Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD[1]

InforMing the PAthway of COPD Treatment (IMPACT, 2018) Trial Summary

SUMMARY

- **IMPACT** included individuals (≥40yr) with symptomatic COPD (CAT ≥10); with either 1) FEV1 <50% and ≥1 moderate (mod) or severe exacerbation in past year OR 2) FEV1 50-80% and ≥2 mod or ≥1 severe exacerbation in past year.
- 71% of participants were on an inhaled corticosteroid (ICS)-containing regimen at time of screening.
- Participants who received triple therapy (TT) [fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg **TRELEGY**] versus ICS/LABA [fluticasone furoate 100 mcg/vilanterol 25 mcg **BREO**] or LAMA/LABA [umeclidinium 62.5 mcg/vilanterol 25 mcg **ANORO**]; x 1 year:
  - Had lower rates of moderate or severe exacerbations (TT vs LABA/ICS: RR=0.85 [0.80, 0.90]; TT vs LAMA/LABA: RR=0.75 [0.70, 0.81])* -- primarily driven by lower rates of moderate exacerbations.
  - Had lower risk of mortality vs LAMA/LABA only (HR=0.58 [0.38, 0.88] **NNT≈112**/yr)
  - Had higher risk of pneumonia (TT: 7.52%; ICS/LABA: 6.82%; LAMA/LABA: 4.59% | TT vs LAMA/LABA: RR=1.63 **NNH≈35**/yr)
  - **For every 100 patients treated with TT vs LAMA/LABA x 1 year:**
    ~3 fewer moderate-to-severe COPD exacerbations
    ~1 less death
    ~2-3 more cases of pneumonia
  - Post-hoc analyses[2,3]: In ICS-naïve patients, the magnitude of effect of TT vs LAMA/LABA on rate of exacerbations was less certain (RR=0.88; 0.76, 1.03) and no mortality benefit was demonstrated (HR=1.49; 0.55, 4.06). This suggests that abrupt ICS withdrawal may be associated with worse outcomes.

Bottom Line:

- Patients on ICS-containing regimens should not have ICS abruptly discontinued.
- In patients with symptomatic (CAT≥10) moderate to severe COPD (FEV1≤80%), who continue to experience exacerbations on current therapy, triple therapy reduces the risk of future exacerbations. Compared to dual therapies, triple therapy may also result in improvements to health-related quality of life (**NNT≈13**, per St. George's Respiratory Questionnaire (SGRQ) responder analysis - though mean score change from baseline was not clinically significant between groups).

*Model-estimated rates of exacerbations assume equal distribution of exacerbations across patients, thus rates may not reflect real-world circumstances.

BACKGROUND

- COPD exacerbations impact health status and lung function, with moderate to severe COPD exacerbations being associated with increased risk of further exacerbations, hospitalization, and mortality.[4-8]
- **IMPACT** was published Apr 2018; it is one of the first major trials that assessed triple therapy vs. dual therapy in COPD patients with high symptom burden and high exacerbation risk.
  - **TRIBUTE**[9] (Mar 2018 – TT vs. LABA/LAMA), **ETHOS**[10] (2020 – 4-arm TT vs. comparators)
- This trial led to the approval of **TRELEGY ELLIPTA** – the first single-inhaler triple therapy on the market (2018).
- **IMPACT** and **ETHOS** are the two main triple therapy trials that have informed the strong recommendations in the *2023 Canadian Thoracic Society (CTS) Guideline on Pharmacotherapy in Patients With Stable COPD*[4] for use of triple therapy in patients with moderate to severe COPD and high symptom burden/high exacerbation risk.

IMPACT TRIAL DESIGN AND POPULATION[1,11,12] (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN: designed by the sponsor (GlaxoSmithKline©) and their "academic partners"

- Randomized, double-blind, 3-arm parallel-group, multicenter trial performed in 37 countries (including Canada) from June 2014 to July 2017.
- 2-week run-in period (to assess compliance with symptom diary and establish baseline SABA use); individuals continued their baseline inhaler(s) (including ICS-containing regimens) prior to site-based computerized randomization for treatment allocation.

