0.02 (-0.44,0.39)	0.28 (-0.06,0.63)	0.28 (0.01,0.54)	0.78 (0.34,1.22)	0.57 (0.24,0.90)	0.04 (-0.19,0.27)	Glyco	NA	NA	NA	0.11 (-0.21,0.43)
	-0.99 (-1.16,-0.82)	-0.81 (-1.38,-0.24)	-0.17 (-0.60,0.26)	0.14 (-0.24,0.51)	0.13 (-0.16,0.41)	0.64 (0.22,1.05)	0.43 (0.06,0.79)	-0.11 (-0.40,0.19)	-0.15 (-0.44,0.15)	Acl	NA	NA	NA
	-1.03 (-1.40,-0.66)	-0.85 (-1.51,-0.19)	-0.21 (-0.75,0.33)	0.09 (-0.40,0.59)	0.09 (-0.35,0.53)	0.60 (0.22,0.97)	0.39 (-0.11,0.88)	-0.15 (-0.59,0.30)	-0.19 (-0.63,0.25)	-0.04 (-0.45,0.37)	Tio5	NA	NA
	-0.80 (-0.98,-0.62)	-0.62 (-1.13,-0.11)	0.02 (-0.36,0.40)	0.32 (0.01,0.64)	0.32 (0.11,0.53)	0.82 (0.41,1.24)	0.62 (0.31,0.92)	0.08 (-0.14,0.31)	0.04 (-0.17,0.25)	0.19 (-0.06,0.44)	0.23 (-0.19,0.65)	Tio18	

Notes: Comparisons between treatments should be read from left to right. The mean difference (MD) with 95% confidence interval (95%CI) are shown in the cells. MD more than 0 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in bold. Higher scores indicate better symptom control.

Abbreviations: Acl, acclidinium; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC250, fluticasone/salmeterol 250/50mcg; SFC500, fluticasone/salmeterol 500/50mcg; Tio5, tiotropium 5mcg; Tio18, tiotropium 18mcg; TioOlo, tiotropium/olodaterol; Umec, umecclidinium; UmecVil, umecclidinium/vilanterol.

Table S3 Treatment effects on TDI score at week 24 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

NMA results (combining direct and indirect estimates)	Direct evidence									
	Placebo	NA	NA	-0.96 (-1.45,-0.48)	-1.09 (-1.57,-0.61)	-1.37 (-1.75,-1.00)	1.00 (-1.50,-0.50)	-0.93 (-1.19,-0.66)	-0.96 (-1.28,-0.64)	-0.83 (-1.04,-0.63)
	0.33 (-0.26,0.93)	Ipra	NA	NA	NA	NA	NA	NA	NA	-1.20 (-1.77,-0.64)
	-1.09 (-1.46,-0.72)	-1.43 (-2.11,-0.74)	SFC500	NA	-0.42 (-1.03,0.20)	0.00 (-0.45,0.45)	NA	NA	NA	NA
	-0.94 (-1.24,-0.65)	-1.28 (-1.92,-0.64)	0.15 (-0.32,0.62)	UmecVil	NA	NA	0.30 (-0.15,0.75)	NA	NA	0.03 (-0.43,0.48)
	-1.35 (-1.69,-1.01)	-1.68 (-2.35,-1.02)	-0.26 (-0.52,0.00)	-0.41 (-0.85,0.04)	IndaGlyco	NA	NA	0.21 (-0.26,0.68)	NA	0.51 (0.04,0.98)
	-1.27 (-1.58,-0.96)	-1.60 (-2.27,-0.94)	-0.18 (-0.54,0.18)	-0.33 (-0.75,0.10)	0.08 (-0.30,0.46)	AcIForm	NA	NA	0.43 (0.09,0.76)	NA
	-0.85 (-1.29,-0.41)	-1.18 (-1.91,-0.45)	0.24 (-0.33,0.82)	0.10 (-0.32,0.52)	0.50 (-0.05,1.05)	0.42 (-0.11,0.96)	Umec	NA	NA	NA
	-0.96 (-1.21,-0.72)	-1.30 (-1.92,-0.68)	0.13 (-0.28,0.54)	-0.02 (-0.39,0.35)	0.38 (0.01,0.76)	0.31 (-0.08,0.69)	-0.12 (-0.61,0.38)	Glyco	NA	0.10 (-0.33,0.53)
	-0.91 (-1.22,-0.61)	-1.25 (-1.91,-0.58)	0.18 (-0.25,0.61)	0.03 (-0.39,0.45)	0.44 (0.02,0.85)	0.36 (0.04,0.67)	-0.07 (-0.60,0.47)	0.05 (-0.33,0.44)	AcI	NA
-0.87 (-1.06,-0.68)	-1.20 (-1.77,-0.64)	0.22 (-0.17,0.62)	0.07 (-0.23,0.38)	0.48 (0.12,0.84)	0.40 (0.05,0.75)	-0.02 (-0.48,0.44)	0.09 (-0.17,0.36)	0.04 (-0.31,0.40)	Tio18	

Notes: Comparisons between treatments should be read from left to right. The mean difference (MD) with 95% confidence interval (95%CI) are shown in the cells. MD more than 0 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in bold. Higher scores indicate better symptom control.

