Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD[1]

Efficacy and Safety of Triple Therapy in Obstructive Lung Disease

ETHOS (2020) Trial Summary

SUMMARY

- **ETHOS** compared two LAMA/LABA/ICS triple therapy (TT) regimens (TT320: GLY/FFD/BUD 18/9.6/320mcg per dose, TT160: GLY/FFD/BUD 18/9.6/160mcg per dose) to two dual therapy regimens (LAMA/LABA: GLY/FFD 18/9.6mcg per dose, LABA/ICS: FFD/BUD 9.6/320mcg per dose) in a 1 year trial of 8588 COPD patients with moderate-very severe airflow limitation, high symptom burden, and ≥1 moderate-severe exacerbation within the past year. 80% of participants were on ICS-containing regimens prior to randomization.
- TT had **lower rates of moderate-severe exacerbations*** compared to dual therapy (TT320 vs LAMA/LABA RR 0.76 [0.69-0.83] and TT320 vs LABA/ICS RR 0.87 [0.79-0.95]) but there was no difference in severe exacerbations between TT320 and LAMA/LABA. (Primary outcome driven by a reduction of moderate exacerbations vs inadequate power to detect difference in severe outcomes?)
- TT320 results showed a **reduction in all-cause mortality** (TT320 vs LAMA/LABA: HR 0.54 [0.34-0.87]; ARR 1% **NNT≈100**/yr) but no mortality difference within the ICS-naïve subgroup,[6] which suggests abrupt ICS withdrawal impacted the results.
  - The mortality result should be **interpreted with caution;** it was a secondary endpoint (and abrupt ICS withdrawal may have been a confounding factor).
  - There was no mortality difference between TT320 and the other study arms.
- ICS-containing groups had **higher rates of confirmed pneumonia** (TT320 vs LAMA/LABA: 4.2% vs 2.3% **NNH≈53**/yr).
- For every **100 patients** treated with TT320 (**BREZTRI**) LAMA/LABA/ICS vs LAMA/LABA x 1 year:
  - **~2 fewer moderate-to-severe COPD exacerbations**† *(primary outcome)*
  - **~1 less death** *(secondary outcome)*
  - **~2 more cases of pneumonia** *(safety outcome)*

Bottom Line:

- In patients with moderate-very severe COPD, and ≥1 moderate-severe exacerbation within the past year, triple therapy appears more effective than dual therapy at reducing rates of moderate-severe COPD exacerbations. While triple therapy might offer a mortality benefit, **ETHOS** wasn't designed to establish this effect, and subgroup analysis suggests abrupt ICS discontinuation confounded results. Further study is warranted.

*Model-estimated rates of exacerbations assume equal distribution of exacerbations across patients; rates may not reflect real-world circumstances.
†RxFiles raw calculation suggests result may not be statistically significant.

BACKGROUND [10, 13-14]

- COPD is a progressive disease affecting millions; it's the 3rd leading cause of death worldwide.
- Goals of therapy include reducing symptoms, improving health status, preventing exacerbations, and reducing mortality rates.
- The mainstay of pharmacological treatment for COPD has been inhaled therapy added in a stepwise approach starting with long-acting bronchodilator(s) and eventually titrating up to triple therapy with LAMA/LABA/ICS.
- CTS'23 COPD guidelines and the GOLD'25 report differ regarding when to escalate from dual to triple inhaled therapy.
- While two previous trials compared safety and efficacy of single-inhaler triple therapy vs. single-inhaler dual therapy [IMPACT, TRIBUTE] no inhaler study has proven reduced all-cause mortality in patients with COPD.