POPULATION:

- **INCLUSION included:** ≥40yr, symptomatic COPD (CAT ≥10), current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at screening; either, 1) FEV1 <50% and ≥1 mod or severe exacerbation* in past year, or 2) FEV1 50-80% and ≥2 mod or ≥1 severe exacerbation in past year (spirometry confirmed); on LAMA, LABA, ICS of any combo
  *mod=exacerbation leading to treatment with antibiotics or systemic corticosteroid; severe=exacerbation leading to in-patient hospitalization or death
- **EXCLUSION included:** current diagnosis of asthma (subjects could have a prior history), unstable or life-threatening cardiac disease (myocardial infarction or unstable angina <6mo, unstable/life-threatening cardiac arrhythmia requiring intervention <3mo, NYHA Class IV heart failure), use of long-term oxygen therapy >3L/min at rest, long-term antibiotic therapy, systemic steroids within 30 days of screening
- **POPULATION at screening:** (well-balanced across groups)
  - **n=10,355**; mean age 65.3±8.3yr, White 78%, male 66%, former smokers 65%
  - ≥5yr history COPD 63%
  - FEV1≥50% to <80% predicted [GOLD Grade 2 (mod)] 36%, FEV1<50% predicted [GOLD Grade 3 or 4 (severe to very severe)] 64%
  - ≥2 moderate or ≥1 severe exacerbation in the past year 70%
  - Mean COPD Assessment Test (CAT) 20.1±6.1 (moderate-high symptom burden)
  - blood eosinophil count ≥150 cells/mcL 57%
  - COPD therapy: ICS-containing regimen 71%
  - Comorbidities(present in ≥5%): hypertension 51%, hypercholesterolemia 31%, diabetes mellitus 15%, coronary artery disease 9%, osteoporosis 7%, cardiac arrhythmia 5%

INTERVENTION/COMPARISON:

- **52 weeks of a once-daily combination of**: **triple therapy** (fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg **TRELEGY**) versus **ICS/LABA** (fluticasone furoate 100 mcg/vilanterol 25 mcg **BREO**) or **LAMA/LABA** (umeclidinium 62.5 mcg/ vilanterol 25 mcg **ANORO**) as control (2:2:1 stratification)
  - Powered to detect a 12% and 15% reduction in annual rates of mod and severe exacerbations for triple therapy vs ICS/LABA and LAMA/LABA, respectively.
  - Is comparison fair? Uncertain - 71.5% of LAMA/LABA group had ICS abruptly discontinued.

OUTCOMES – over 52-week study period:

- **Primary:** annual rate of model-estimated on-treatment mod and severe exacerbations
- **Secondary/Others**:
  - annual rate of severe exacerbations, time to first mod or severe exacerbation, change in baseline trough FEV1 and SGRQ) scores
  - various additional subgroup, responder, mortality, and safety analyses

