Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD [1]

WISDOM Trial Summary

SUMMARY

The **WISDOM** trial evaluated the benefits and risks of stepwise ICS withdrawal from triple therapy (ICS + LABA + LAMA) vs continuation in patients with severe COPD (FEV_1 <50%) over 52 weeks.

Bottom Line:

Overall, in patients with severe COPD receiving triple therapy who discontinue their ICS, the risk of **time to first moderate-severe COPD exacerbation is similar** between the groups; however, there is **a small, non-clinically significant decline in lung function and a transient increased risk of severe exacerbations in the first 6 months following ICS discontinuation.**

- **In subgroups with high exacerbation risk (frequent exacerbations, high baseline eosinophils or asthma overlap) there may be greater risks associated with discontinuation** (e.g. more moderate and severe exacerbations)

BACKGROUND

- ICS has been shown to reduce exacerbation rates especially in addition to LABA (and LAMA) resulting in guidelines at the time recommending combination therapy with an ICS and LABA in severe COPD patients[3,4,5,6]
- Exacerbations of COPD are associated with a decline in lung function and health status[2]
- Increasing concern of the net clinical benefit vs long-term safety of ICS in COPD patients due to long term adverse effects of ICS including pneumonia, mycobacterial infection, diabetes and fractures (Schroeder 2024)[7,8]
- Evidence is limited for regimens in severe COPD that include LAMA, LABA or both in combination with an ICS

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

DESIGN: 1 year, randomized, 200 centers and 23 countries, double blinded, parallel group active controlled study, allocation concealed trial

POPULATION:

- **INCLUSION:** Age >40, current or former smokers (10 pack year), diagnosed with severe or very severe COPD defined as an FEV_1<50% and less than 70% of the forced vital capacity after bronchodilation with a documented history of moderate or severe exacerbation(s) in last 12 months {Exacerbations must be retrospectively recorded in notes, may include physician assessment and treatment changes (e.g. steroids, antibiotics, physician directed increase in bronchodilator use}
- **EXCLUSION:** Presence of disease other than COPD (defined as a disease or condition that in the investigator may put patient at risk), current clinical diagnosis of asthma, history of thoracotomy with pulmonary resection, unstable or life threatening cardiac arrhythmia, clinical diagnosis of bronchiectasis, respiratory tract infection or COPD exacerbation occurring within 6 weeks prior to initial screening, history of myocardial infarction within 3 months prior to initial screening, or hospitalization for cardiac failure within the past year.
- **POPULATION: n= 2488 enrolled,** mean age 64 yrs, 82.5% male, 66.6% previous smokers 81.4% White, 0.4% Black, 12.4% Asian
  - Mean population FEV_1 post bronchodilation at baseline was 0.93L (32.8% predicted), mean COPD duration ~ 8 years
  - Comorbidities: cardiac: 28.2%, vascular 45.8% (HTN: 39.7%), diabetes: 6.4%, # of comorbidities: 0: 17.9%, 1: 21.8%, ≥2: 60.3%
  - Medication use at baseline: LAMA 46.9%, LABA 64.6%, ICS 69.9%, triple therapy 39%

INTERVENTION/COMPARISON: Tapering of ICS in 3 steps over a 12-week period and continuation of dual therapy with LAMA/LABA (tiotropium, salmeterol) vs **continuation of triple therapy with ICS/LAMA/LABA** (fluticasone propionate, tiotropium, salmeterol)

- Patients did a 6-week run-in of triple therapy with 18µg of tiotropium (HandiHaler) once daily, 50µg of salmeterol (MDI) twice and 500 µg of fluticasone propionate (MDI) twice daily and then randomized between LAMA/LABA or triple therapy. The aim was a controlled, gradual withdrawal of ICS.
- Tapering steps occurred at weeks 0,6,12 weeks after this the intervention group used a placebo in addition to dual therapy resulting in 9 months of comparison of dual vs triple therapy.

RESULTS – over 12 months

Clinical Endpoints	Withdrawal Group n=1242	ICS Continuation Group n= 1243 treated	ICS withdrawal vs ICS continuation	Comments
PRIMARY ENDPOINT				
Time to first moderate or severe COPD exacerbation during 12-month study	-	-	**HR 1.06 (0.94 -1.19)**	- The primary outcome showed the time to first quartile to have an event. This focused on short term risks however, could underestimate or overestimate true differences. See Post Hoc Analysis endpoints for further information
Time by which 25% of patients had a moderate or severe COPD exacerbation (first quartile)	110 days	107 days	-	
SECONDARY ENDPOINTS				
Time to first severe COPD exacerbation	-	-	**HR 1.20 (0.98 – 1.48)**	- Severe exacerbations had a transient increase in the withdrawal group.
Adjusted event rate for moderate or severe exacerbation per patient yr	0.95 (0.87- 1.04)	0.91 (0.83- 0.99)	Not Reported	
Change from baseline in lung function *(FEV_1 decline)*	-	-	*Adjusted mean change in FEV_1:* Week 18: ↓38mL (P<0.001) Week 52: ↓43mL (P=0.001)	- The greatest decline in FEV_1 was observed upon complete withdrawal of ICS.
Change from baseline in mMRC score *(Scale of 0-4; higher scores indicate more severe dyspnea; absence of breathlessness given a score of -1 per trial protocol)*	Week 18: ↓0.001 Week 52: ↑0.035	Week 18: ↓0.03 Week 52: ↓0.028	*Mean difference in mMRC score:* Week 18: 0.029 (P=0.36) NS Week 52: 0.063 (P=0.06) NS	- No MCID for mMRC has been identified but no significant differences noted.
Change from baseline in SGRQ score *(Scale of 0-100; higher scores indicate worse function/health status; MICD=4-points)*	Week 27: ↑0.55-points Week 52: ↑1.15-points	Week 27: ↓0.42-points Week 52: ↓0.07-points	*Mean difference in SGRQ score:* Week 27: 0.97-points (P=0.08) NS Week 52: 1.22-points (P=0.047)	- Although health status changes slightly favored the ICS continuation group, the difference was not clinically significant (below MCID of 4-points).

