Long-Term Triple Therapy (TT) De-escalation to Indacaterol/Glycopyrronium Breezhaler in Patients with Chronic Obstructive Pulmonary Disease (COPD)[1]

SUNSET Trial Summary

SUMMARY

The **SUNSET** trial assessed the safety & efficacy of rapidly de-escalating long-term triple therapy (TT) with ICS/LABA/LAMA, to dual therapy with LABA/LAMA, in patients with moderate to severe airflow obstruction & infrequent exacerbations.

Bottom Line:

- Patients on long-term TT with moderate to severe airflow obstruction & infrequent exacerbations may experience no change in time to first exacerbation, exacerbation rates, & minimal lung function ↓ FEV_1 if de-escalated to dual therapy.
- Subgroup analysis found that those with baseline eosinophils ≥300 cells/mcL ($0.3x10^9$/L), may predict those at greater risk of these events if de-escalated to dual therapy.

BACKGROUND

- Indications for TT include patients who are either, at low exacerbation risk who continue to have high symptom burden, based on an mMRC score ≥10 &/or a CAT score ≥2, & FEV_1 <80% predicted, despite dual LABA/LAMA therapy, or those at high risk of exacerbation +/- high symptom burden.[14] Many COPD patients experience infrequent exacerbations yet still receive TT.[2,3,4,15] Weighing the risks vs benefits of ICS exposure is important to ensure patients receive appropriate therapy & are exposed only to necessary medications.
- Long-term ICS exposure has been associated with increased risk of pneumonia, diabetes onset & progression, fractures, & mycobacterial infections.[7,8,9,10,15]
- Long-term TT was defined as use for ≥6 months. Airflow obstruction was defined as a GOLD grade of 2 or 3.[1,5]
- **WISDOM** (2014) was a similar RCT that examined stepwise ICS withdrawal in patients with severe to very severe COPD. Results showed that risk of moderate or severe exacerbations was similar between those who continued ICS, & those who followed stepwise withdrawal of ICS.[11]

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

INTERVENTION vs CONTROL: Indacaterol/glycopyrronium Breezhaler 110/50µg once daily vs Tiotropium Handihaler 18µg once daily + salmeterol/fluticasone propionate Accuhlaer/Diskus BID 50/500µg[1]

INCLUSION: Moderate to severe airflow obstruction, FEV_1 <80% but ≥30% predicted, age ≥40, 15min post-bronchodilator FEV_1/FVC <0.7, post-bronchodilator FEV_1 <80% but ≥40% predicted normal value, current or former smokers with ≥10 pack years, & **on triple therapy for at least 6 months** prior to study.[1] (Note, those with exacerbation risk but relatively minimal loss of lung function will possibly have pre-selected for a subgroup of COPD'ers who are somewhat more likely to benefit from ICS therapy)

EXCLUSION:>1 exacerbation requiring corticosteroids, antibiotics, or hospitalization in the past year, history of asthma, blood eosinophil count >600/mm^3, requirement for long-term oxygen therapy (>12h/day), pregnant or lactating women, & α-1 anti-trypsin deficiency.[1]

POPULATION at baseline: n=1053 underwent randomization; mean age 65 yrs, 70% male, 99% White.[1]

- Mean duration of COPD: 8 yrs, FEV_1(L): 1.6, FEV_1 (% predicted): 56.6, mMRC ≥2: 71%, blood eosinophils ≥300 cells/mcL: 23%[1]

DESIGN:

- Multicenter, randomized, double blind, triple-dummy, parallel group, active control, allocation concealed, 6-month duration, non-inferiority trial.[1]
- 28-day run in period using tiotropium + salmeterol/fluticasone, randomized on day 29 in a 1:1 ratio.[1]
- TT was hard stopped after 29-day run in period with no dose taper.[1]
- Blinding achieved through triple dummy design: Each group used 3 inhalers with either 1 or 2 matching placebo devices.[1]
- Study was supported & funded by Novartis Pharma AG, the makers of **Breezhaler**.[1]

OUTCOMES – Over 26 weeks:

- **Primary: Demonstrate noninferiority of indacaterol/glycopyrronium vs tiotropium + salmeterol/fluticasone on change from baseline in post dose trough FEV_1 after 26 weeks of treatment.**[1]
  - Non-inferiority margin FEV_1 change from baseline of –50mL.[1]
  - **FEV_1 ↓ of 100mL** is generally considered to be a **minimally important difference**. [12,13]
- **Secondary**: **Effect of baseline blood eosinophil level on trough FEV_1 & exacerbation rate over 26 weeks,** moderate to severe exacerbations over 26 weeks, comparisons of trough FEV_1 & FVC over 26 weeks, Transition Dyspnea Index (TDI) & St. George's Respiratory Questionnaire (SGRQ) scores after week 12 & 26.[1]

RESULTS

Follow up over 26 weeks

Primary Endpoint	Indacaterol/ Glycopyrronium n=527	Tiotropium + salmeterol/fluticasone n=526	Mean change from baseline	Comments
Trough FEV_1	-29 mL	-3 mL	-26 mL (-53 to 1 mL) P=0.05	**Dual therapy is inferior to triple therapy**, outcome crosses non-inferiority margin of –50mL, however this change is unlikely to be minimally clinically significant

