S1 Table. Selected studies and methodology of the different clinical trials.

	Design	Treatment arms	Duration	Primary endpoint	N
Indacaterol/glycopyrronium					
Bateman ED, et al. ERJ 2013 [1] SHINE	RCT	IND/GLY 110/50 Indacaterol 150 Glycopyrronium 50, Tiotropium 18 (open-label) Placebo	26 weeks	Trough FEV_1	2144
Dahl R, et al. Respir Med 2013 [2] ENLIGHTEN	RCT	IND/GLY 110/50 Placebo	52 weeks	Safety	339
Mahler D, et al. Eur Respir J 2013 [3] BLAZE	Cross-over	IND/GLY 110/50 Tiotropium (blinded) Placebo	6 weeks	Dyspnea (TDI)	247

	Design	Treatment arms	Duration	Primary endpoint	N
Wedzicha J, et al. Lancet Respir Med 2013 [4] SPARK	RCT	IND/GLY 110/50 Glycopyrronium 50 Tiotropium (open label)	64 weeks	Exacerbations	2224
Beeh K-M, et al. Respir Med 2014 [5] BRIGHT	Cross-over	IND/GLY 110/50 Tiotropium (partial blinded) Placebo	3 weeks	Endurance	85
Larbig M, et al. APRS Congress 2015 [6] RADIATE	RCT	IND/GLY 110/50 Tiotropium 18 Placebo	52 weeks	Trough FEV_1 SGRQ Exacerbations	1216
Watz H, et al. BMC Pulm Med 2016 [7] MOVE	Cross-over	IND/GLY 110/50 Placebo	3 weeks	Peak IC Average daily activity-related energy expenditure.	194

	Design	Treatment arms	Duration	Primary endpoint	N
Aclidinium/formoterol					
D'Urzo D, et al. Respir Res 2014 [8] AUGMENT COPD	RCT	ACLI/FOR 400/12, ACLI/FOR 400/6 Aclidinium 400 Formoterol 12 Placebo	24 weeks	Morning post-dose FEV_1 Trough FEV_1	1692
Singh D, et al. BMC Pulm Med 2014 [9] ACLIFORM	RCT	ACLI/FOR 400/12, ACLI/FOR 400/6 Aclidinium 400 Formoterol 12 Placebo	24 weeks	Morning post-dose FEV_1 Trough FEV_1	1729

	Design	Treatment arms	Duration	Primary endpoint	N
Bateman ED, et al. Respir Res 2015 [10] AUGMENT COPD + ACLIFORM	RCT	ACLI/FOR 400/12, ACLI/FOR 400/6 Aclidinium 400 Formoterol 12 Placebo	24 weeks	Morning post-dose FEV_1 Trough FEV_1	3421
Donohue JF, et al. Respir Med 2016 [11]	RCT	ACLI/FOR 400/12 Formoterol 12	52 weeks	Safety	590
D'Urzo D, et al. ATS Poster 2014 [12]	RCT	ACLI/FOR 400/12, ACLI/FOR 400/6 Aclidinium 400 Formoterol 12 Placebo	52 weeks	Not defined	1668

	Design	Treatment arms	Duration	Primary endpoint	N
Umeclidinium/vilanterol					
Donohue JF, et al. Respir Med 2013 [13]	RCT	UMEC/VIL 62.5/25 Umeclidinium 62.5 Vilanterol 25 Placebo	24 weeks	Trough FEV_1	1532
Decramer M, et al. Lancet Respir Med 2014 (Study 1 and 2) [14]	RCT	UMEC/VIL 125/25, UMEC/VIL 62.5/25 Tiotropium 18 Vilanterol 25	24 weeks	Trough FEV_1	1718
Maleki-Yazdi MR, et al. Respir Med 2014 [15]	RCT	UMEC/VIL 62.5/25 Tiotropium 18	24 weeks	Trough FEV_1	905