RESULTS[1-3,11-13] follow up over 52 weeks

CLINICAL ENDPOINTS	TRIPLE THERAPY n=4151	LABA/ICS n=4134	LAMA/ LABA n=2070	TRIPLE THERAPY vs LABA/ICS		TRIPLE THERAPY vs LAMA/LABA		COMMENTS
PRIMARY OUTCOME (ITT)**								
Rate of mod or severe exacerbations/yr	0.91 (0.87, 0.95)	1.07 (1.02, 1.12)	1.21 (1.14, 1.29)	RR=0.85 (0.80, 0.90)*	↓0.16 exacerbations per patient-year	RR=0.75 (0.70, 0.81)*	↓0.3 exacerbations per patient-year	Triple therapy vs LAMA/LABA: approximately 1 fewer moderate-to-severe exacerbation for every 3 patient-years of treatment.
SECONDARY/OTHER OUTCOMES (ITT)**								
Rate of severe exacerbations/yr	0.13 (0.12, 0.14)	0.15 (0.13, 0.16)	0.19 (0.17, 0.22)	RR=0.87 (0.76, 1.01)	NS	RR=0.66 (0.56, 0.78)*	↓0.06 exacerbations per patient-year	Subgroup; eosinophil counts[13] ≥0.15x10^9/L: TT vs LAMA/LABA had a greater magnitude of effect (0.95 vs 1.39; RR=0.68; 0.62, 0.75); though benefit persisted in those with <0.15x10^9/L (0.85 vs 0.97; RR=0.88; 0.78, 0.99)
Rate of mod exacerbations/yr	0.75 (0.71, 0.79)	0.89 (0.85, 0.93)	0.97 (0.91, 1.04)	RR=0.84 (0.79, 0.93)*	↓0.14 exacerbations per patient-year	RR=0.77 (0.71, 0.84)*	↓0.22 exacerbations per patient-year	
% patients with moderate or severe exacerbation[15]	47%	49%	50%		NS		NNT≈34/yr	
% patients with severe exacerbation[15]	11%	11%	13%		NS		NNT≈50/yr	
Trough FEV1 mean change from baseline (mL)	94mL (86, 102)	-3mL (-12, 6)	40mL (28, 52)	Mean difference=97mL (85, 109)*		Mean difference=54mL (39, 69)*		Minimum clinically important difference (MCID) for trough FEV1=100 mL; none of agents achieved – TT CI crosses threshold
SGRQ score mean change from baseline (points)	–5.5 (–5.9, –5.0)	–3.7 (–4.2, –3.2)	–3.7 (–4.4, –3.0)	Mean difference: –1.8 points (–2.4, –1.1)*		Mean difference: –1.8 points (–2.6, –1.0)*		MCID for SGRQ=4 points; absolute difference between agents (-1.8) does not achieve MCID, although TT had greater rate of response per MCID vs both dual therapies
SGRQ score rate of response	42%	34%	34%	OR=1.41 (1.29, 1.55)*	NNT≈13/yr	OR=1.41 (1.26, 1.57)*	NNT≈13/yr	
Dyspnea responder (n=5058) (TDI ↑ ≥1 unit per MCID)	36%	29%	30%	OR=1.36 (1.19, 1.55)	NNT≈15/yr	OR=1.33 (1.13, 1.57)	NNT≈17/yr	
MORTALITY (ITT)***								
All-cause mortality	1.3% (0.99, 1.74)	1.3% (0.98, 1.75)	2.2% (1.59, 2.96)	HR=0.95 (0.64, 1.40) NS		HR=0.58 (0.38, 0.88)		TT demonstrated lower rates of mortality compared to LAMA/LABA (HR=0.58; 0.38, 0.88; NNT≈112/yr)
SAFETY (ITT)***								
Any serious AE	21.56%	20.56%	22.70%					Rates of adverse effects (AE) were generally similar across groups. Pneumonia$^{radiologically\ confirmed}$ TT 3.7% vs LAMA/LABA 1.9% (NNH≈56/yr)[15]
Drug-related serious AE	1.54%	1.38%	1.30%					
Pneumonia (investigator-reported)	7.52%	6.82%	4.59%	RR=1.11	NNH≈143/yr	RR=1.63	NNH≈35/yr	
Oral candidiasis	3.88%	3.53%	1.98%			RR=1.96	NNH≈53/yr	
POST-HOC ANALYSES -- Effects of ICS Withdrawal[2,3]								
Rate of mod or severe exacerbation/yr	ICS at screening ***n=7360***	0.98 (0.93, 1.03)		1.38 (1.29, 1.48)			RR=0.71 (0.65, 0.77)*	↓0.4 exacerbations per patient-year	Individuals on ICS at screening had higher exacerbation rates than ICS-naïve when switched to LAMA/LABA versus TT. ICS-naïve patients demonstrated a numerical mod or severe exacerbation benefit from TT vs LAMA/LABA (CI ranged from modest benefit to negligible harm), but did not demonstrate mortality benefit.
	No ICS at screening ***n=2995***	0.73 (0.67, 0.80)		0.83 (0.73, 0.94)			RR=0.88 (0.76, 1.03)	NS	
Rate of severe exacerbation/yr	ICS at screening	0.14 (0.13, 0.16)		0.22 (0.19, 0.26)			RR=0.65 (0.54, 0.80)*	↓0.08 exacerbations per patient-year	
	No ICS at screening	0.09 (0.07, 0.11)		0.14 (0.10, 0.19)			RR=0.65 (0.45, 0.93)	↓0.05 exacerbations per patient-year	Subgroup; excluding first 30 days to account for acute ICS withdrawal: benefit of TT was maintained over LAMA/LABA in prior ICS users (RR=0.77; 0.75, 0.88)
All-cause mortality	ICS at screening	1.03%		2.13%			HR=0.44 (0.27, 0.71)*		{Interpretation may be limited by smaller sample size of ICS-naïve group}
	No ICS at screening	1.79%		1.06%			HR=1.49 (0.55, 4.06) NS		

