Supplemental Table 1: Study Design, Duration, and Inclusion Criteria of Selected Trials for LABA Monotherapy Network

Author, Year	Study Name or Code	Trial Design	Randomized	Centers/ Countries	Inclusion criteria	Trial Duration	Reference
Ferguson, 2014	1222.11	RCT, DB, MC, PC, PG	625	54 centers/ 6 countries	post-bronchodilator forced expiratory volume in 1 second (FEV1) less than 80% predicted; FEV1/forced vital capacity (FVC) less than 70% predicted; age at least 40 years with a smoking history of more than 10 pack-years	48 weeks	Ferguson et al (2014). Efficacy and safety of olodaterol once daily delivered via Respimat® in patients with GOLD 2–4 COPD: results from two replicate 48-week studies. Int J Chron Obstruct Pulmon Dis, 9, 629-45.
Ferguson, 2014	1222.12	RCT, DB, MC, PC, PG	644	51 centers/ 4 countries	post-bronchodilator forced expiratory volume in 1 second (FEV1) less than 80% predicted; FEV1/forced vital capacity (FVC) less than 70% predicted; age at least 40 years with a smoking history of more than 10 pack-years	48 weeks	Same as above
Koch, 2014	1222.13	RCT, DB, DD, MC, PC, PG	906	93 centers/ 20 countries	age at least 40 years; diagnosis of COPD according to GOLD; 1 post-bronchodilator forced expiratory volume in 1 second less than 80% of predicted normal; post-bronchodilator FEV1/forced vital capacity less than 70%; and current or ex-smokers with a smoking history of more than 10 pack-years	48 weeks	Koch et al (2014). Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat® versus placebo and formoterol twice daily in patients with GOLD 2–4 COPD: results from two replicate 48-week studies. International journal of chronic obstructive pulmonary disease, 9, 697.

Koch, 2014	1222.14	RCT, DB, DD, MC, PC, PG	937	98 centers/ 20 countries	age at least 40 years; diagnosis of COPD according to GOLD; 1 post-bronchodilator forced expiratory volume in 1 second less than 80% of predicted normal; post-bronchodilator FEV1/forced vital capacity less than 70%; and current or ex-smokers with a smoking history of more than 10 pack-years	48 weeks	Same as above
Singh, 2014	ACLIFORM-COPD	RCT, DB, MC, PC, PG	1729	193 centers/ 22 countries	Male and female patients ≥40 years of age who were current or former cigarette smokers with a smoking history ≥10 pack-years and diagnosed with moderate-to severe COPD according to GOLD 2010 criteria. Aside from salbutamol and ICS, additional permitted medications included oral sustained-release methylxanthines, oxygen therapy (<15 hours/day), and oral or parenteral corticosteroids equivalent to ≤10 mg/day of prednisone or 20 mg every other day, provided treatment was stable ≥4 weeks pre-screening	24 weeks	Singh et al (2014). Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC pulmonary medicine, 14(1), 1.
D'Urzo, 2014	AUGMENT COPD	RCT, DB, MC, PC, PG	1692	222 centers/ 3 countries	diagnosis of COPD; age ≥ 40 years; smoking history ≥ 10 pack-years; post FEV1 pred. <80%; post FEV1/FVC < 70% Other COPD medications, such as theophylline, ICS, oral or parenteral corticosteroids (≤10 mg/day or 20 mg every other day of prednisone) were allowed if treatment was stable ≥4 weeks prior to screening. Use of albuterol/salbutamol as rescue medication was permitted	24 weeks	Anthony et al (2014). Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. Respiratory research, 15(1), 123.
Yao, 2014	B2333	RCT, DB, MC, PC, PG	563	29 centers/ 3 countries	diagnosis of moderate-to-severe COPD by GOLD 2007 criteria; age ≥ 40 years; smoking history ≥ 10 pack-years; post FEV1 pred. ≥ 30% & < 80%; post FEV1/FVC < 70%	26 weeks	Yao et al (2014). Effect of once-daily indacaterol in a predominantly Chinese population with chronic obstructive pulmonary disease: A 26-week Asia-

