Table S1. Summary of the design of the trials with open triple combinations

Studies	Design	Treatment arms	Inhalers	Duration	Primary outcome	N *
Multiple comparators						
Hoshino M, Ohtawa J. Respiration 2013 [1]	RCT	FP/SAL + TIO FP/SAL SAL TIO	Accuhaler + Handihaler Accuhaler Accuhaler Handihaler	16 weeks	Airway dimensions by CT scan	68
Aaron SD, et al. Ann Intern Med 2007 OPTIMAL [2]	RCT	FP/SAL + TIO SAL + TIO TIO	pMDI + Handihaler pMDI + Handihaler Handihaler	1 year	% patients with an exacerbation	449
Saito T, et al. Int J COPD 2015 EAGLE [3]	Crossover	FP/SAL + TIO FP/SAL TIO	Accuhaler + Handihaler Accuhaler Handihaler	4 weeks	airway conductance AUC_{0-4}	53
Singh D, et al. Thorax 2008 [4]	Crossover	FP/SAL + TIO FP/SAL TIO	Accuhaler + Handihaler Accuhaler Handihaler	2 weeks	post-dose specific airways conductance AUC_{0-4}	30

Studies	Design	Treatment arms	Inhalers	Duration	Primary outcome	N *
Cazzola M, et al. Respir Med 2007 [5]	RCT	FP/SAL + TIO FP/SAL TIO	Accuhaler + Handihaler Accuhaler Handihaler	3 months	Trough FEV_1	90
Triple vs LAMA						
Hoshino M, Ohtawa J. Respirology 2011 [6]	RCT	FP/SAL + TIO TIO	Accuhaler + Handihaler Handihaler	142 weeks	Airway dimensions by CT scan	30
Maltais F, et al. Eur Respir J 2013 [7]	RCT	FP/SAL + TIO TIO	Accuhaler + Handihaler Handihaler	8 weeks	Exercise endurance time	255
Hanania N, et al. Respir Med 2012 [8]	RCT	FP/SAL + TIO TIO	Accuhaler + Handihaler Handihaler	24 weeks	Trough FEV_1	342
Jung KS, et al. Respir Med 2012 [9]	RCT	FP/SAL + TIO TIO	Accuhaler + Handihaler Handihaler	24 weeks	Trough FEV_1	479
Feng JF, et al. Medicine 2018 [10]	RCT	BUD/FORM + TIO TIO	Turbuhaler + handihaler Handihaler	12 weeks	Dyspnea on the 6-minute walk test	113

Studies	Design	Treatment arms	Inhalers	Duration	Primary outcome	N *
Lee SD, et al. Respirology 2015 [11]	RCT	BUD/FORM + TIO TIO	Turbuhaler + handihaler Handihaler	12 weeks	Trough FEV_1	578
Williamson PA, et al. Chest 2010 [12]	Crossover	BUD/FORM + TIO TIO	Turbuhaler + handihaler Handihaler	2 weeks	Trough FEV_1	22
Welte T, et al. AJRCCM 2009 CLIMB [13]	RCT	BUD/FOR + TIO TIO	Turbuhaler + handihaler Handihaler	12 weeks	Trough FEV_1	660
Triple vs LABA/ICS						
Frith PA, et al. Thorax 2015 GLISTEN [14]	RCT	FP/SAL + TIO FP/SAL + GB FP/SAL	Accuhaler + Handihaler Accuhaler + Breezhaler Accuhaler	12 weeks	Trough FEV_1	773
Siler TM, et al. COPD 2016 [15]	RCT	FP/SAL + UMEC FP/SAL	Accuhaler + Ellipta Accuhaler	12 weeks	Trough FEV_1	1225
Singh D, et al. Respir Med 2016 TRIDENT [16]	Crossover	BDP/FOR + GB BDP/FOR	pMDI + pMDI pMDI	7 days	FEV_1 $AUC_{0\text{-}12h}$	178

Studies	Design	Treatment arms	Inhalers	Duration	Primary outcome	N *
Siler TM, et al. Respir Med 2015 [17]	RCT	FF/VI + UMEC FF/VI	Ellipta + Ellipta Ellipta	12 weeks	Trough FEV_1	1238

* N: referred to the number of subjects randomized to any of the treatment arms for RCT and referred to the complete population randomized for the crossover studies. RCT: Randomized controlled trial. BDP: beclomethasone dipropionate; FOR: formoterol fumarate; GB: glycopyrronium bromide; IND: indacaterol; FF: Fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; TIO: tiotropium; SAL: salmeterol; FP: fluticasone propionate; FEV_1: forced expiratory volume in the first second; SGRQ: St. George's Respiratory Questionnaire;: pMDI: pressured metered dose inhaler; AUC: Area under the curve; CT: computed tomography

Table S2. Summary of characteristics of the patients of the trials with open triple combinations

Study	Age (years)	Male (%)	Smokers (%)	ICS (%)	FEV_1 (L)	FEV_1 (%)	Reversibility (%)	Exac./yr	≥ 2 exac. (%)
Multiple comparators									
Hoshino M, Ohtawa J. Respiration 2013 [1]	73	86.6	–	–	1.38	–	–	–	–
Aaron SD, et al. Ann Intern Med 2007 OPTIMAL [2]	67.5	57.9	32.4	72.8	1.12	42.2	–	– *	– *
Saito T, et al. Int J COPD 2015 EAGLE [3]	67.3	98	36	–	–	59.3	4.1	0.1	–
Singh D, et al. Thorax 2008 [4]	62.7	77.0	47.0	53.3		47.1	6.78	0.2	–
Cazzola M, et al. Respir Med 2007 [5]	66.9	86.6	80.0	66.6	–	39.0	12.8	–	–
Triple vs LAMA									
Hoshino M, Ohtawa J. Respirology 2011 [6]	73	87.5	–	–	1.36	64.6	–	–	–
Maltais F, et al. Eur Respir J 2013 [7]	–	–	–	–	–	–	–	–	–
Hanania N, et al. Respir Med 2012 [8]	61.3	50.0	59.0	–	1.67	–	–	–	6.3
Jung KS, et al. Respir Med 2012 [9]	67.0	97.3	–	–	1.22	47.4	–	–	–