Secondary Endpoints & eosinophil subgroup analysis	Measure (CI)	Comments
Mean change in trough FEV_1 **(eosinophil ≥300 cells/mcL)**	-69 mL (-125 to –12 mL)	When TT is de-escalated in those with eosinophil ≥300 cells/mcL, greater reduction in lung function is observed through FEV_1 measurement.
Mean change in trough FEV_1 **(eosinophil <300 cells/mcL)**	-13 mL (-44 to 17mL)	
Exacerbation rate (mod-severe)	RR 1.08 (0.83 to 1.40)	When TT is de-escalated, no change in exacerbation rate was observed in the total population, however in those with eosinophil ≥300 cells/mcL an increased exacerbation rate is observed. High eosinophils had higher rates of exacerbation.
Exacerbation rate (mod-severe) **(eosinophil ≥300 cells/mcL)**	RR 1.86 (1.06 to 3.29)	
Exacerbation rate (mod-severe) **(eosinophil <300 cells/mcL)**	RR 0.97 (0.72 to 1.32)	
Time to first exacerbation	HR 1.11 (0.85 to 1.46)	When TT is de-escalated there is no change in time to first exacerbation in the total population, however in those with eosinophil ≥300 cells/mcL there is a shorter time to first exacerbation.
Time to first exacerbation **(eosinophil ≥300 cells/mcL)**	HR 1.80 (0.98 to 3.28)	

Comments: **[Note eosinophil units reported in study as >300 cells/mcL; equivalent to $0.3x10^9$/L as commonly reported in Canadian labwork.]**

- Endpoints compare intervention vs control in either the total study population or in those with eosinophil ≥ or <300 cells/mcL if specified by ().
- Mean change in trough FEV_1 (**eosinophils <150 cells/mcL**): **13 mL** (-29 to 54 mL), (**eosinophils 150-<300 cells/mcL**): **-42 mL** (-87 to 2 mL), (**eosinophils >300 cells/mcL): -69 mL** (-125 to -12 mL).[1]
- Upon de-escalation of TT to dual therapy, some decline in FEV_1 is observed when eosinophils are between 150-<300 cells/mcL; a greater decline is observed when eosinophils >300 cells/µL.
- Use of rescue medication was similar between intervention & control groups (Δ=0.177 puffs/day (-0.01 to 0.36).[1]

Safety Endpoints	Indacaterol/glycopyrronium n=527 (%)	Tiotropium + salmeterol/fluticasone n=526 (%)
Patients with at least one AE	426 (80.8)	434 (82.5)
Patients with at least One serious adverse event (SAE)	32 (6.1)	34 (6.5)
Death	4 (0.8)	5 (1.0)
Pneumonia	6 (1.1)	9 (1.7)
HTN	7 (1.3)	10 (1.9)
Oral candidiasis	12 (2.3)	18 (3.4)
Bronchitis	13 (2.5)	5 (1.0)
Cough	24 (4.6)	15 (2.9)

- Statistical analysis not provided.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Study design: double-blind, triple dummy design reduced influence of study bias.
- High compliance rates in both intervention (98.7%) & control (97.9%) groups.
- 92% power for primary outcome.
- Eosinophil subgroup analysis.
- Generalizability of study population to those with moderate-severe airflow obstruction.
- Additional reporting of TDI & SGRQ scores to show impact on patient important outcomes.
- Provided FAS (full analysis set) & PPS (per protocol set) data.

LIMITATIONS:

- Generalizability of medication compliance to real-world adherence rates.[6]
- Only demonstrates the effects of one dual therapy regimen.
- Lack of Generalizability to mixed asthma/COPD population.

UNCERTAINTIES:

- What is a clinically meaningful change in FEV_1 & are the study results clinically relevant?
- Are the benefits of continuing TT greater on moderate or severe exacerbations, in pt with eosinophils >300 cells/mcL?
- What effects did switching bronchodilators after run-in have on the results?
- What impact did abrupt ICS discontinuation have on the results?
- Did pt experience ICS withdrawal & if so, did this impact the results of the trial?
- Why did the absence of an ICS taper seem to not have a greater impact on the study outcomes?
- Is an ICS taper less important in a moderate-severe population, in comparison to a severe-very severe population?

Abbreviations:
Δ=change **AE**=adverse events **FEV_1**=forced expiratory volume in 1 second **FVC**=forced vital capacity **HR**=hazard ratio **HTN**=hypertension **ICS**=inhaled corticosteroids **LABA**=long-acting beta-2 agonists **LAMA**=long-acting muscarinic antagonists **MRC**=Medical Research Council Dyspnea Scale **pt**=patient(s) **RR**=risk ratio **SAE**=serious adverse event **TT**=triple therapy

Other notes of interest:

RxFILES RELATED LINKS

WISDOM Trial Summary; **IMPACT** Trial Summary; **ETHOS** Trial Summary; **TRIBUTE** Trial Summary; **FLAME** Trial Summary; COPD drug comparison chart - COPD | RxFiles

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