ETHOS TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN:

- Randomized, double-blind, phase 3, parallel-group, multicentre trial (26 countries; 812 sites). Duration 52 weeks.
- ***Industry involvement:*** *AstraZeneca* funded the trial, was involved in trial design, and reviewed/provided feedback on the manuscript.
- Enrollment & randomization of 8588 participants from June 2015-July 2018. Randomization stratified by exacerbation history (1 or ≥2 moderate-severe exacerbations*), FEV_1 (25%-<50% or 50-<65%), eosinophils (<150 or ≥150 cells/mcL), and country.
  *definition: moderate exacerbation = resulted in treatment with systemic glucocorticoids, antibiotics, or both for ≥3 days; severe exacerbation = resulted in hospitalization or death.
- 1–4-week screening period*: All maintenance inhalers discontinued, except ICS*. Participants given scheduled ipratropium & as-needed albuterol during this time. *Ipratropium and pre-study ICS discontinued on day of randomization.*

POPULATION

- **Inclusion criteria:** age 40-80, COPD (FEV_1:FVC <0.7), CAT≥10, FEV_1 25-65%, ≥2maintenance inhalers, ≥10 pack yr smoking history, history of moderate-severe exacerbation(s)* within the past year; if FEV_1 <50%: ≥1 mod-severe exacerbation; if FEV_1 ≥50%: ≥2 moderate or ≥1 severe exacerbation
- **Exclusion criteria:** Current asthma (or diagnosed within the past 5-10 years), COPD from alpha-1 antitrypsin deficiency, acute worsening of COPD resulting in treatment with oral corticosteroids or antibiotics within 6 weeks prior to screening, significant diseases or conditions other than COPD (including CV disease).
- **POPULATION at baseline:**
  Groups reasonably balanced at baseline; average age 65, male 60%, white 85%, ≥1 CV risk factor 71%, current smoker 41%, smoking history 47-48 pack yr, average COPD duration 8yr, CAT = 20, FEV_1 <50% = 71% (mean FEV_1 43%), ≥2 mod-severe exacerbations past 12 months = 56%, eosinophils: ≥150 cells/mcL = 60%, ≥300 cells/mcL = 15%, bronchodilator reversibility 31%, **ICS use prior to randomization ~80%**.
  Most common therapies prior to randomization: LAMA/LABA/ICS (39%), LABA/ICS (31%), LAMA/LABA (14%). [11]

INTERVENTION/COMPARISON:

- Subjects received the same device: Aerosphere pressurized MDI 2 puffs bid. (PRN SABA available from screening to end of study). Device training provided during screening visits 1-4. Adherence to ≥70% of the inhaler regimen required to be eligible for randomization; monitored throughout study via eDiary.

- 4 study arms: 2 triple therapy regimens with different ICS dose vs 2 different dual therapy medication combinations. Allocated 1:1:1:1.
    1. **TT320**: Glycopyrrolate 9mcg / Formoterol 4.8mcg / Budesonide 160mcg per puff (18/9.6/320mcg per dose) **BREZTRI AEROSPHERE**
    2. **TT160**: Glycopyrrolate 9mcg / Formoterol 4.8mcg / Budesonide 80mcg per puff (18/9.6/160mcg per dose)
    3. **LAMA/LABA**: Glycopyrrolate 9mcg / Formoterol 4.8mcg per puff (18/9.6mcg per dose) **BEVESPI AEROSPHERE**
    4. **LABA/ICS**: Formoterol 4.8mcg / Budesonide 160mcg (9.6/320mcg per dose)

OUTCOMES – 52 weeks

- **Primary:** Rate of moderate-severe exacerbations.
- **Secondary:** All-cause mortality, time to first moderate-severe exacerbation, rate of severe exacerbations, and others.
- **Subgroup Analysis**: Exacerbation history, ICS use prior to randomization, blood eosinophil counts.
- **Discontinuation rate**: 19-25%; slightly lower for triple therapy than dual therapy groups.

