Supplementary Table 1: Overview of triple therapy clinical trials in patients with COPD.

Items	BDP/FOR/GLY			FF/UMEC/VI		BUD/FOR/GLY	
	TRILOGY	TRINITY	TRIBUTE	FULFIL	IMPACT	KRONOS	ETHOS
Study duration	12 months	12 months	12 months	24 weeks, with extension to 52 weeks for first 430 patients	52 weeks	24 weeks	52 weeks
Treatment[a]	BDP/FOR/GLY (*n*=687) BDP/FOR (*n*=680)	BDP/FOR/GLY (*n*=1077) Tiotropium (*n*=1074) BDP/FOR+tiotropium (*n*=538)	BDP/FOR/GLY (*n*=764) IND/GLY (*n*=768)	FF/UMEC/VI (*n*=911) BUD/FOR (*n*=899)	FF/UMEC/VI (*n*=4151) FF/VI (*n*=4134) UMEC/VI (*n*=2070)	BUD/FOR/GLY (*n*=640) FOR/GLY (*n*=627) BUD/FOR (*n*=316) BUD/FOR DPI (*n*=319)	320-μg-BUD/FOR/GLY (*n*=2137) 160-μg-BUD/FOR/GLY (*n*=2121) FOR/GLY (*n*=2120) BUD/FOR (*n*=2131)
Eligible criteria	>40 years; FEV_1<50%; ⩾1 moderate or severe exacerbation; CAT≥10; No triple therapy in previous 2 months; TRILOGY also required Baseline Dyspnea Index focal score>10			>40 years; CAT≥10; FEV_1<50%; FEV_1 50–80% and ≥2 exacerbations or ≥1 hospitalization	>40 years; CAT≥10; FEV_1<50% and >1 exacerbation; FEV_1 50–80% and ≥2 exacerbations or ≥1 hospitalization	40–80 years Current or former smokers (≥10 pack-years) FEV_1 25–80% CAT total score≥10	40–80 years CAT≥10 FEV_1 25–65% Current or former smokers (≥10 pack-years) FEV_1<50% and ≥1 exacerbation; FEV_1 50–80% and ≥2 exacerbations or ≥1 hospitalization
Devices	Fine particle metered dose inhalers (MDI)			Dry Powder (Ellipta) inhalers		Co-suspension metered dose inhalers (MDI)	
Results[b]							
Exacerbation rate (adjusted annualized)							
Moderate-severe							

RR (95% CI)	0.77 (0.65–0.92)	0.80 (0.69–0.92)[*]; 1.01 (0.85–1.21)[†]	0.85 (0.72–0.995)	0.65 (0.49–0.86)	0.85 (0.80–0.90)[‡] 0.75 (0.70–0.81)[§]	0.48 (0.37–0.64)[‖]; 0.82 (0.58–1.17)[¶]; 0.83 (0.59–1.18)[**]	0.76 (0.69–0.83)[††] 0.87 (0.79–0.95)[△] 0.75 (0.69–0.83)[‡‡] 0.86 (0.79–0.95)[△△]
P value	=0.005	0.0025[c*]; 0.89[†]	0.043[c]	0.002	<0.001[c‡]; <0.001[c§]	<0.0001[‖]; 0.2792[¶]; 0.312[**]	<0.001[c††]; 0.003[c△]; <0.001[c‡‡]; 0.002[c△△]
Severe (hospitalization)							
RR (95% CI)	Not stated	0.68 (0.50–0.94)[*]; 1.18 (0.77–1.80)[†]	0.79 (0.55–1.13)	Not stated	0.87 (0.76–1.01)[‡] 0.66 (0.56–0.78)[§]		0.84 (0.69–1.03)[††] 0.80 (0.66–0.97)[△] 0.88 (0.72–1.08)[‡‡] 0.83 (0.69–1.01)[△△]
P value		0.0174[*]; 0.45[†]	=0.189		0.06[‡]; <0.001[§]		0.09[††]; 0.02[△]; not stated[‡‡]; not stated[△△]
Pre-dose FEV_1 change from baseline, L							
Week 26						Week 24	
MD (95% CI)	0.081 (0.052–0.109)	BDP/FOR/GLY *vs*. Tiotropium; BDP/FOR/GLY *vs*. open triple	0.02	0.17 (0.15–0.19)[d]	Not stated	0.022 (0.004–0.039)[‖]; 0.074 (0.052–0.095)[¶]; 0.059 (0.038–0.080)[**]	Not stated
P value	<0.001[d]	<0.001; NS	NS	<0.001		0.0139[d‖]; <0.0001[d¶]; <0.0001[d**]	
Week 52						Week 24 (FEV_1 AUC_{0-4})	
MD (95% CI)	0.063 (0.032–0.094)	0.06 (0.04–0.09); –0.003 (–0.03 to 0.03)	0.019	0.18 (0.13–0.23)	0.10 (0.09–0.11)[‡]; 0.05 (0.04–0.07)[§]	0.016 (-0.006 to 0.038)[‖]; 0.104 (0.077–0.131)[¶]; 0.091 (0.064–0.117)[**]	Not stated