Study	Age (years)	Male (%)	Smokers (%)	ICS (%)	FEV_1 (L)	FEV_1 (%)	Reversibility (%)	Exac./yr	≥ 2 exac. (%)
Feng JF, et al. Medicine 2018 [10]	64.9	77.8	54.0	52.8	–	45.1	–	–	–
Lee SD, et al. Respirology 2015 [11]	66.6	97.2	–	–	–	35.8	–	–	–
Williamson PA, et al. Chest 2010 [12]	65.0	63.1	–	–	–	42.0	–	–	–
Welte T, et al. AJRCCM 2009; CLIMB [13]	62.4	76.3	41.6	66.5	1.1	38.1	5.9	1.4	–
Triple vs LABA/ICS									
Frith PA, et al. Thorax 2015; GLISTEN [14] **	68.0	62.0	35.7	66.3	1.55	57.35	22.41	–	35.7 (> 1)
Siler TM, et al. COPD 2016 [15] Study 1	62.7	65.0	50.0	55.0	1.31	46.8	16.2	–	–
Siler TM, et al. COPD 2016 [15] Study 2	64.5	69.0	36.0	59.0	1.15	43.9	16.1	–	–
Singh D, et al. Respir Med 2016; TRIDENT [16]	62.7	66.9	54.5	–	1.41	48.9	16.4	–	–
Siler TM, et al. Respir Med 2015 [17] Study 1	64.9	67.4	39.3	–	–	44.2	14.8	–	–
Siler TM, et al. Respir Med 2015 [17] Study 12	62.6	65.5	58.2	–	–	46.3	13.2	–	–

Results referred to the triple therapy arm in randomized controlled trials and for the complete population in crossover studies.

* At least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomization, as per protocol

** Results referred to the salmeterol/fluticasone + tiotropium combination.

Table S3. Description of the main adverse effects with BDP/FF/GB fixed-dose triple therapy expressed as percentages

	TRILOGY[18]	TRINITY [19]	TRIBUTE [20]
Treatment-emergent adverse events	**54**	**55**	**64**
COPD	31	33	36
Nasopharyngitis	6	5	6
Pneumonia	3	3	4
Hypertension	3		2
Headache	2	4	6
Ischaemic heart disease	1	2	
Viral respiratory tract infection	2	1	3
Oral candidiasis	2		
Cough		2	2
Dyspnoea			3
Back pain			3
Cardiac failure			2
Ischaemic heart disease			1
Serious treatment-emergent adverse events	**15**	**13**	**15**
COPD	10	7	8
Pneumonia	2	2	2
Ischaemic heart disease	<1	1	<1
Cardiac failure	1	<1	1
Death			<1
Atrial fibrillation			0
Respiratory failure			<1

Lung neoplasm			1
Treatment-related adverse events	**4**	**2**	**6**
Oral candidiasis	1	<1	2
Muscle spasms	1	1	
Dry mouth	1	<1	<1
Dysphonia		<1	
Cough			<1
Serious treatment-related adverse events	**<1**	**0**	**<1**
Severe treatment-related adverse events	**11**	**8**	**11**
Treatment-emergent adverse events leading to study drug discontinuation	**5**	**3**	**5**
Treatment-emergent adverse events leading to death	**2**	**2**	**2**
MACE (Major adverse cardiovascular events)	**2**	**2**	

* MACE: Major adverse cardiovascular events, includes acute myocardial infarction, arrhythmias, cardiovascular death, heart failure, and stroke. Treatment emergent adverse effects were those captured throughout the study. Treatment-related adverse effects were all events judged by the investigator as having reasonable causal association to a medical product.

Table S4. Description of the main adverse effects with FF/UMEC/VI fixed-dose triple therapy expressed as percentages.

	FULFIL [21]	IMPACT [22]
Adverse events of special interest*		
Cardiovascular effects	4.3	11
Pneumonia	2.2	8
Local steroid effects	2.1	
Anticholinergic syndrome	1.8	4
Hypersensitivity	1.1	
Hyperglycemia/diabetes	0.5	
Decreased bone mineral density	0.4	
lower respiratory tract infection (excluding pneumonia)	0.3	5
Ocular effects	0.1	
Urinary retention	0.1	
Asthma/bronchospasm	0	<1
Cardiovascular effects	11	
Urinary retention		<1

* Adverse events of special interest are based on an analysis of a group of prespecified adverse events that are associated with the use of inhaled glucocorticoids, long-acting muscarinic antagonists, or long-acting β_2-agonists

Table S5. Description of the main adverse effects with BUD/FOR/GB fixed-dose triple therapy expressed as percentages.

	KRONOS [23]
Nasopharyngitis	8
Upper respiratory tract infection	10
Chronic obstructive pulmonary disease	3
Bronchitis	3
Muscle spasms	3
Dysphonia	3
Hypertension	2
Dyspnea	1
Back pain	1
Nausea	1

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