KEY RESULTS

Clinical Endpoints N = 8509 (mITT)	Triple Therapy Intervention Groups		Dual Therapy Control Groups		Relative Risk/Hazard Ratio NNT/NNH or ARR/ARI		Comments
	TT 320 n = 2137	TT160 n = 2121	LAMA/LABA n = 2120	LABA/ICS n = 2131	TT320 vs LAMA/LABA	TT320 vs LABA/ICS	
PRIMARY ENDPOINT							TT320 vs LAMA/LABA: approximately 1 less moderate-to-severe exacerbation for every 3 patient-years of treatment.
Moderate-severe exacerbation* (rate/year)	1.08	1.07	1.42	1.24	RR 0.76 (0.69-0.83) ↓0.34 exacerbations per patient-year	RR 0.87 (0.79-0.95) ↓0.16 exacerbations per patient-year	
SECONDARY ENDPOINT							TT320 vs LAMA/LABA: TT320 delayed time to first exacerbation by **~1.1 months** (3.7mo vs 2.6mo)[4] **Moderate-severe exacerbation rates**[4] similar in those on ICS at screening: 1.14 vs 1.51 RR 0.76 (0.68-0.84) vs no ICS at screening: 0.84 vs 1.11 RR 0.75 (0.61-0.94) **Blood eosinophil count**[11] (0.15x10^9/L=150 cells/mcL) -Higher eosinophils associated with greater certainty of benefit on exacerbation rate: Eosinophils <0.15x10^9/L: HR 0.87 (0.75-1.02) NS Eosinophils ≥0.15x10^9/L: HR 0.68 (0.61-0.77) **Mortality**[6,8] -On ICS at screening: 1.3% vs 3%; HR 0.41 (0.25-0.69) -No ICS at screening: 1.8% vs 1.2%; HR 1.49 (0.49-4.55) NS **Quality of life/health status** -SGRQ mean difference -1.88 points not clinically significant but TT320 more likely to achieve MCID (improve QOL/health status) than LAMA/LABA.
All-cause mortality**	1.3%	1.8%	2.3%	1.6%	HR 0.54 (0.34-0.87) **NNT≈ 100**/yr¥	HR 0.78 (0.47-1.3) NS	
Severe exacerbation (rate/year)	0.13	0.14	0.15	0.16	RR 0.84 (0.69-1.03) NS	RR 0.80 (0.66-0.97) ↓0.03 exacerbations per patient-year	
Mod-severe exacerbation (%)	48%	48%	50%	51%	HR 0.88 (0.81-0.96) **NNT≈ 50**/yr¥,†	HR 0.89 (0.81-0.97) **NNT≈ 34**/yr¥	
Severe exacerbation (%)[15]	10%	11.5%	11%	12%	NS	**NNT≈ 50**/yr¥	
SGRQ mean difference (MD) from baseline at week 52	-6.4	-6	-4.5	-4.9	MD -1.88 (-2.84 to -0.91)	MD -1.47 (-2.43 to -0.51)	
SGRQ responders (%) at week 52 (MCID ↓≥4-points)	44%	43%	37%	39%	OR 1.4 (1.2-1.6) **NNT≈ 15**/yr¥	OR 1.2 (1.1-1.4) **NNT≈ 20**/yr¥	
TDI responders (%) over 52 wk[16] (MCID ↑≥1 unit)	48%	47%	43%	44%	**NNT≈ 20**/yr¥	**NNT≈ 25**/yr¥	
Safety¥ (on-treatment analysis; N = 8529)							All **ICS-containing** study arms had **higher rates of pneumonia** vs LAMA/LABA; no statistically significant differences for other safety endpoints listed here. TT320 vs LAMA/LABA: ↑ oral candidiasis (3% vs 1.1%; **NNH ≈ 53**/yr ¥) & ↑ dysphonia/aphonia (1.8% vs 0.3%; **NNH ≈ 67**/yr ¥) No statistically significant difference in diabetes (3.4% vs 2.5%) or bone fractures (2.1% vs 2.1%).
SAE (serious adverse events)	19.9%	21%	20.4%	20.6%			
AE leading to early discontinuation	5.6%	5.3%	6.9%	6.6%			
Any AE	63.8%	63.8%	61.7%	64.5%			
Major adverse CV events	1.4%	1.4%	2.1%	1.1%			
Pneumonia (confirmed by an independent clinical endpoint committee)	4.2%	3.5%	2.3%	4.5%	**NNH ≈ 53**/yr NS¥		