Abbreviations: AcI, acclidinium; AcIForm, acclidinium/formoterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC500, fluticasone/salmeterol 500/50mcg; Tio18, tiotropium 18mcg; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

Table S4 Treatment effects on proportion of TDI responders at week 12 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

NMA results (combining direct and indirect estimates)	Direct evidence									
	Placebo	NA	NA	NA	NA	0.36 (0.26,0.49)	0.25 (0.10,0.61)	0.33 (0.21,0.52)	0.50 (0.41,0.61)	0.60 (0.44,0.81)
	0.73 (0.42,1.27)	Ipra	NA	NA	NA	NA	NA	NA	NA	0.66 (0.46,0.96)
	0.31 (0.18,0.55)	0.43 (0.23,0.81)	SFC500	1.03 (0.76,1.40)	1.44 (0.97,2.13)	NA	NA	NA	NA	NA
	0.32 (0.21,0.49)	0.44 (0.27,0.74)	1.03 (0.70,1.52)	UmeclVil	NA	NA	NA	NA	NA	1.50 (1.21,1.86)
	0.45 (0.22,0.93)	0.62 (0.28,1.35)	1.44 (0.91,2.28)	1.39 (0.77,2.53)	IndaGlyco	NA	NA	NA	NA	NA
	0.37 (0.26,0.53)	0.50 (0.26,0.97)	1.17 (0.60,2.30)	1.14 (0.66,1.97)	0.82 (0.36,1.84)	AcIForm	NA	NA	1.33 (0.98,1.81)	NA
	0.42 (0.28,0.61)	0.57 (0.33,0.98)	1.33 (0.76,2.33)	1.28 (0.85,1.93)	0.92 (0.45,1.90)	1.13 (0.67,1.92)	Umec	1.11 (0.87,1.41)	NA	0.98 (0.77,1.25)
	0.42 (0.28,0.62)	0.57 (0.31,1.03)	1.33 (0.72,2.45)	1.28 (0.80,2.07)	0.92 (0.43,1.98)	1.13 (0.66,1.95)	1.00 (0.74,1.36)	Glyco	NA	NA
	0.51 (0.40,0.64)	0.69 (0.38,1.26)	1.62 (0.87,2.99)	1.56 (0.97,2.52)	1.12 (0.52,2.41)	1.38 (0.96,1.96)	1.22 (0.77,1.92)	1.22 (0.76,1.95)	AcI	NA
0.48 (0.35,0.67)	0.66 (0.42,1.03)	1.55 (0.97,2.45)	1.49 (1.16,1.93)	1.07 (0.56,2.06)	1.32 (0.81,2.14)	1.16 (0.85,1.60)	1.16 (0.78,1.73)	0.96 (0.64,1.43)	Tio18	

Notes: Comparisons between treatments should be read from left to right. The odds ratio (OR) with 95%CI are shown in the cells. OR more than 1 favors the column-defining

treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**.

Abbreviations: AcI, acclidinium; AcIForm, acclidinium/formoterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC500, fluticasone/salmeterol 500/50mcg; Tio18, tiotropium 18mcg; Umec, umeclidinium; UmeclVil, umeclidinium/vilanterol.

Table S5 Treatment effects on proportion of TDI responders at week 24 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