							Pacific study. Respirology, 19(2), 231-238.
Celli, 2014	DB2113361	RCT, DB, MC, PC, PG	1493	153 centers/ 14 countries	diagnosis of COPD; age ≥ 40 years; smoking history ≥ 10 pack-years; FEV1 pred. ≤ 70%; post FEV1/FVC < 70%; mMRC dyspnea score ≥ 2	24 weeks	Celli et al (2014). Once-daily umeclidinium/vilanterol 125/25 μg therapy in copd: a randomized, controlled study. CHEST Journal, 145(5), 981-991.
Donohue, 2013	DB2113373	RCT, DB, MC, PC, PG	1536	163 centers/ 13 countries	diagnosis of COPD; age ≥ 40 years; smoking history ≥ 10 pack-years; post FEV1 pred. ≤ 70%; post FEV1/FVC < 70%; mMRC dyspnea score ≥ 2	24 weeks	Donohue et al (2013). Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respiratory medicine, 107(10), 1538-1546.
Bateman, 2013	SHINE, QVA2303	RCT, DB, MC, PC, PG, AC	2144	166 centers/ 19 countries	Male or female adults aged ≥40 years; moderate-to-severe stable COPD (Stage II or Stage III) according to the GOLD Guidelines 2008; current or ex-smokers who had a smoking history of at least 10 pack-years (defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.); a post-bronchodilator FEV1 ≥30% and < 80% of the predicted normal, and post-bronchodilator FEV1/FVC < 0.7 at Visit 2 (Day 14). Post refers to 1 hour after sequential inhalation of 84 μg (or equivalent dose) of ipratropium bromide and 400 μg of salbutamol. Symptomatic patients, according to daily electronic diary data between Visit 2 (Day 14) and Visit 3 (Day 1), with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3 (the main study diary was used)	26 weeks	Bateman et al (2013). Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. European Respiratory Journal, 42(6), 1484-1494.

Maltais, 2014	418, GSK study number: DB2114418	RCT, DB, MC, PC	308	42 centers/ 7 countries	Current or former smokers; ⩾40 years of age; had a smoking history of ⩾10 pack-years; had a clinical diagnosis of moderate-to-severe stable COPD (post-bronchodilator FEV1/forced vital capacity [FVC] <70% and FEV1 ⩾35% and ⩽70% predicted); a score of ⩾2 on the Modified Medical Research Council Dyspnoea Scale at Visit 1; and a resting functional residual capacity (FRC) ⩾120% of predicted (to ensure patients were hyper-inflated, as hyperinflation is associated with exercise intolerance)	12 weeks	Maltais, F., Singh, S., Donald, A. C., Crater, G., Church, A., Goh, A. H., & Riley, J. H. (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.
Maltais, 2014	417, GSK study number: DB2114417	RCT, DB, MC, PC	349	31 centers/ 6 countries	Current or former smokers; ⩾40 years of age; had a smoking history of ⩾10 pack-years; had a clinical diagnosis of moderate-to-severe stable COPD (post-bronchodilator FEV1/forced vital capacity [FVC] <70% and FEV1 ⩾35% and ⩽70% predicted); a score of ⩾2 on the Modified Medical Research Council Dyspnoea Scale at Visit 1; and a resting functional residual capacity (FRC) ⩾120% of predicted (to ensure patients were hyper-inflated, as hyperinflation is associated with exercise intolerance)	12 weeks	Same as above
Rossi, 2002	FICOPD II	RCT, PC,DB, MC	431	81 centers worldwide	FEV1<70% of the predicted value and ≥ 0.75 L, FEV1 vital capacity ratio of <88% of that predicted in men and <89% in women; >10 pack-years smoking history	12 months	Rossi et al (2002). Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. CHEST Journal, 121(4), 1058-1069.
Dahl, 2001	FICOPD I	RCT, PC, DB, DD, MC	394	57 centers/ Europe, Russia, Canada, USA	FEV1 <70%;FEV1/FVC<88% for men and <89% for women; symptom criteria; excluded if used oral corticosteroids 4 wks prior	12 weeks	Dahl et al (2001). Inhaled formoterol dry powder versus ipratropium bromide in chronic