	Design	Treatment arms	Duration	Primary endpoint	N
Maltais F, et al. Ther Adv Respir Dis 2014 (Study 417 & 418) [16]	Cross-over	UMEC/VIL 125/25, UMEC/VIL 62.5/25 Vilanterol 25 Umeclidinium 125 Umeclidinium 62.5 Placebo	12 weeks	Endurance Trough FEV_1	655
Zheng J, et al. Int J COPD 2015 [17]	RCT	UMEC/VIL 125/25 UMEC/VIL 62.5/25 Placebo	24 weeks	Trough FEV_1	580
Siler TN, et al. Int J COPD 2016 [18]	RCT	UMEC/VIL 62.5/25 Placebo	12 weeks	SGRQ	496

	Design	Treatment arms	Duration	Primary endpoint	N
Tiotropium/olodaterol					
Beeh K-M, et al. Pulm Pharmacol Ther 2015 [19] VIVACITO	Cross-over	TIO/OLO 2,5/5; TIO/OLO 5/5 Tiotropium 2,5 or 5 Olodaterol 5 Placebo	6 weeks	FEV_1 $AUC_{0–24}$	219
Buhl R, et al. Eur Respir J 2015 [20] TONADO 1 and 2	RCT	TIO/OLO 2,5/5; TIO/OLO 5/5 Tiotropium 2,5 or 5 Olodaterol 5	52 weeks	FEV_1 $AUC_{0–3}$ Trough FEV_1 SGRQ	5162
Singh D, et al. Respir Med 2015 [21] OTEMTO 1 and 2	RCT	TIO/OLO 2,5/5; TIO/OLO 5/5 Tiotropium 5 Placebo	12 weeks	FEV_1 $AUC_{0–3}$ Trough FEV_1 SGRQ	1621

	Design	Treatment arms	Duration	Primary endpoint	N
Guo L, et al. Can Thorac Soc Congress 2015 [22] TORRACTO	RCT	TIO/OLO 2,5/5; TIO/OLO 5/5 Placebo	12 weeks	Endurance	404
O'Donnell D, et al. ATS Congress 2015 [23] MORACTO 1 and 2	Cross-over	TIO/OLO 2,5/5; TIO/OLO 5/5 Tiotropium 5 Olodaterol 5 Placebo	6 weeks	IC at rest Endurance	586

Abbreviations: ACLI/FOR, aclidinium/formoterol; AUC, area under the curve; FEV_1, forced expiratory volume in one second; IND/GLY, indacaterol/glycopyrronium; SGRQ, St. George's Respiratory Questionnaire; TDI, transitional dyspnea index; TIO/OLO, tiotropium/olodaterol; UMEC/VIL, umeclidinium/vilanterol

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S2 Table. Patients' characteristics included in the different clinical trials.[a]

	Age (years)	Males (%)	Smokers (%)	ICS (%)	FEV_1 (mL)	FEV_1 (%)	BDT	Reversible (%)	Exacerb ≥ 2 (%)
Indacaterol/glycopyrronium									
Bateman ED, et al. ERJ 2013 [1] SHINE	64.0	76.4	40.5	56.5	1,500	55.7	20.4%	NA	5.9
Dahl R, et al. Respir Med 2013 [2] ENLIGHTEN	62.5	77.3	45.3	45.8	1,620	56.3	15.7%	NA	6.7
Mahler D, et al. Eur Respir J 2013 [3] BLAZE	62.8	70.3	45.5	54.9	1,600	56.1	20.6%	NA	6.9
Wedzicha J, et al. Lancet Respir Med 2013 [4] SPARK	63.1	76.0	38.0	75.0	1,040	37.0	17.2%	NA	22.0
Beeh K-M, et al. Respir Med 2014 [5] BRIGHT	62.1	63.1	53.6	31.0	1,600	55.9	22.6%	NA	2.4