Clinical Endpoints	Withdrawal Group n=1244 assigned, 1242 treated, 1011 completed	ICS Continuation Group n= 1244 assigned, 1243 treated, 1016 completed	Comments
Safety Outcomes			
Any adverse effect (AE)	890 (71.7%)	880 (70.8%)	No significant differences in safety outcomes Numerically, higher number of deaths in withdrawal group; uncertain significance although some concern as a safety endpoint
AE leading to discontinuation	127 (10.2%)	115 (9.3%)	
Any serious adverse event (SAE)	300 (24.2%)	292 (23.5%)	
Death during study	40 (3.2%)	34 (2.7%)	
AE requiring hospitalization	271 (21.8%)	273 (22%)	
Pneumonia	68 (5.5%)	72 (5.8%)	

Clinical Endpoints of POST HOC ANALYSIS[9]	Withdrawal Group	ICS Continuation Group	RR Over 9 Months	Comments
Adjusted event rate for moderate or severe exacerbation per patient-year year **EOSINOPHILS <300 CELLS/mcL***	0.90 (0.81–1.00)	0.86 (0.78–0.96)	RR: 1.04 (0.89-1.21) p=0.59 NS	As eosinophils increase there is greater harm associated with discontinuing ICS. Specifically, those with eosinophils ≥300 cells/mcL (0.30×10^9/L) were more likely to benefit from ICS continuation.
Adjusted event rate for moderate or severe exacerbation per patient-year year **EOSINOPHILS ≥300 CELLS/mcL***	1.07 (0.87–1.33)	0.69 (0.55–0.87)	RR: 1.56 (1.14-2.13) p=0.0055	
Adjusted event rate for severe exacerbation per patient-year **EOSINOPHILS <300 CELLS/mcL***	0.20 (0.16–0.24)	0.19 (0.16–0.24)	RR not reported, No difference shown	
Adjusted event rate for severe exacerbation per patient-year **EOSINOPHILS ≥300 CELLS/mcL***	0.25 (0.17–0.38)	0.15 (0.10–0.24)	RR: 1.67 (calculated) Point Estimate in favor of ICS continuation	

*** EOSINOPHILS** (blood eosinophil count): 300cells/mcL equivalent to 0.30×10^9/L

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Robust study design: 12 month randomized, double-blinded, multicenter study with similar baseline characteristics
- Larger sample size than prior ICS withdrawal studies allowing for subgroup analysis and more confidence in results
- Dropout rate was 19% however they did an ITT analysis where all patients who received one dose were included and dropout reasons (eg. AE's, non adherent, declined study medications) were balanced between groups
- Objective primary outcome and lung function allows for limited report bias
- No new safety concerns occurred with long term ICS use
- Outcomes align with more current studies such as SUNSET (as patient eosinophils increase benefits of continued ICS may be greater)

LIMITATIONS:

- Study population was mostly white males however there was no significant different in subgroup analysis between sexes; subgroup analysis between races was not done
- Inclusion/exclusion criteria may limit generalizability and introduce selection bias (Does not include low risk COPD patients, or patients who had an exacerbation <6 weeks ago)
- Run-in period may alter safety outcomes. (Preferentially selects out those more likely to tolerate and do well with the medications/regimens/devices
- Authors institute received funding from many major drug companies to conduct clinical trials

UNCERTAINTIES:

- What would the net clinical benefit/harm be over a longer term beyond 1 year? (ICS harms like fractures or diabetes only emerge after long term use)
- How generalizable are the results to mild/moderate COPD patients?
- Does using the first quartile for time to first exacerbation exaggerate the differences between the groups?
- How will real world adherence to COPD treatment influence the findings

Other notes of interest:

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

RxFILES RELATED LINKS

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

Abbreviations:

AE=adverse events **FEV_1**=forced expiratory volume in 1 second **HR**=hazard ratio **ICS**=Inhaled Corticosteroid **ITT**= Intention to Treat **LABA**=Long-Acting Beta Agonist **LAMA**=Long-Acting Muscarinic Antagonist **MCID**=minimum clinically important difference **mMRC** =modified Medical Research Council (dyspnea scale) **SGRQ**=St. George's Respiratory Questionnaire

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1. Population perhaps more suitable for ICS withdrawal

- Severe COPD but with low eosinophils (<300 cells/mcL or 0.30 × 10^9/L)
- Low exacerbation history
- Optimized on LABA + LAMA therapy
- Patient or provider desire to discontinue ICS

2. Population to Consider ICS continuation

- DO NOT CONSIDER DISCONTINUATION WITH COMORBID ASTHMA
- High exacerbation (≥2 moderate exacerbations) or hospitalization (1 hospitalization) risk
- COPD with high eosinophils ≥300 cells/mcL (0.30 × 10^9/L)
- Low QoL due to COPD otherwise optimally managed on LAMA/LABA

3.Plan if ICS discontinuation occurs

- Educate patient on inhaler technique and adherence, exacerbations and an action plan and reinforce this periodically
- Monitor closely for the first 6 months post discontinuation: symptoms, FEV_1, rescue inhaler use
- Continue regular monitoring for optimal COPD control (e.g. exacerbations, symptom burden
- Restart ICS if exacerbations occur, QoL decrease or eosinophils increase >300 cells/mcL (0.30 × 10^9/L)

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