NMA results (combining direct and indirect estimates)	Direct evidence									
	Placebo	NA	NA	0.61 (0.40,0.92)	0.63 (0.45,0.87)	0.43 (0.34,0.55)	0.62 (0.46,0.85)	0.61 (0.50,0.76)	0.57 (0.47,0.69)	0.69 (0.55,0.85)
	1.54 (0.94,2.53)	Ipra	NA	NA	NA	NA	NA	NA	NA	0.42 (0.27,0.65)
	0.56 (0.41,0.78)	0.37 (0.20,0.65)	SFC500	NA	0.64 (0.43,0.94)	0.95 (0.74,1.24)	NA	NA	NA	NA
	0.60 (0.48,0.75)	0.39 (0.23,0.65)	1.07 (0.73,1.55)	UmecVil	NA	NA	1.23 (0.94,1.62)	NA	NA	1.08 (0.80,1.45)
	0.45 (0.35,0.58)	0.29 (0.17,0.50)	0.80 (0.57,1.11)	0.75 (0.54,1.03)	IndaGlyco	NA	NA	1.22 (0.93,1.60)	NA	1.48 (1.13,1.93)
	0.48 (0.38,0.60)	0.31 (0.18,0.53)	0.85 (0.64,1.12)	0.79 (0.58,1.09)	1.06 (0.78,1.45)	AcIForm	NA	NA	1.27 (1.03,1.57)	NA
	0.69 (0.50,0.94)	0.45 (0.25,0.79)	1.22 (0.78,1.91)	1.15 (0.85,1.55)	1.53 (1.03,2.28)	1.44 (0.98,2.13)	Umec	NA	NA	NA
	0.58 (0.48,0.69)	0.37 (0.22,0.62)	1.02 (0.72,1.45)	0.96 (0.74,1.25)	1.28 (0.98,1.68)	1.21 (0.91,1.60)	0.84 (0.59,1.19)	Glyco	NA	1.15 (0.95,1.41)
	0.59 (0.48,0.73)	0.38 (0.22,0.66)	1.05 (0.75,1.47)	0.98 (0.73,1.33)	1.31 (0.96,1.81)	1.24 (0.99,1.56)	0.86 (0.59,1.25)	1.02 (0.78,1.35)	AcI	NA
0.65 (0.56,0.76)	0.42 (0.26,0.68)	1.16 (0.82,1.63)	1.09 (0.87,1.35)	1.45 (1.11,1.89)	1.37 (1.04,1.80)	0.95 (0.68,1.32)	1.13 (0.93,1.37)	1.10 (0.85,1.43)	Tio18	

Notes: Comparisons between treatments should be read from left to right. The odds ratio (OR) with 95%CI are shown in the cells. OR more than 1 favors the column-defining

treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**.

Abbreviations: AcI, acclidinium; AcIForm, acclidinium/formoterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC500, fluticasone/salmeterol 500/50mcg; Tio18, tiotropium 18mcg; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

Table S6 Treatment effects on SGRQ score at week 12 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

		Direct evidence											
		Placebo	1.29 (-1.19,3.78)	3.68 (1.03,6.33)	NA	NA	4.03 (1.79,6.38)	4.72 (3.33,6.11)	NA	7.9 (3.6,12.2)	4.24 (2.42,6.05)	2.50 (1.60,3.40)	2.63 (1.24,4.03)
NMA results (combining direct and indirect estimates)	1.37 (-0.52,3.25)	lpra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.67 (-0.24,3.59)
	4.59 (3.04,6.14)	3.22 (0.96,5.49)	FFVI	NA	-1.30 (-3.45,0.85)	NA	NA	NA	NA	NA	NA	NA	-1.25 (-2.77,0.28)
	3.77 (1.66,5.88)	2.40 (-0.26,5.06)	-0.82 (-3.16,1.52)	SFC250	NA	0.48 (-1.50,2.45)	NA	NA	NA	NA	NA	NA	NA
	4.48 (2.88,6.07)	3.11 (0.82,5.39)	-0.11 (-1.78,1.55)	0.71 (-1.52,2.94)	SFC500	-0.53 (-2.26,1.20)	NA	0.64 (-0.51,1.78)	NA	NA	NA	NA	3.00 (-4.61,10.61)
	4.22 (2.93,5.51)	2.85 (0.78,4.93)	-0.37 (-2.01,1.27)	0.45 (-1.22,2.12)	-0.26 (-1.74,1.23)	UmecVil	NA	NA	NA	NA	NA	NA	-1.30 (-2.35,-0.25)
	4.72 (3.04,6.40)	3.35 (0.83,5.88)	0.13 (-2.16,2.42)	0.95 (-1.75,3.65)	0.25 (-2.07,2.57)	0.50 (-1.62,2.62)	TioOlo	NA	NA	NA	NA	-2.09 (-3.46,-0.72)	NA
	5.37 (3.76,6.99)	4.00 (1.71,6.30)	0.78 (-0.97,2.53)	1.60 (-0.68,3.88)	0.90 (-0.09,1.88)	1.15 (-0.40,2.71)	0.65 (-1.68,2.98)	IndaGlyco	NA	-2.40 (-4.01,-0.79)	NA	NA	-2.88 (-4.54,-1.22)
	4.32 (2.73,5.91)	2.96 (0.65,5.26)	-0.27 (-2.25,1.71)	0.55 (-1.87,2.98)	-0.15 (-2.13,1.82)	0.10 (-1.65,1.86)	-0.40 (-2.71,1.92)	-1.05 (-3.03,0.93)	Umec	-0.64 (-2.17,0.89)	NA	NA	-0.46 (-2.05,1.13)
	3.70 (2.65,4.75)	2.33 (0.32,4.35)	-0.89 (-2.50,0.73)	-0.07 (-2.21,2.07)	-0.77 (-2.33,0.78)	-0.52 (-1.86,0.83)	-1.02 (-3.00,0.96)	-1.67 (-3.20,-0.14)	-0.62 (-2.11,0.86)	Glyco	NA	NA	-0.10 (-1.10,0.90)
	2.54 (1.51,3.56)	1.17 (-0.98,3.32)	-2.05 (-3.92,-0.19)	-1.23 (-3.59,1.12)	-1.94 (-3.85,-0.03)	-1.68 (-3.34,-0.03)	-2.19 (-4.15,-0.22)	-2.84 (-4.76,-0.91)	-1.79 (-3.68,0.10)	-1.17 (-2.65,0.32)	Acl	NA	NA
	2.63 (0.95,4.32)	1.27 (-1.27,3.80)	-1.96 (-4.25,0.33)	-1.14 (-3.84,1.56)	-1.84 (-4.17,0.48)	-1.59 (-3.71,0.54)	-2.09 (-3.75,-0.42)	-2.74 (-5.07,-0.40)	-1.69 (-4.01,0.63)	-1.07 (-3.06,0.92)	0.10 (-1.88,2.07)	Tio5	NA
	3.09 (2.11,4.06)	1.72 (-0.12,3.56)	-1.50 (-2.89,-0.11)	-0.68 (-2.64,1.28)	-1.39 (-2.80,0.03)	-1.13 (-2.16,-0.11)	-1.63 (-3.58,0.31)	-2.28 (-3.72,-0.85)	-1.24 (-2.71,0.24)	-0.61 (-1.61,0.39)	0.55 (-0.87,1.97)	0.46 (-1.49,2.40)	Tio18