*Model-estimated rates based on modeling rates adjusted for continuous and categorical covariates listed in the supplementary appendix.[11]
**All-cause mortality analyzed using ITT (intention-to-treat) population.
†RxFiles raw calculation suggests result may not be statistically significant.
¥NNT / NNH calculated by RxFiles.
Note: Focus on TT320 vs LAMA/LABA as these are most representative of options in current practice; TT160 not commercially available; guidelines do not recommend LABA/ICS for COPD unless concomitant asthma, which was largely excluded in this trial.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Appears well designed, appropriate duration for COPD trial, reasonable generalizability to moderate-very severe COPD patients without significant comorbid disease.
- Utilized relevant definitions (COPD diagnosis, symptom severity, moderate-severe exacerbation)
- Baseline demographics well-balanced between treatment arms.
- The same medication from each therapeutic class was used for each study arm and all participants utilized the same device.

LIMITATIONS:

- Included patients taking ICS-containing inhalers at baseline; results more difficult to interpret regarding benefit of triple therapy vs effect of abrupt ICS withdrawal.
- Inclusion criteria selected patients who would be more likely to benefit from ICS (e.g. high symptom burden [CAT ≥10], moderate-very severe airflow obstruction [FEV1 25-65%], and low-high exacerbation risk [based on occurrence of the following within the past year: ≥1 severe exacerbation, ≥1 moderate exacerbation {if FEV1 <50%}, or ≥2 moderate exacerbations {if FEV1 50-65%}]). Most participants also had elevated eosinophils (>150cells/mcL in 75%).

- Although a recent asthma diagnosis was excluded, past diagnosis was accepted, and ~30% of patients had bronchodilator reversibility; those with concomitant COPD + asthma were likely to have more favourable results from ICS-containing regimens given its established benefit on the inflammatory component of asthma.
- Patients with significant diseases such as cardiovascular conditions, which are a common comorbidity among COPD patients, were excluded.
- 46% of patients (7445/16033) were excluded during eligibility assessment.
- Significant differences in long-term safety outcomes, such as diabetes and bone fractures, in those taking ICS-containing products, may not be captured within this one-year trial and further study may provide more insight regarding potential risk.

UNCERTAINTIES:

- Only 1 delivery device was used. Can results be extrapolated to DPI (dry powder inhalers) in patients with very severe COPD and poor inspiratory flow?
- Would the benefit be sustained if comparing real-life use of once daily LAMA/LABA vs twice daily triple therapy?
- Does triple therapy have a role for initial treatment of COPD?

Other notes of interest:

Cost ($🍁/30 day): LAMA/LABA: $77-$107
LABA/ICS: $66-$191
LAMA/LABA/ICS: $150-160

RxFILES RELATED LINKS

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

Abbreviations

Δ=change, **AE**=adverse events **BUD**=budesonide **COPD=**chronic obstructive pulmonary disease **EOS**=blood eosinophil count **FEV1**=forced expiratory volume in one second **FFD**=formoterol fumarate dihydrate **FVC**=forced vital capacity **GLY**=glycopyrronium **ICS**=inhaled corticosteroid **ITT**=intention-to-treat **LABA**=long-acting beta-2 agonist **LAMA**=long-acting muscarinic antagonist **MCID**=minimal clinically important difference **MD**=mean difference **mITT**=modified intention-to-treat **mo**=months **NNH=**number needed to harm **NNT**=number needed to treat **QOL**=quality of life **SAE**=serious adverse events **SGRQ=**St. George's Respiratory Questionnaire **TDI=**transition dyspnea index **TT**=triple therapy **Tx**=treatment **URTI**=upper respiratory tract infection

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