COPD LANDMARK TRIALS: Triple Therapy Overview

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POPULATION / CHARACTERISTICS	IMPACT 2018[1,2]	ETHOS 2020[3,4]	TRIBUTE 2018[5]
Inclusion criteria & baseline characteristics *^pre-study AECOPD criteria varied by FEV_1*	*N=10355, Duration: 52 weeks*	*N=8588, Duration: 52 weeks*	*N=1532, Duration: 52 weeks*
	Age ≥40 (average 65yr); COPD duration ≥5yr: 63%	Age 40-80 (average 65yr); average COPD duration 8yr	Age ≥40 (average 64yr); average COPD duration 8yr
	FEV_1 <80% (mean 46%), CAT ≥10 (mean 20.1 points)	FEV_1 25-65% (mean 43%), CAT ≥10 (mean 20 points)	FEV_1 <50% (mean 36%), CAT ≥10 (mean not reported)
	≥1 moderate-severe exacerbation in past yr^: >99%	≥1 moderate-severe exacerbation in past yr^: 99.9%	≥1 moderate-severe exacerbation in past yr: 100%
	≥1 maintenance inhaler (pre-study: ICS 71%; TT 38%) High exacerbation risk at baseline: 70% of patients	≥2 maintenance inhalers (pre-study: ICS 80%; TT 39%)	Maint. inhaler(s) ≥2 mo prior to study: LAMA or any 2 of LAMA, LABA, ICS; no triple therapy (pre-study ICS 65%)
	Baseline eosinophils (EOS) ≥0.15x10⁹/L: 57%	Baseline eosinophils ≥0.15x10⁹/L ~60%; ≥0.3x10⁹/L ~15%	Average eosinophils: 0.23-0.247x10⁹/L
	Excluded (ineligible) at screening: ~25%	Excluded (ineligible) at screening: 46%	Excluded (ineligible) at screening: 27%
Intervention (LAMA/LABA/ICS) **Comparator** (LAMA/LABA) *(some RCTs had multiple study arms)*	UMEC/VIL/FF 62.5/25/100mcg DPI (***TRELEGY Ellipta***) UMEC/VIL 62.5/25mcg DPI (***ANORO Ellipta***) *Dose - all study arms: 1 inhalation daily*	GLY/FFD/BUD 9/4.8/160mcg pMDI (***BREZTRI Aerosphere***) GLY/FFD 9/4.8mcg pMDI (🇺🇸 ***BEVESPI Aerosphere***) *Dose - all study arms: 2 inhalations BID*	GLY/FFD/BDP 9/5/87mcg pMDI (***TRIMBOW MDI****) *Dose: 2 inhalations BID* GLY/IND 43/85mcg DPI (***ULTIBRO Breezhaler***) *Dose: Contents of 1 cap inhaled via Breezhaler daily*
OUTCOMES – TRIPLE THERAPY (LAMA/LABA/ICS) **VS DUAL THERAPY** (LAMA/LABA)			
1° outcome — **Rate of mod-severe exacerbations per patient/year†**	0.91 vs 1.21; RR 0.75 (0.7-0.81)[1]	1.08 vs 1.42; RR 0.76 (0.69-0.83)[3]	0.5 vs 0.59; RR 0.85 (0.72-0.995)[5]
Subgroup analysis: Eosinophils (EOS)	EOS <0.15x10⁹/L: 0.85 vs 0.97; RR 0.88 (0.78-0.99)[6] EOS ≥0.15x10⁹/L: 0.95 vs 1.39; RR 0.68 (0.62-0.75)[6]	EOS <0.15x10⁹/L: rate not reported; HR 0.87 (0.75-1.02) NS[4] EOS ≥0.15x10⁹/L: rate not reported; HR 0.68 (0.61-0.77)[4]	EOS <0.2x10⁹/L: rate not reported; RR 0.87 (0.69-1.1) NS[5] EOS ≥0.2x10⁹/L: rate not reported; RR 0.81 (0.65-1.01) NS[5]
Subgroup analysis: Pre-study ICS status	ICS at screening: 0.98 vs 1.38; RR 0.71 (0.65-0.77)[10] No ICS at screening: 0.73 vs 0.83; RR 0.88 (0.76-1.03) NS[10]	ICS at screening: 1.14 vs 1.51; RR 0.76 (0.68-0.84)[8] No ICS at screening: 0.84 vs 1.11; RR 0.75 (0.61-0.94)[8]	
2° outcomes — **Rate of severe exacerbations per patient/year†**	0.13 vs 0.19; RR 0.66 (0.56-0.78)[1]	0.13 vs 0.15; RR 0.84 (0.69-1.03) NS[3]	0.07 vs 0.09; RR 0.79 (0.06-1.13) NS[5]
All-cause mortality	1.3% vs 2.2% (NNT≈112/yr); HR 0.58 (0.38-0.88)[6]	1.3% vs 2.3% (NNT≈ 100/yr); HR 0.54 (0.34-0.87)[3]	0.4% vs 1%;[5] HR not reported (NS)¥
Subgroup analysis: Pre-study ICS status	ICS at screening: 1.03% vs 2.13%; HR 0.44 (0.27-0.71)[11] No ICS at screening: 1.79% vs 1.06%; HR 1.49 (0.55-4.06) NS[11]	ICS at screening: 1.3% vs 3% HR 0.41 (0.25-0.69)[9] No ICS at screening: 1.8% vs 1.2% HR 1.49 (0.49-4.55) NS[9]	
SGRQ response (MCID ↓4-points)	MCID achieved: 42% vs 34% (NNT≈13/yr); OR 1.4 (1.3-1.6)[1]	MCID achieved: 44% vs 37% (NNT≈15/yr); OR 1.4 (1.2-1.6)[4]	MCID achieved: 41% vs 36%; OR 1.22 (0.99-1.51) NS[5]
	Mean difference: ↓1.8-points (↓2.6 to ↓1);[1] ?clinical significance	Mean difference: ↓1.88-points (↓2.84 to↓0.91);[4] ?clinical significance	
FEV_1 outcomes (MCID ↑100mL)	Mean difference: ↑54mL (↑36 to ↑69);[1] ?clinical significance		MCID achieved: 23% vs 16%; OR 1.19 (0.91-1.55) NS[5]
Safety — **Pneumonia**	Radiologically confirmed: 3.7% vs 1.9%[7] (NNH≈56/yr)¥ Investigator-reported: 7.5% vs 4.6%[1] (NNH≈35/yr)¥	4.2% vs 2.3%[3] (NNH≈ 53/yr)¥ (Confirmed by an independent clinical end-point committee)	4% vs 4%;[5] RR not reported (NS)¥
	-↑oral candidiasis: 3.9% vs 2%[1] (NNH ≈ 53/yr)¥ - Excluded patients on long-term oxygen (>3L/min at rest).	-↑dysphonia/aphonia 1.8% vs 0.3%[4] (NNH≈67/yr)¥ - Excluded significant disease (e.g. cardiovascular disease).	-TT more benefit in chronic bronchitis vs emphysema. -Small N; unable to detect differences in 2° outcomes.
Additional considerations	-Mild COPD (FEV ≥80%), low symptom burden (CAT <10), and no exacerbations in past year excluded; lack insight re: role of triple therapy for initial treatment of COPD. -Abrupt ICS discontinuation in majority of those in LAMA/LABA group may have confounded results (?increased exacerbation risk after stopping ICS). -Patients in these RCTs who had bronchodilator reversibility (18%IMPACT, 31%ETHOS, 8.6%,TRIBUTE) were more likely to have a favourable response to ICS-containing treatment arms. -Significant results were noted in some secondary outcomes, however the studies lacked sufficient power, limiting confidence in the magnitude of the effect. -Eosinophils ≥0.15x10⁹/L were associated with a more substantial reduction in exacerbations; the role of baseline eosinophil counts may help inform COPD treatment changes.		
Bottom Line	Reduced rates of moderate-severe exacerbations with use of triple therapy are seen consistently across these RCTs; results also trended in favour of ↓severe exacerbation rates, ↓mortality, and improved health status at the risk of increased ICS-related side effects, most notably pneumonia. Triple therapy is likely to benefit those with moderate-very severe airflow limitation (FEV1 <80%), high symptom burden (CAT≥10), and a history of moderate-severe exacerbation(s) within the past year.		
RxFiles Trial Summaries	***IMPACT*** *– Link to trial summary*	***ETHOS*** *– Link to trial summary*	***TRIBUTE*** *– Link to trial summary*