Notes: Comparisons between treatments should be read from left to right. The mean difference (MD) with 95% confidence interval (95%CI) are shown in the cells. MD less than 0

favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**. Lower scores indicate better quality of life.

Abbreviations: Acl, acclidinium; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; lpra, ipratropium; NA, results not available; SFC250, fluticasone/salmeterol 250/50mcg; SFC500, fluticasone/salmeterol 500/50mcg; Tio5, tiotropium 5mcg; Tio18, tiotropium 18mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

Table S7 Treatment effects on SGRQ score at week 24 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

	Direct evidence														
	Placebo	NA	4.08 (0.63,7.53)	3.12 (1.04,5.20)	-1.86 (-9.21,5.48)	3.86 (0.45,7.28)	NA	3.01 (0.97,5.05)	2.56 (-1.07,6.20)	4.69 (2.31,7.07)	3.41 (1.91,4.91)	2.50 (-0.45,5.45)	2.2 (1.30,3.10)	2.38 (1.73,3.03)	
NMA results (combining direct and indirect estimates)	0.10 (-3.69,3.88)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2.10 (-0.21,4.41)	
	4.08 (-0.35,8.51)	3.98 (-1.84,9.81)	FFVI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
	3.12 (-0.35,6.59)	3.02 (-2.11,8.16)	-0.96 (-6.59,4.67)	BudeForm	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	0.86 (-1.04,2.75)	0.76 (-3.39,4.90)	-3.22 (-8.04,1.59)	-2.26 (-6.22,1.69)	SFC500	NA	NA	1.13 (0.48,1.78)	NA	NA	NA	NA	NA	NA	NA
	3.32 (1.52,5.12)	3.22 (-0.78,7.21)	-0.76 (-5.54,4.02)	0.20 (-3.71,4.11)	2.46 (-0.04,4.97)	UmeclVil	NA	NA	NA	NA	-0.82 (-2.91,1.27)	NA	NA	NA	-0.85 (-2.65,0.95)
	3.43 (-0.74,7.60)	3.33 (-2.30,8.97)	-0.65 (-6.73,5.44)	0.31 (-5.11,5.74)	2.58 (-2.00,7.16)	0.12 (-4.43,4.66)	TioOlo	NA	NA	NA	NA	NA	NA	-1.23 (-2.31,-0.15)	NA
	2.92 (1.14,4.70)	2.82 (-1.23,6.87)	-1.16 (-5.93,3.61)	-0.20 (-4.10,3.70)	2.06 (0.46,3.67)	-0.40 (-2.78,1.98)	-0.51 (-5.05,4.02)	IndaGlyco	NA	NA	NA	-1.50 (-2.77,-0.23)	NA	NA	-1.94 (-0.68,-3.19)
	3.04 (0.65,5.44)	2.95 (-1.53,7.42)	-1.04 (-6.07,4.00)	-0.08 (-4.29,4.14)	2.19 (-0.85,5.23)	-0.27 (-3.27,2.72)	-0.39 (-5.20,4.42)	0.12 (-2.85,3.10)	AcIForm	NA	NA	NA	-0.78 (-2.19,0.63)	NA	NA
	3.49 (0.27,6.70)	3.39 (-1.49,8.26)	-0.59 (-6.07,4.88)	0.37 (-4.36,5.09)	2.63 (-1.06,6.32)	0.17 (-3.00,3.33)	0.05 (-5.21,5.32)	0.57 (-3.05,4.19)	0.44 (-3.57,4.45)	Umecl	NA	NA	NA	NA	NA
	2.93 (1.52,4.35)	2.84 (-1.08,6.76)	-1.15 (-5.80,3.50)	-0.19 (-3.93,3.56)	2.08 (-0.05,4.21)	-0.38 (-2.53,1.76)	-0.50 (-4.90,3.91)	0.02 (-1.89,1.92)	-0.11 (-2.89,2.67)	-0.55 (-4.01,2.91)	Glyco	NA	NA	NA	-0.56 (-1.60,0.49)
	2.58 (0.53,4.63)	2.48 (-1.82,6.79)	-1.50 (-6.38,3.38)	-0.54 (-4.57,3.49)	1.72 (-1.05,4.50)	-0.74 (-3.46,1.99)	-0.85 (-5.50,3.80)	-0.34 (-3.05,2.37)	-0.46 (-2.79,1.86)	-0.91 (-4.72,2.91)	-0.35 (-2.84,2.13)	AcI	NA	NA	NA
	2.20 (-0.72,5.12)	2.10 (-2.68,6.88)	-1.88 (-7.19,3.42)	-0.92 (-5.46,3.61)	1.34 (-2.13,4.82)	-1.12 (-4.55,2.31)	-1.23 (-4.21,1.75)	-0.72 (-4.14,2.70)	-0.84 (-4.62,2.93)	-1.29 (-5.63,3.06)	-0.73 (-3.98,2.51)	-0.38 (-3.95,3.19)	Tio5	NA	NA
	2.20 (1.07,3.32)	2.10 (-1.51,5.71)	-1.88 (-6.45,2.69)	-0.92 (-4.57,2.73)	1.34 (-0.69,3.37)	-1.12 (-2.83,0.58)	-1.24 (-5.56,3.09)	-0.72 (-2.56,1.11)	-0.85 (-3.49,1.80)	-1.29 (-4.56,1.99)	-0.74 (-2.26,0.79)	-0.38 (-2.72,1.96)	-0.00 (-3.13,3.13)	Tio18	NA