(denotes 95% confidence interval)

*p<0.001
**Model-estimated rates of exacerbations adjust for outliers and pre-defined covariates; assumes equal distribution of exacerbations across patients (note: actual rates were similar)
***Rates extracted from manufacturer's *Clinical Study Report*[13] may differ slightly from those in published article/supplemental materials

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Asked an important question regarding the relative benefits vs risks of triple therapy in patients with high disease burden and exacerbation risk
- Large sample size, double-blinded trial
- Groups were well-balanced at baseline based on relevant prognostic characteristics
- Employed clear diagnostic and categorization criteria for exacerbations, mandatory pneumonia screening, and external adjudication of serious adverse events
- Analyzed a variety of patient-important outcomes – including rate of exacerbations, health-related quality of life, dyspnea, mortality

LIMITATIONS:

- Over 70% of patients were receiving ICS at baseline, 71.5% of LAMA/LABA group had steroid withdrawn – resulting in biasing of results in favour of triple therapy
- Duration of the trial limits the assessment of long-term mortality and safety benefits (FDA recommends a trial duration of ≥3yr when assessing mortality in COPD treatment studies).
- Industry-sponsored trial raises risk of bias - sponsor-designed, paid for editorial support, lead author is employee of sponsor
- Fewer patients in LAMA/LABA group decreases statistical precision of secondary/other results
- High treatment discontinuation rates in dual therapy groups may lead to over-estimation of benefits of triple therapy (TT: 18%, ICS/LABA: 25%, LAMA/LABA: 27%)

UNCERTAINTIES:

- Is a 0.3 absolute reduction in rates of moderate to severe exacerbations meaningful to patients?
- Is there a patient group that benefits from ICS withdrawal?
- Considering worsened FEV1 in ICS/LABA group vs. LAMA/LABA, does LAMA have a greater effect on lung function/obstruction than LABA?
- Does triple therapy improve mortality outcomes in ICS-naïve patients (~30% of **IMPACT** patients)?
- What is the magnitude of effect of triple therapy on exacerbations in ICS-naïve patients?

ADJUSTED RATES OF MODERATE TO SEVERE EXACERBATIONS BY PRIOR MEDICATION USE – POST-HOC ANALYSIS[2]

Prior COPD Medication Class	Triple Therapy	LAMA/LABA	Triple Therapy vs LAMA/LABA	
Triple therapy (ICS/LAMA/LABA)	1.22 (1.15, 1.30)	1.76 (1.61, 1.91)	RR=0.70 (0.63, 0.77)	p<0.001
ICS/LABA	0.71 (0.65, 0.78)	0.93 (0.82, 1.06)	RR=0.76 (0.65, 0.89)	p<0.001
LAMA/LABA	0.89 (0.77, 1.03)	1.08 (0.88, 1.32)	RR=0.82 (0.64, 1.06)	NS
LAMA	0.62 (0.51, 0.75)	0.62 (0.47, 0.82)	RR=0.99 (0.71, 1.39)	NS