†Model-estimated rates based on modeling rates adjusted for continuous and categorical covariates listed in the supplementary appendix. ¥ Not provided in manuscript/supplement – calculated by RxFiles.

Abbreviations: **Δ**=change **AECOPD**=acute exacerbation of COPD **BDP**=beclomethasone dipropionate **BUD**=budesonide **CAT**=COPD assessment test **COPD**=chronic obstructive pulmonary disease **EOS**=eosinophils (blood eosinophil count) 0.15x10⁹/L=150 cells/mcL **FEV_1**=forced expiratory volume in 1 second **FF**=fluticasone furoate **FFD**=formoterol fumarate dihydrate **GLY**=Glycopyrronium **HR**=hazard ratio **ICS**=inhaled corticosteroid **IND**=indacaterol **LABA**=long-acting beta agonist **LAMA**=long-acting muscarinic antagonist **MCID**=minimal clinically important difference **mo**=month(s) **MOD**=moderate **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-significant **OR**=odds ratio **RCT**=randomized controlled trial **RR**=risk ratio **SEV**=severe **SIG**=significant **TT**=triple therapy **UMEC**=umeclidinium **VIL**=vilanterol

COPD exacerbation definitions: moderate exacerbation=resulted in treatment with antibiotics &/or systemic corticosteroids; severe exacerbation=resulted in hospital admission or death.
***TRIMBOW** approved but not yet marketed in Canada (as of January 2026).

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