P value	<0.001	<0.0001; 0.85	NS	<0.001	<0.001[‡]; <0.001[§]	0.1448[d‖]; <0.0001[d¶]; <0.0001[d**]	
SGRQ total score change from baseline at Week 52							
MD (95% CI)	-1.69 (-3.2 to -0.17)	BDP/FOR/GLY superior to Tiotropium Open triple superior to BDP/FOR/GLY	-1.64	-2.7 (-5.5 to 0.2)	-1.8 (-2.4 to -1.1)[‡]; -1.8 (-2.6 to -1.0)[§]	-1.22 (-2.30 to -0.15)[‖]; -0.45 (-1.78 to 0.87)[¶]; -1.26 (-2.58 to 0.06)[**]	-1.88 (-2.84 to -0.91)[††] -1.47 (-2.43 to -0.51)[△] -1.51 (-2.48 to -0.54)[‡‡] -1.10 (-2.06 to -0.14)[△△]
P value	0.03	both <0.05	<0.01	0.07	<0.001[‡]; <0.001[§]	0.03[‖]; 0.50[¶]; 0.06[**]	*P*<0.05 for all
All-cause mortality							
	2.2%, 2.4%	1.9%, 2.7%, 1.5%	2.1%, 2.7%	Not stated	1.2% vs. 1.2% *vs*. 1.9%	1%, 0.5%, 1%, 0.3%	1.3%, 1.8%, 2.3%, 1.6%
HR (95% CI)	Not stated	Not stated	Not stated	Not stated	0.95 (0.64–1.40)[‡]; 0.58 (0.38–0.88)[§]	Not stated	0.54 (0.34–0.87)[††] 0.78 (0.47–1.30)[△] 0.79 (0.52–1.20)[‡‡] 1.13 (0.72–1.80)[△△]
Patients with pneumonia, *n* (%)	23 (3); 18 (3)	28 (3); 19 (2); 12 (2)	28 (4); 27 (4)	20 (2.2); 7 (0.8) over 24 weeks	317 (8); 292 (7); 97 (5)	12 (2); 10 (2); 6 (2); 4 (1)	98 (4.6); 85 (4.0); 61 (2.9); 107 (5.0)
HR (95% CI)	Not stated	Not stated	Not stated	Not stated	1.02 (0.87–1.19)[‡] 1.53 (1.22–1.92)[§]	Not stated	1.78 (1.26–2.53)[††] 0.89 (0.67–1.19)[△] 1.46 (1.01–2.09)[‡‡] 0.73 (0.54–0.99)[△△]

[a] N values are the number of patients in the intention-to-treat population; [b] Results are presented as the sequence listed in treatment column; [c] Primary endpoint of the study; [d] Coprimary endpoints; *BDP/FOR/GLY *vs*. Tiotropium; [†]BDP/FOR/GLY *vs*. BDP/FOR+tiotropium; [‡]FF/UMEC/VI *vs*. FF/VI; [§]FF/UMEC/VI *vs*. UMEC/VI;

||BUD/FOR/GLY *vs*. FOR/GLY; ¶BUD/FOR/GLY *vs*. BUD/FOR; **BUD/FOR/GLY *vs*. BUD/FOR DPI; ††320-µg-BUD/FOR/GLY *vs*. BOR/GLY; △320-µg-BUD/FOR/GLY *vs*. BUD/FOR; ‡‡160-µg-BUD/FOR/GLY *vs*. BOR/GLY; △△160-µg-BUD/FOR/GLY *vs*. BUD/FOR. AUC: Area under the curve; BDP: Beclomethasone-dipropionate; BUD: Budesonide; CAT: COPD assessment test; CI: Confidence interval; COPD: Chronic Obstructive Pulmonary Disease; DPI: Dry powder inhaler; FEV_1: Forced expiratory volume in one second; FF: Fluticasone-furoate; FOR: Formoterol; GLY: Glycopyrronium; IND: Indacaterol; HR: Hazard ratio; MD: Mean difference; MDI: Metered dose inhalers; RR: Rate ratio; SGRQ: St George's Respiratory Questionnaire; UMEC: Umeclidinium; VI: Vilanterol.