	Age (years)	Males (%)	Smokers (%)	ICS (%)	FEV_1 (mL)	FEV_1 (%)	BDT	Reversible (%)	Exacerb ≥ 2 (%)
Larbig M, et al. APRS Congress 2015 [6] RADIATE	64.6	70.8	42.8	57.5	1,500	56.4	18.4%	NA	NA
Watz H, et al. BMC Pulm Med 2016 [6] MOVE	62.8	65.5	56.7	NA	NA	61.6	NA	NA	NA
Aclidinium/formoterol									
D'Urzo D, et al. Respir Res 2014 [7] AUGMENT COPD	64.2	50.1	51.6	NA	NA	53.2	17.2%	NA	NA
Singh D, et al. BMC Pulm Med 2014 [8] ACLIFORM	62.7	67.8	47.0	22.1	1,420	54.6	NA	34.8	NA
Bateman ED, et al. Respir Res 2015 [9] AUGMENT COPD + ACLIFORM	63.4	59.6	49.2	15.8	1400	53.9	NA	NA	NA
Donohue JF, et al. Respir Med 2016 [10]	63.9	55.1	46.9	35.2	NA	51.8	NA	NA	NA
D'Urzo D, et al. ATS Poster 2014 [9]	64.2	20.1	51.6	NA	1340	53.2	NA	43.3	NA

	Age (years)	Males (%)	Smokers (%)	ICS (%)	FEV_1 (mL)	FEV_1 (%)	BDT	Reversible (%)	Exacerb ≥ 2 (%)
Umeclidinium/vilanterol									
Donohue JF, et al. Respir Med 2013 [11]	63.1	74	49.0	51.0	NA	47.8	13.9%	31.0	NA
Decramer M, et al. Lancet Respir Med 2014 (Study 1)	63.0	70	46	44	NA	48	12.4%	NA	NA
Decramer M, et al. Lancet Respir Med 2014 (Study 2)	65.0	65	42	47	NA	47.7	14.9%	NA	NA
Maleki-Yazdi MR, et al. Respir Med 2014 [12]	61.9	68	59	54	1,410	46.2	150 mL	27	NA
Maltais F, et al. Ther Adv Respir Dis 2014 (Study 417)	61.6	56.1	63.2	28.2	NA	51.3	12.6%	34.5	NA
Maltais F, et al. Ther Adv Respir Dis 2014 (Study 418)	62.6	54.7	60.6	39.4	NA	51.3	16.2%	38.9	NA
Zheng J, et al. Int J COPD 2015	64.0	94.0	29.0	56.0	1,131	NA	NA	44	NA
Siler TN, et al. Int J COPD 2016	64.1	58.0	55.0	45.0	NA	46.5	11.5%	22	NA

	Age (years)	Males (%)	Smokers (%)	ICS (%)	FEV_1 (mL)	FEV_1 (%)	BDT	Reversible (%)	Exacerb ≥ 2 (%)
Tiotropium/olodaterol									
Beeh K-M, et al. Pulm Pharmacol Ther 2015 VIVACITO	61.1	58.9	62.6	41.1	1,553	54.0	193 mL 15.9%	NA	NA
Buhl R, et al. Eur Respir J 2015 TONADO 1 & 2	63.8	71.2	38.9	49.2	1,344	49.3	164 mL	NA	NA
Singh D, et al. Respir Med 2015 OTEMTO 1	64.7	56.2	54.7	41.9	1,502	54.9	NA	NA	NA
Singh D, et al. Respir Med 2015 OTEMTO 2	65.2	65.8	45.5	35.6	1,566	54.8	NA	NA	NA
Guo L. et al. Can Thorac Soc Congress 2015 TORRACTO	62.0	66.6	41.3	NA	1,660	58.6	NA	NA	NA
O'Donnell D, et al. ATS Congress 2015 MORACTO 1	62.2	72.0	NA	NA	1,713	58.6	173 mL	NA	NA

	Age (years)	Males (%)	Smokers (%)	ICS (%)	FEV_1 (mL)	FEV_1 (%)	BDT	Reversible (%)	Exacerb ≥ 2 (%)
O'Donnell D, et al. ATS Congress 2015 MORACTO 2	61.2	70.0	NA	NA	1,728	57.7	168 mL	NA	NA

Abbreviations: APRS, Asian-Pacific Respiratory Society; BDT, bronchodilator response to one short-acting β-agonist; FEV_1, forced expiratory volume in the first second; ICS, inhaled steroids use at baseline; NA, not available.

[a]Data referred to the active treatment arm with the commercialized dose in Europe of the double bronchodilator arm, except for the studies with a cross-over design that is referred to the complete cohort.

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