Notes: Comparisons between treatments should be read from left to right. The mean difference (MD) with 95% confidence interval (95%CI) are shown in the cells. MD less than 0 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**. Lower scores indicate better quality of life.

Abbreviations: AcI, acridinium; AcIForm, acridinium/formoterol; BudeForm, budesonide/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC500, fluticasone/salmeterol 500/50mcg; Tio5, tiotropium 5mcg; Tio18, tiotropium 18mcg; TioOlo, tiotropium/olodaterol; Umecl, umeclidinium; UmeclVil, umeclidinium/vilanterol.

Table S8 Treatment effects on proportion of SGRQ responders at week 12 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

		Direct evidence										
		Placebo	NA	NA	NA	0.62 (0.43,0.89)	NA	NA	0.53 (0.39,0.72)	NA	0.51 (0.34,0.76)	0.73 (0.60,0.88)
NMA results (combining direct and indirect estimates)	0.74 (0.46,1.19)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.83 (0.57,1.19)
	0.48 (0.30,0.76)	0.65 (0.39,1.09)	FFVI	NA	NA	NA	NA	NA	NA	NA	NA	1.27 (0.90,1.81)
	0.51 (0.35,0.73)	0.68 (0.43,1.09)	1.06 (0.67,1.66)	SFC500	0.96 (0.71,1.30)	NA	0.99 (0.69,1.43)	NA	NA	NA	NA	NA
	0.52 (0.39,0.69)	0.70 (0.47,1.06)	1.09 (0.73,1.62)	1.03 (0.79,1.34)	UmeclVil	NA	NA	NA	NA	NA	NA	1.16 (0.90,1.51)
	0.39 (0.26,0.59)	0.53 (0.33,0.85)	0.82 (0.51,1.30)	0.77 (0.52,1.16)	0.75 (0.54,1.05)	TioOlo	NA	NA	NA	NA	NA	1.56 (1.17,2.07)
	0.45 (0.33,0.63)	0.61 (0.40,0.94)	0.95 (0.63,1.43)	0.90 (0.68,1.19)	0.87 (0.69,1.10)	1.16 (0.82,1.65)	IndaGlyco	NA	NA	1.29 (1.05,1.59)	NA	1.37 (1.12,1.69)
	0.50 (0.37,0.67)	0.67 (0.38,1.17)	1.03 (0.60,1.79)	0.98 (0.61,1.57)	0.95 (0.63,1.43)	1.27 (0.76,2.10)	1.09 (0.70,1.69)	AcIForm	NA	NA	1.56 (1.15,2.12)	NA
	0.60 (0.43,0.84)	0.81 (0.53,1.24)	1.25 (0.83,1.89)	1.18 (0.85,1.65)	1.15 (0.89,1.49)	1.53 (1.07,2.18)	1.32 (1.01,1.72)	1.21 (0.77,1.89)	Umecl	0.94 (0.73,1.20)	NA	1.03 (0.80,1.32)
	0.57 (0.42,0.76)	0.77 (0.51,1.15)	1.18 (0.80,1.75)	1.12 (0.83,1.51)	1.09 (0.88,1.35)	1.45 (1.04,2.01)	1.25 (1.01,1.53)	1.14 (0.75,1.73)	0.95 (0.77,1.16)	Glyco	NA	1.06 (0.89,1.26)
	0.72 (0.59,0.89)	0.98 (0.59,1.64)	1.51 (0.92,2.50)	1.43 (0.94,2.18)	1.39 (0.99,1.97)	1.85 (1.18,2.92)	1.60 (1.09,2.34)	1.46 (1.09,1.96)	1.21 (0.82,1.79)	1.28 (0.90,1.82)	AcI	NA
	0.61 (0.46,0.82)	0.83 (0.57,1.20)	1.27 (0.89,1.83)	1.21 (0.91,1.59)	1.17 (0.99,1.38)	1.56 (1.17,2.09)	1.34 (1.10,1.64)	1.23 (0.82,1.86)	1.02 (0.83,1.25)	1.08 (0.92,1.26)	0.84 (0.59,1.19)	Tio18