							obstructive pulmonary disease. American journal of respiratory and critical care medicine, 164(5), 778-784.
Gross, 2008	N/A	RCT, PC, DB, DD, MC	228	38 centers/ USA	post-broncho FEV1 30%-70%; FEV1/FVC<0.70; ≥ 10 pack-years; excluded if exacerbation in 1 month prior	12 weeks	Gross et al (2008). Efficacy and safety of formoterol fumarate delivered by nebulization to COPD patients. Respiratory medicine, 102(2), 189-197.
Kornmann, 2011	INLIGHT-2, B2336	RCT, PC, DB, MC, DD	1002	# centers NR/ Canada, Colombia, Europe and Russia, Slovakia, India, Peru, Taiwan	FEV1 ≥ 30% and <80%;FEV1/FVC<70%;reversible and non-reversible patients included; ≥ 20 pack-years smoking history; excluded if hospitalization 6 wks prior	26 weeks	Kornmann et al (2011). Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. European Respiratory Journal, 37(2), 273-279.
Korn, 2011	INSIST, B2349	RCT, DB, MC, DD	1123	142 centers across 8 countries	Post-bronchodilator FEV1 ≥30% and <80%, FEV1/FVC <70%; ≥ 10 pack-years smoking history; Excluded if exacerbation in 6 weeks prior	12 weeks	Korn et al (2011). Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. Respiratory medicine, 105(5), 719-726.
Kinoshita, 2012	B1302	RCT, PC, DB, MC	347	73 centers; Japan, Taiwan, Korea, India, Hong Kong, and Singapore	Post broncho FEV1<80% and ≥30% of predicted normal value, Post broncho FEV1/FVC<70%, ≥ 20 pack-years smoking history; excluded if exacerbation in 6 wks prior	12 weeks	Kinoshita et al (2012). Efficacy and safety of indacaterol 150 and 300 µg in chronic obstructive pulmonary disease patients from six Asian areas including Japan: A 12-week, placebo-controlled study. Respirology, 17(2), 379-389.

Donohue, 2010	INHANCE, B2335S	RCT, PC, DB (except for tiotropium arm), MC, DD; Adaptive seamless	1683	# centers NR/ Argentina, Canada, Europe, India, Italy, Korea, Taiwan, USA	FEV1 ≥ 30% and <80%; FEV1/FVC<70%; reversible and non-reversible patients included; ≥ 20 pack-years smoking history; excluded if hospitalization 6 wks prior	26 weeks	Donohue et al (2010). Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. American journal of respiratory and critical care medicine, 182(2), 155-162.
Dahl, 2010	INVOLVE, B2334	RCT, PC, DB, MC, DD	1304	# centers NR/ 25 countries in S. America, Europe, Russia, Africa, and Asia	FEV1 ≥ 30% and <80%; FEV1/FVC<70%; reversible and non-reversible patients included; ≥ 20 pack-years smoking history; excluded if hospitalization 6 wks prior to trial or during run-in period	52 weeks	Dahl et al (2010). Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax, 65(6), 473-479.
Gotfried, 2012; Kerwin, 2011	B2354	RCT, PC, DB, MC	323	# centers NR/USA	FEV1 ≥ 30% and <80%; FEV1/FVC<70%; ≥ 10 pack-year smoking history; Excluded if exacerbation in 6 wks prior	12 weeks	Gotfried et al (2012). Efficacy of indacaterol 75 µg once-daily on dyspnea and health status: results of two double-blind, placebo-controlled 12-week studies. COPD: Journal of Chronic Obstructive Pulmonary Disease, 9(6), 629-636. Kerwin et al (2011). Efficacy and tolerability of indacaterol 75 µg once daily in patients aged≥40 years with chronic obstructive pulmonary disease: results from 2 double-blind, placebo-controlled 12-week studies. Clinical therapeutics, 33(12), 1974-1984.

