Triple Inhaled vs Dual LABA-LAMA Inhaled Therapy in Severe to Very-Severe COPD[1]

TRIBUTE Trial Summary[1]

SUMMARY

- TRIPLE therapy (TT) with ICS/LABA/LAMA **(BDP/FFD/GLY)** lowered the rate of moderate to severe exacerbations compared to DUAL therapy with LAMA-LABA **(GLY/IND)** in symptomatic COPD patients with severe to very-severe airflow limitation. The adjusted rate estimates for mod-severe exacerbations per year were 0.5 for TT vs 0.59 for LAMA/LABA. In absolute terms, for every ~11 patients treated for 1 year, one mod-severe exacerbation will be prevented (mostly moderate). In this RCT, those with chronic bronchitis benefited the most. Symptom burden, per SGRQ score, was also trending toward a noticeable improvement for 1 out of every 20 patients. Adverse events and serious adverse events were similar between groups, and there was no increase in pneumonia. However, the RCT was small (only 1532 participants), many of whom had their ICS abruptly stopped on trial entry. As of 2025, two other RCTs - **ETHOS, IMPACT** – provide mostly consistent, but more robust data and insight.

Bottom Line: Triple therapy with ICS/LABA/LAMA may be offered to **symptomatic, severe COPD patients experiencing exacerbations**.

BACKGROUND

- COPD treatment typically follows a stepwise approach. Escalation to triple therapy (ICS/LAMA/LABA) is recommended for patients based on continued symptom burden &/or exacerbations despite dual therapy (LAMA/LABA or ICS/LABA). Evidence for the relative risk-benefit of inhaled TT is **lacking**.

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

DESIGN: May 2015 – July 2017

- Randomized, blinded (patient, investigator, site staff, sponsor personnel), parallel-group, double-dummy, 2-arm active control; stratified; allocation concealed (interactive tech response system – centralized); multi-site/country, 187 sites across 17 countries; 2 week open-label run-in on dual tx (LAMA/LABA); mITT (received at least 1 dose, & 1 follow up assessment); per-protocol done as sensitivity analysis; followed x1 year.
- **Funded by** Chiesi Farmaceutici (study registered at outset; no protocol changes)

POPULATION: n=1532

- **Inclusion criteria:** symptomatic COPD, severe to very-severe airflow limitation, ≥1 mod-severe exacerbation see abbreviations and definitions at end of document in previous year despite receiving inhaled maintenance meds; age >40, current or ex-smoker, FVC <0.7, FEV_1 <50%; symptomatic at screening, on either dual (ICS/LABA; ICS/LAMA), or monotherapy LAMA). Note: ~65% were on ICS prior to RCT, and this was stopped on entry to 2 week run-in.
- **Exclusion criteria**: current asthma, clinically significant CVD or lab abnormalities, unstable concurrent disease; patients on previous triple therapy.
- **POPULATION at baseline:** age 64, male 72%, white 92%; 80% had an FEV1 of 30-50%; 20% had FEV1 of <30%; ~85% with ≥1 concomitant disease e.g. hypertension; ~8yr since diagnosis; blood eosinophil count: 240 to 230 cells/mcL; ~13.5% had reversibility; chronic bronchitis ~56%, emphysema ~31%, mixed ~14%; reasonably balanced at baseline

INTERVENTION/COMPARISON:

- 2 study arms: **Triple Therapy (TT)** with **ICS/LABA/LAMA (BDP/FFD/GLY) vs. Dual Therapy** with **LAMA/LABA (GLY/IND)**, specifically:
  - Beclomethasone dipropionate (**BDP**) 87mcg + formoterol fumarate (**FFD**) 5mcg + glycopyrronium (**GLY**) 9mcg = ***TRIMBOW Inhaler*** – 1 dose (**2** inhalations) **twice** per day via pressured MDI Aerosphere
  - Indacaterol (**IND**) 85mcg, glycopyrronium (**GLY**) 43 mcg = ***ULTIBRO Inhaler*** – **1** inhalation **daily** via DPI Breezhaler (It is uncertain if glycopyrronium doses (with different delivery) are considered equivalent to one another)
- Is comparison fair? Uncertain.
  - Likely reasonable, but it's not just 3 vs 2 agents; it is also different meds {chosen b/c this dual combo superior to LAMA monotx, and combo LABA+ICS}.
  - However, given 65% of patients at baseline had their ICS discontinued, trial design favoured the intervention that reinstituted the ICS.
- Rescue with SABA permitted (if >6hr spirometry assessment)