Notes: Comparisons between treatments should be read from left to right. The odds ratio (OR) with 95%CI are shown in the cells. OR more than 1 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**.

Abbreviations: AcI, acclidinium; AcIForm, acclidinium/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC500, fluticasone/salmeterol 500/50mcg; Tio18, tiotropium 18mcg; TioOlo, tiotropium/olodaterol; Umecl, umeclidinium; UmeclVil, umeclidinium/vilanterol.

Table S9 Treatment effects on proportion of SGRQ responders at week 24 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

		Direct evidence											
		Placebo	NA	0.65 (0.46,0.90)	NA	0.59 (0.46,0.77)	NA	0.74 (0.54,1.02)	0.45 (0.33,0.62)	0.63 (0.46,0.87)	0.74 (0.62,0.90)	0.52 (0.42,0.66)	0.70 (0.61,0.80)
NMA results (combining direct and indirect estimates)	0.84 (0.54,1.30)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.855 (0.60,1.22)
	0.65 (0.44,0.95)	0.77 (0.43,1.39)	BudeForm	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	0.55 (0.39,0.77)	0.65 (0.38,1.12)	0.85 (0.51,1.42)	SFC500	NA	NA	0.77 (0.53,1.12)	1.13 (0.88,1.47)	NA	NA	NA	NA	NA
	0.60 (0.49,0.74)	0.72 (0.46,1.14)	0.94 (0.60,1.45)	1.11 (0.76,1.62)	UmevVil	NA	NA	NA	1.20 (0.91,1.57)	NA	NA	NA	1.15 (0.88,1.50)
	0.49 (0.34,0.70)	0.59 (0.33,1.04)	0.76 (0.45,1.29)	0.90 (0.55,1.47)	0.81 (0.54,1.23)	TioOlo	NA	NA	NA	NA	NA	NA	1.42 (1.19,1.70)
	0.55 (0.44,0.68)	0.65 (0.42,1.03)	0.85 (0.54,1.32)	1.00 (0.71,1.40)	0.90 (0.70,1.17)	1.11 (0.73,1.68)	IndaGlyco	NA	NA	1.23 (1.05,1.45)	NA	NA	1.32 (1.12,1.55)
	0.53 (0.40,0.72)	0.64 (0.38,1.08)	0.83 (0.51,1.35)	0.98 (0.73,1.30)	0.88 (0.62,1.25)	1.09 (0.68,1.73)	0.98 (0.70,1.35)	AcIForm	NA	NA	1.17 (0.86,1.58)	NA	NA
	0.69 (0.50,0.95)	0.82 (0.48,1.39)	1.06 (0.64,1.76)	1.25 (0.79,1.99)	1.13 (0.83,1.55)	1.40 (0.86,2.26)	1.26 (0.87,1.82)	1.29 (0.83,1.99)	Umev	NA	NA	NA	NA
	0.71 (0.60,0.83)	0.84 (0.54,1.31)	1.09 (0.72,1.67)	1.29 (0.91,1.84)	1.17 (0.93,1.47)	1.44 (0.97,2.13)	1.29 (1.06,1.57)	1.32 (0.96,1.83)	1.03 (0.72,1.46)	Glyco	NA	NA	1.00 (0.83,1.21)
	0.55 (0.42,0.71)	0.66 (0.40,1.10)	0.85 (0.53,1.36)	1.01 (0.69,1.48)	0.91 (0.65,1.27)	1.12 (0.72,1.75)	1.01 (0.73,1.39)	1.03 (0.75,1.42)	0.80 (0.53,1.22)	0.78 (0.58,1.06)	AcI	NA	NA
	0.70 (0.55,0.89)	0.84 (0.51,1.38)	1.08 (0.69,1.71)	1.28 (0.84,1.94)	1.16 (0.84,1.58)	1.42 (1.09,1.86)	1.28 (0.93,1.76)	1.31 (0.90,1.92)	1.02 (0.68,1.53)	0.99 (0.74,1.33)	1.27 (0.89,1.81)	Tio5	NA
	0.71 (0.61,0.84)	0.85 (0.57,1.29)	1.11 (0.73,1.69)	1.31 (0.92,1.86)	1.18 (0.98,1.43)	1.45 (0.98,2.15)	1.31 (1.07,1.59)	1.34 (0.97,1.85)	1.04 (0.74,1.46)	1.01 (0.86,1.19)	1.30 (0.96,1.76)	1.02 (0.76,1.36)	Tio18