Gotfried, 2012; Kerwin, 2011	B2355	RCT, PC, DB, MC	318	# centers NR/ USA	FEV1 ≥ 30% and <80%; FEV1/FVC<70%; ≥ 10 pack-year smoking history; Excluded if exacerbation in 6 wks prior	12 weeks	Same as above
Feldman, 2010	INLIGHT 1, B2346	RCT, PC, DB, MC, DD	416	103 centers/ USA, Australia/ New Zealand, Belgium	FEV1 ≥ 30% and <80%; FEV1/FVC<70%; reversible and non-reversible patients included; excluded if hospitalization 6 wks prior	12 weeks	Feldman et al (2010). Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomised, 12-week study. BMC pulmonary medicine, 10(1), 1.
Stockley, 2006	SMS40026	RCT, PC, DB, MC	634	# centers NR/19 European countries	FEV1 <70%; ≤ 10% reversibility FEV1 predicted; included if ≥ 2 exacerbations in previous year	52 weeks	Stockley et al (2006). Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. Thorax, 61(2), 122-128.
Chapman, 2002	N/A	RCT, PC, DB, MC	408	52 centers/ Canada, UK, Netherlands, Sweden, Russia Denmark	FEV1 ≤ 85%; FEV1/FVC ≤ 70%; symptoms criteria; 5-15% reversibility FEV1 predicted; ≥ 10 pack-year smoking history; excluded if exacerbation 4 wks prior	24 weeks	Chapman et al (2002). The addition of salmeterol 50 microg bid to anticholinergic treatment in patients with COPD: a randomized, placebo controlled trial. Chronic obstructive pulmonary disease. Canadian respiratory journal: journal of the Canadian Thoracic Society, 9(3), 178-185.
Van Rutten, 1999	N/A	RCT, PC, DB, MC , DD	97	3 centers/ Netherlands	FEV1 40-65%; FEV1/FVC ≤ 60% (post salbutamol); symptom criteria; ≥ 10 pack-years smoking history	12 weeks	Van-Rutten et al (1999). An empirical comparison of the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) in a clinical trial setting. Thorax, 54(11), 995-1003.
Calverley,	TORCH	RCT,	3087	444 centers/ 42	FEV1 <60%; FEV1/FVC<70%; <10%	3 years	Calverley et al (2007).

2007; Jones, 2011		PC, DB, MC		countries	increase FEV1 predicted post-broncho.		Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine, 356(8), 775-789. Jones et al (2011). Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. Respiratory research, 12(1), 71.
Celli, 2003	N/A	RCT, PC, DB, MC, DD	825	189 centers/ 15 countries	FEV1 20-70%; FEV1/FVC<65%; <15% reversibility FEV1; symptom criteria; ≥ 15 pack-years smoking history; excluded if exacerbation 6 wks prior	12 weeks	Celli et al (2003). Symptoms are an important outcome in chronic obstructive pulmonary disease clinical trials: results of a 3-month comparative study using the Breathlessness, Cough and Sputum Scale (BCSS). Respiratory medicine, 97, S35-S43.
Hanania, 2003	SFCA3007	RCT, PC, DB, MC	540	76 centers/ USA	FEV1 >40% and <65%; FEV1/FVC<70%; symptoms criteria; ≥ 20 pack-years smoking history; excluded if oral corticosteroids 6 wks prior	24 weeks	Hanania et al (2003). The efficacy and safety of fluticasone propionate (250 µg)/salmeterol (50 µg) combined in the Diskus inhaler for the treatment of COPD. Chest, 124(3), 834-843.
Calverley, 2003	TRISTAN	RCT, PC, DB, MC	1091	196 centers/ 25 countries	FEV1 25-70%; FEV1/FVC<70%; increase ≥ 10% FEV1 post-broncho.; ≥ 10 pack-years smoking history; included if ≥ 1 exacerbation previous year and ≥ 1 exacerbation per year in previous 3 years	52 weeks	Calverley et al (2003). Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. The Lancet,