OUTCOMES – 52 weeks:

- **Primary:** Rate of moderate-severe exacerbations; **Secondary**: moderate and severe exacerbations; change from baseline in scores for various tests, e.g. FEV_1

RESULTS ~ 52 Weeks	n=764	n=768		
Clinical Endpoints	**BDP/FFD/GLY**	**GLY/IND**	**Rate Ratio**	**Comments**
1°: Adjusted rate of *moderate to severe* exacerbations per patient per year* mITT	**0.50**, 0.45-0.57	**0.59**, 0.53-0.67	**0.848** 0.723-0.995	Note: adjusted rate ratio shows statistical significance, however, 95% CI for actual rates for each arm overlap* Absolute difference of 0.09 *mod-sev* exacerbations per patient per year; this equates to 1 mod-sev exacerbation prevented per ~11 patients every year or an **NNT≈11**/yr (assumes exacerbations distributed equally between patients)**
• Per-protocol results for 1° outcome were consistent with the mITT; the rate ratio 0.840, 0.721-1.000 (borderline significance)				
Adjusted rate of *moderate* exacerbations per patient per year*	**0.41,** 0.36-0.47	**0.47,** 0.41-0.54	**0.866** 0.723-1.037 **NS**	*Moderate and severe* exacerbations Rate ratios not statistically significant on their own; trend towards a small reduction - absolute difference of 0.06 exacerbations per patient per year; if assume significance, this equates to 1 *moderate* exacerbation prevented per 17 patients every year (assumes exacerbations distributed equally between patients)**
Adjusted rate of *severe* exacerbations per patient per year*	**0.07,** 0.06-0.10	**0.09,** 0.07-0.12	**0.787** 0.055-1.125 **NS**	*Severe* exacerbations: little to no absolute change in, but trending in favour of triple therapy. If assume significance: 1 severe exacerbation prevented per ~50 patients per year.
* rate ratio is based on modeling rates adjusted for the variables listed in the stats section, thus the 95% CI included as per model. ** assuming exacerbations distributed equally between patients skews analysis since a few patients generally have more exacerbations than the rest, the actual NNT would be larger.				
Secondary/Other Endpoints/Subgroup Analysis, Select ~ 52 Weeks				
Patients with: chronic bronchitis			**0.752**, 0.605-0.935	Adjusted mean change in FEV_1 from baseline: BDP/FFD/G LY>> IND/GLY @ wks 12, 40, and overall. Subgroup showing and accounting for most benefit were *patients with chronic bronchitis*. Responder analysis favoured triple therapy; non-significant for pre-dose FEV_1; borderline significance for the SGRQ score, ?**NNT≈20**/yr. (COPD Assessment score was -0.8 vs -0.6.) There were no multiplicity adjustments for secondary endpoints. Use of rescue medication was similar for both groups.
Patients with: emphysema			**0.995**, 0.754-1.314 **NS**	
… mixed bronchitis and emphysema			**0.939**, 0.605-1.459 **NS**	
… with eosinophils of ≥200 cells/mcL			**0.806**, 0.646-1.007 **NS**	
… with eosinophils of <200 cells/mcL			**0.872**, 0.692-1.098 **NS**	
Time to 1st mod-sev exacerbation			**HR 0.901**, 0.763-1.064 **NS**	
Time to 1st severe exacerbation			**HR 0.864**, 0.613-1.219 **NS**	
Responder analysis – Pre-dose FEV_1	23%	16%	**OR=1.19** 0.91-1.55 **NS**	
Responder analysis – SGRQ total score	41%	36%	**OR=1.22** 0.99-1.51 **NS**	
Pneumonia	4%	4%		Serious adverse events (SAE): were similar between groups and generally favoured the triple therapy group. CV events, BP, heart rate, and ECG parameters, were similar.
Serious Adverse Events (SAE)	15%	17%		
All-cause mortality	0.4%	1.0%		
AE leading to discontinuation	5%	5%		