Notes: Comparisons between treatments should be read from left to right. The odds ratio (OR) with 95%CI are shown in the cells. OR more than 1 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in **bold**.

Abbreviations: AcI, acclidinium; AcIForm, acclidinium/formoterol; BudeForm, budesonide/formoterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC500, fluticasone/salmeterol 500/50mcg; Tio5, tiotropium 5mcg; Tio18, tiotropium 18mcg; TioOlo, tiotropium/olodaterol; Umev, umeclidinium; UmevVil, umeclidinium/vilanterol.

Table S10 Treatment effects on adverse events at week 12 -NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

		Direct evidence										
		Placebo	1.02 (0.75,1.39)	NA	0.75 (0.26,2.15)	NA	1.07 (0.76,1.51)	1.21 (0.92,1.60)	0.85 (0.42,1.70)	NA	1.20 (0.73,1.99)	1.20 (0.95,1.51)
NMA results (combining direct and indirect estimates)	1.07 (0.83,1.38)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	1.32 (0.87,2.00)	0.85 (0.51,1.42)
	0.99 (0.74,1.34)	0.93 (0.64,1.35)	FFVI	NA	1.08 (0.73,1.59)	NA	NA	NA	NA	NA	NA	1.15 (0.86,1.53)
	1.04 (0.77,1.42)	0.98 (0.66,1.45)	1.05 (0.72,1.53)	SFC250	NA	1.05 (0.84,1.33)	NA	NA	NA	NA	NA	NA
	1.09 (0.79,1.49)	1.02 (0.69,1.51)	1.10 (0.81,1.48)	1.04 (0.73,1.49)	SFC500	1.09 (0.79,1.50)	NA	NA	NA	NA	NA	0.48 (0.16,1.41)
	1.12 (0.90,1.39)	1.04 (0.75,1.45)	1.13 (0.83,1.53)	1.07 (0.85,1.34)	1.03 (0.78,1.35)	UmeclVil	NA	NA	NA	NA	NA	0.96 (0.66,1.41)
	1.25 (0.96,1.63)	1.17 (0.82,1.66)	1.26 (0.85,1.87)	1.20 (0.80,1.80)	1.15 (0.76,1.73)	1.12 (0.79,1.58)	TioOlo	NA	NA	NA	0.96 (0.72,1.26)	NA
	1.01 (0.77,1.33)	0.95 (0.67,1.35)	1.02 (0.74,1.42)	0.97 (0.67,1.42)	0.93 (0.65,1.34)	0.91 (0.67,1.24)	0.81 (0.56,1.18)	Umec	1.05 (0.82,1.35)	NA	NA	1.11 (0.85,1.45)
	1.09 (0.82,1.46)	1.02 (0.71,1.48)	1.10 (0.78,1.55)	1.05 (0.71,1.55)	1.00 (0.69,1.47)	0.98 (0.71,1.35)	0.87 (0.59,1.29)	1.08 (0.87,1.33)	Glyco	NA	NA	0.99 (0.73,1.35)
	1.17 (0.85,1.61)	1.10 (0.73,1.65)	1.18 (0.77,1.83)	1.12 (0.72,1.75)	1.08 (0.69,1.68)	1.05 (0.71,1.54)	0.94 (0.62,1.42)	1.16 (0.76,1.75)	1.07 (0.70,1.65)	Acl	NA	NA
	1.23 (0.98,1.53)	1.15 (0.85,1.56)	1.24 (0.85,1.79)	1.18 (0.80,1.72)	1.13 (0.77,1.66)	1.10 (0.80,1.50)	0.98 (0.75,1.28)	1.21 (0.86,1.71)	1.12 (0.78,1.62)	1.05 (0.71,1.54)	Tio5	NA
	1.12 (0.94,1.35)	1.05 (0.79,1.41)	1.13 (0.88,1.46)	1.08 (0.78,1.48)	1.03 (0.77,1.40)	1.01 (0.80,1.27)	0.90 (0.65,1.24)	1.11 (0.90,1.37)	1.03 (0.82,1.30)	0.96 (0.67,1.38)	0.92 (0.69,1.22)	Tio18