- Should triple therapy be used first-line over dual-therapies in patients who have moderate to high symptom burden and are at high risk for exacerbations? (CTS recommendation)

Other notes of interest:

Costs: Umeclidinium + Vilanterol + Fluticasone furoate **TRELEGY** 62.5+25+100/200mcg DPI☎✆ ($160/30 days), Vilanterol + Fluticasone furoate **BREO** 25+100mcg DPI☎✆ ($116/30 days), Umeclidinium + Vilanterol **ANORO** 62.5+25mcg DPI☎▼ ($107/30 days)

RxFILES RELATED LINKS

ETHOS Trial Summary; **TRIBUTE** Trial Summary; **WISDOM** Trial Summary; **SUNSET** Trial Summary; **FLAME** Trial Summary

Abbreviations: AE=Adverse Event **CAT**=COPD Assessment Test **CI**=Confidence Interval **COPD**=Chronic Obstructive Pulmonary Disease **CTS**=Canadian Thoracic Society **FDA**=Food and Drug Administration **FEV1**=Forced Expiratory Volume in 1 Second **GOLD**=Global Initiative for Chronic Obstructive Lung Disease **HR**=Hazard Ratio **ICS**=Inhaled Corticosteroid **ITT**= Intent to Treat **LABA**=Long-Acting Beta Agonist **LAMA**=Long-Acting Muscarinic Antagonist **MCID**=Minimum Clinically Important Difference **NNH**=Number Needed to Harm **NNT**=Number Needed to Treat **NYHA**=New York Heart Association **OR**=Odds Ratio **RR**=Rate Ratio **SABA**=Short-Acting Beta Agonist **SGRQ**=St. George's Respiratory Questionnaire **TDI**=transition dyspnea index **TT**=Triple Therapy

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Additional Author Commentary

1) Does IMPACT provide evidence that triple therapy offers meaningful benefit to patients with COPD?

Appreciating the true impact of triple therapy in IMPACT should keep in mind the specifics of the population included. Otherwise, the benefits of triple therapy may be overstated if over-generalized, owing to the high rate of baseline ICS use in the trial. In alignment with current COPD treatment guidelines, some clinicians advocate for increased use of triple therapy in patients **at high risk of exacerbations** due to the potential mortality benefits. Controversially, other clinicians perceive triple therapy as marginally beneficial, costly, and potentially harmful.

In the **IMPACT** trial, there were only small absolute differences in the rates of patients that experienced clinically significant improvements in symptom-based outcomes on triple therapy vs. LAMA/LABA (e.g., SGRQ 8%; Transient Dyspnea Index 6%). **For patients who were previously on an ICS**, the benefits of triple therapy over dual therapies on rates of moderate or severe exacerbations are more certain compared to ICS-naïve patients. However, triple therapy did result in lower rates of severe exacerbations in both ICS-exposed and ICS-naïve patients compared to LAMA/LABA (ICS exposed: RR=0.65[0.54, 0.80]; ICS naïve: RR=0.65 [0.45, 0.93]), which may translate to fewer hospitalizations and improved health outcomes. A mortality benefit for ICS-naïve patients was not demonstrated in this study, leading to an unanswered question; did triple therapy lower risk of mortality, or did ICS-withdrawal increase risk of mortality?

Thus, the decision to initiate triple therapy is nuanced and should be **individualized** to each patient, considering factors such as exacerbation history, symptom burden, prior ICS use, infection risk (i.e. pneumonia), and goals of care. The **IMPACT** trial does provide evidence that triple therapy lowers the rate of exacerbations in a high disease burden, high symptom burden, high exacerbation risk population vs dual therapies, and the relative benefit vs risk depends on patient-related factors. Not every patient who has experienced a moderate-severe exacerbation will necessarily benefit substantially from triple therapy; and as with other preventative therapies, the clinical value offered should include, but not be restricted to, symptomatic improvement.