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Well randomized/designed
- Outcomes of importance to patients
- 1 yr RCT, reasonable length for a COPD study at the time

LIMITATIONS

- Fairly small RCT limiting power to assess outcomes
- Although moderate and severe exacerbations counted, the use of exacerbation rate (# of exacerbations) as opposed to patients with 1 or more exacerbations, limits interpretation of patients that may derive benefit. Specifically, some patients may have had a lot of exacerbations, whereas others may not have had any.
- Sudden stopping/discontinuation of ICS prior to trial enrolment/entry favoured the TT arm when ICS therapy was resumed.
- No record of whether patients quit smoking during the intervention
- Patients had to use two inhalers, plus the prn inhaler
- Sample size too small to detect differences in safety outcomes

UNCERTAINTIES

- What would results have looked like if patients on previous ICS did not have their ICS stopped?
- Would different medications within the same class offer similar effect?
- Why did the groups with ≥200 and <200 cells/mcL eosinophils have similar results?

Other notes of interest:

Costs: **Dual Tx Cost-Range ~$76-107** (**ULTIBRO** Breezehaler ☎✆ 1 cap inhaled daily = $95/30 days)
Triple Tx Cost-Range ~$150-160 (**BREZTRI** ☎✆ 2 puffs BID = $150)

RxFILES RELATED LINKS

- Also available, or coming soon!
  - RxFiles.ca/
  - IMPACT Trial Summary
  - ETHOS Trial Summary
  - COPD Drug Comparison Chart
  - Inhaler Devices Chart
  - COPD Newsletter 2026
  - COPD 3-Device Inhaler Colour Comparison Chart – Jan 2026
  - COPD Q&A Summary 2026

ACKNOWLEDGEMENTS: Prepared By Loren Regier. July 2025; Revised Jan 2026 **Reviewers:** Amy Wiebe, Andrea Holaday, Margaret Jin, Taisa Trischuk

Abbreviations and Definitions: BEC=blood eosinophil count, **AAT** = alpha-1 antitrypsin ☎=EDS ✆=prior approval NIHB ⊗=not covered by NIHB **A1AT**=alpha-1-antitrypsin **AECOPD**=acute exacerbation of COPD **CAP**=community-acquired pneumonia **CAT**=COPD assessment test **CNS**=central nervous system **COPD**=chronic obstructive pulmonary disease **CRP**=C-reactive protein **DPI**=dry powder inhaler **Dx**=disease **EOS**=blood eosinophils **FEV1**=forced expiratory volume in 1 second **FVC**=forced expiratory vital capacity **fx**=function **HA**=headache **HR**=heart rate **ICS**=inhaled corticosteroid inhal'n **soln**=inhalation solution **LABA**=long-acting Beta2-Agonist **LABD**=long acting bronchodilator **LAMA**=long-acting muscarinic antagonist **LLN**=lower limit of normal **mMRC**=modified Medical Research Council dyspnea scale **PRN**=as needed MDI=metered dose inhaler **NIV**=noninvasive ventilation **non-PCOL**=non-pharmacological **PDE**=phosphodiesterase QoL=quality of life RSV=respiratory syncytial virus SABA=short-acting Beta2-Agonist SAMA=short-acting muscarinic antagonist SITT=single inhaler triple therapy Tdap=tetanus diphtheria and pertussis **TMP/SMX**=trimethoprim/sulfamethoxazole **Tx**=treatment **URTI**=upper respiratory tract infection **UTI**=urinary tract infection

COPD exacerbation was defined as a sustained worsening of respiratory symptoms that required treatment with systemic corticosteroids, antibiotics, hospital admission, or any combination thereof. Events were classified as moderate or severe according to European Medicines Agency Committee for Medicinal Products for Human Use guidelines, with **severe exacerbations defined** as those requiring hospital admission or resulting in death.

[1] Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet. 2018 Mar 17;391(10125):1076-1084.