Notes: Comparisons between treatments should be read from left to right. The odds ratio (OR) with 95%CI are shown in the cells. OR more than 1 favors the row-defining treatment

(lower triangle) and the column-defining treatment (upper triangle). Statistically significant results in **bold**.

Abbreviations: Acl, acclidinium; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; Ipra, ipratropium; NA, results not available; SFC250, fluticasone/salmeterol 250/50mcg; SFC500,

fluticasone/salmeterol 500/50mcg; Tio5, tiotropium 5mcg; Tio18, tiotropium 18mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

Table S11 Treatment effects on adverse events at week 24 - NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

NMA results (combining direct and indirect estimates)	Direct evidence										
	Placebo	0.93 (0.69,1.23)	0.76 (0.55,1.06)	0.77 (0.49,1.19)	0.80 (0.53,1.21)	NA	1.12 (0.81,1.53)	NA	0.81 (0.60,1.10)	1.11 (0.84,1.48)	0.92 (0.75,1.14)
	0.93 (0.67,1.29)	FFVI	NA	NA	NA	NA	NA	NA	NA	NA	
	0.76 (0.50,1.16)	0.82 (0.48,1.40)	BudeForm	NA	NA	NA	NA	NA	NA	NA	
	0.77 (0.46,1.28)	0.83 (0.45,1.52)	1.01 (0.52,1.95)	SFC250	NA	NA	NA	NA	NA	NA	
	0.86 (0.65,1.13)	0.92 (0.60,1.42)	1.12 (0.68,1.86)	1.11 (0.62,1.99)	SFC500	NA	1.29 (1.04,1.62)	1.30 (1.01,1.69)	NA	NA	
	0.85 (0.59,1.21)	0.91 (0.56,1.49)	1.11 (0.64,1.92)	1.10 (0.59,2.05)	0.99 (0.65,1.51)	UmecVil	NA	NA	NA	NA	1.19 (0.92,1.53)
	1.15 (0.87,1.51)	1.24 (0.81,1.90)	1.50 (0.91,2.48)	1.49 (0.84,2.66)	1.34 (1.04,1.72)	1.35 (0.91,2.01)	IndaGlyco	NA	NA	0.77 (0.60,1.00)	0.91 (0.71,1.18)
	1.11 (0.70,1.76)	1.20 (0.68,2.12)	1.46 (0.78,2.72)	1.45 (0.73,2.88)	1.30 (0.90,1.88)	1.32 (0.75,2.30)	0.97 (0.62,1.51)	AcIForm	NA	NA	NA
	0.81 (0.54,1.21)	0.88 (0.52,1.47)	1.06 (0.60,1.90)	1.06 (0.55,2.02)	0.95 (0.58,1.54)	0.96 (0.56,1.64)	0.71 (0.44,1.15)	0.73 (0.40,1.34)	Umec	NA	NA
	1.06 (0.84,1.33)	1.14 (0.76,1.70)	1.38 (0.86,2.23)	1.38 (0.79,2.41)	1.23 (0.89,1.72)	1.25 (0.85,1.83)	0.92 (0.68,1.25)	0.95 (0.58,1.55)	1.30 (0.82,2.06)	Glyco	1.18 (0.91,1.53)
1.00 (0.78,1.30)	1.08 (0.71,1.65)	1.32 (0.81,2.15)	1.31 (0.74,2.32)	1.17 (0.83,1.65)	1.19 (0.93,1.52)	0.88 (0.64,1.20)	0.90 (0.55,1.49)	1.24 (0.77,1.99)	0.95 (0.71,1.28)	Tio18	

Notes: Comparisons between treatments should be read from left to right. The odds ratio (OR) with 95%CI are shown in the cells. OR more than 1 favors the row-defining treatment

(lower triangle) and the column-defining treatment (upper triangle). Statistically significant results in **bold**.

Abbreviations: AcIForm, acclidinium/formoterol; BudeForm, budesonide/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; NA, results not available; SFC250, fluticasone/salmeterol 250/50mcg; SFC500, fluticasone/salmeterol 500/50mcg; Tio18, tiotropium 18mcg; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