							361(9356), 449-456.
Mahler, 2002	SFCA3006	RCT, PC, DB, MC, DD	506	65 centers	FEV1 <65% but >70L. FEV1/FVC ≤70%; ≥ 20 pack-year smoking history; excluded if moderate or severe exacerbation during run-in	24 weeks	Mahler et al (2002). Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine, 166(8), 1084-1091.
Brusasco, 2003	N/A	RCT, PC, DB, MC, DD	1207	# centers NR/ 18 countries	FEV1 ≤ 65%;FEV1/FVC ≤ 70%	24 weeks	Brusasco et al (2003). Health outcomes following treatment for 6 months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax, 58(5), 399-404.
Donohue, 2002	N/A	RCT, PC, DB, MC, DD	623	39 centers/ 12 countries	FEV1 ≤ 60%;FEV1/FVC ≤ 70%; >10 pack-years smoking history	36 weeks	Donohue et al (2002). A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest, 122(1), 47-55.

Abbreviations: RCT - randomized clinical trial; DB - double-blind; DD - double-dummy; MC - multi-center; PC - placebo-controlled; PG - parallel-group; AC - active-comparator; BID - twice daily; GSK – GlaxoSmithKline; OD - once daily; LAMA - long-acting muscarinic antagonists; LABA - long-acting beta-2 adrenergic agonist; mMRC - Modified Medical Research Council; NA - not applicable.

Supplemental Table 2: Selected Trials' Patient Characteristics

Trial ID	Author, year (Study ID)	% ICS use per study	% male per study	Age (mean, years) per study	Current smokers (%) per study	% severe or very severe COPD per study
1	Ferguson, 2014 (1222.11)	43%	73%	64.93	39%	54%
2	Ferguson, 2014 (1222.12)	39%	71%	64.63	44%	52%
3	Koch, 2014 (1222.13)	44%	78%	63.78	35%	46%
4	Koch, 2014 (1222.14)	52%	81%	64.10	33%	47%
5	Singh, 2014	20%	68%	63.20	47%	40%
6	D'Urzo, 2014	NR	53%	63.94	52%	42%
7	Yao, 2014 (B2333)	35%	94%	65.40	22%	53%
8	Celli, 2014	47%	65%	62.93	52%	53%
9	Donohue, 2013	51%	71%	63.07	50%	54%
15	Bateman, 2013 (QVA2303)	57%	75%	63.91	40%	36%
17	Maltais, 2014 (418)	39%	55%	62.60	61%	47%
18	Maltais, 2014 (417)	28%	56%	61.60	63%	47%
19	Rossi, 2002	NR	83%	63.00	NR	NR
20	Dahl, 2001	51%	77%	63.49	48%	66%
21	Gross, 2008	21%	56%	63.50	54%	67%
22	Kornmann, 2010 (B2336)	44%	75%	63.33	46%	43%
23	Korn 2011 (B2349)	46%	71%	62.93	44%	46%
24	Kinoshita 2012 (B1302)	24%	97%	66.67	32%	40%
25	Donohue, 2010 (B2335S)	38%	63%	63.50	45%	40%
26	Dahl, 2010 (B2334)	53%	81%	63.67	41%	44%
27	Gotfried 2012, Kerwin 2011 (B2354)	45%	55%	64.00	44%	43%
28	Gotfried 2012, Kerwin 2011 (B2355)	38%	54%	61.50	59%	38%
29	Feldman, 2010 (B2346)	31%	52%	63.00	52%	39%
30	Stockley, 2006	57%	76%	62.00	46%	61%
31	Chapman, 2002	65%	64%	NR	43%	NR
32	Van Rutten, 1999	78%	87%	63.97	NR	75%
33	Calverley, 2007 and Jones, 2011 (TORCH)	0%	76%	65.00	43%	69%
34	Celli, 2003	NR	77%	64.33	NR	72%
35	Hanania, 2003	0%	62%	64.01	50%	76%
36	Calverley, 2003	0%	73%	63.00	50%	65%
37	Mahler, 2002	0%	67%	63.35	49%	NR
38	Brusasco, 2003	NR	76%	64.33	NR	83%
39	Donohue, 2002	67%	75%	65.32	NR	60%

Abbreviations: ICS- inhaled corticosteroid; COPD- Chronic Obstructive Pulmonary Disease; LABA- long-acting beta-2 adrenergic agonist; NR- not reported; ID- identification.