FLAME: Indacaterol+Glycopyrronium versus Salmeterol+Fluticasone for COPD [1]

SUMMARY

FLAME was a multicentre, randomized, double-blind, double dummy, non-inferiority trial involving patients (n=3362) who had moderate-to-severe COPD& ≥ 1 COPD exacerbation in the past year (~75% of included patients were GOLD Group D [high risk for exacerbations and high symptom burden]). Those who received **indacaterol+glycopyrronium 50+110 mcg DPI (Ultibro Breezhaler ☎ ✆) once daily,** compared to **salmeterol+fluticasone 50+500 mcg DPI (Advair ☎ ✆) BID for 52 weeks,** had**:**

- No statistically significant difference in severe exacerbations (requiring hospitalization/ED visit) or mortality
- ↓ ALL (mild, moderate, severe) exacerbations (ARR 0.5, P<0.001), ↓ moderate exacerbations (ARR 0.17, P<0.001), & ↓ number of patients with at least 1 exacerbation (any severity) (NNT= 20/ 1 YEAR [95% CI 13-44/1 YEAR])
- ↑ percentage of patients with minimum clinically important difference (MCID) on SGRQ-C (NNT= 18/1 YEAR)
- ↓ pneumonia (ARR 1.6, P=0.02), ↓ influenza (ARR 1.3, P=0.026), & ↓ oral candidiasis (ARR 3.0, P<0.001)

Bottom Line: In symptomatic patients with previous COPD exacerbation(s), indacaterol+glycopyrronium (Ultibro Breezhaler ☎ ✆) ↓ exacerbations, but ? clinical significance as small ARR & no difference in severe exacerbation; ↑ QOL; & ↓ AE compared to salmeterol+fluticasone (Advair ☎ ✆). Indacaterol+glycopyrronium (Ultibro Breezhaler ☎ ✆) is an effective, safer, and less costly **$98** vs **$162**/month alternative to salmeterol+fluticasone (Advair ☎ ✆) for severe COPD patients. Future studies replicating results of **FLAME** and further investigating relative benefits and harms of LABA+LAMA vs LAMA and "triple therapy" (i.e., LABA+ICS+LAMA) vs "combination therapy" (i.e., LABA+ICS or LABA+LAMA) would be beneficial.

BACKGROUND

- Indacaterol+glycopyrronium (Ultibro Breezhaler ☎ ✆) is a combination LABA+LAMA once daily inhaler approved in 2014 for COPD maintenance bronchodilator therapy.[2]
- Combination LABA+LAMA vs LAMA or LABA monotherapy has demonstrated neutral effects on exacerbations requiring hospitalization, variable effects on all exacerbations, but an ↑ % patients achieving MCID on SGRQ.[3-5]
  - It is not clear which agent should be used preferentially as some guidelines recommend combination LABA+LAMA or LAMA monotherapy to prevent exacerbations (COPD severity not stated) (Grade 1C [6 CHEST/CTS 2015]), and note further high quality research is likely to have an important impact on the estimate of effect.
- In symptomatic patients without frequent exacerbations, combination LABA+LAMA vs combination LABA+ICS demonstrated no clinically significant difference FEV_1 or statistically significant difference in SGRQ, symptoms (TDI), or adverse events (AE).[7]
- In symptomatic patients with frequent exacerbations (CTS severe or GOLD Group C & D), various medications are recommended depending on guidelines: e.g., LABA+LAMA+ICS (Level of evidence 1A[8 Canadian Thoracic Society 2007], ?ungraded[9 Gold 2016]), LABA+ICS (Level of evidence A [9 Gold 2016], Grade 1A [6 CHEST/CTS 2015]), or LAMA (Level of evidence B [9 Gold 2016], Grade 1A [6 CHEST/CTS 2015]). Combination LABA+LAMA is recommended as a second-line alternative (after combination LABA+ICS) (Level of evidence B [9 Gold 2016]); however, until now, it has not been studied vs combination LABA+ICS in this patient population.
  - Cochrane meta-analysis (n=14 trials, n= 11 794 patients), combination LABA+ICS vs LABA monotherapy in moderate-severe COPD demonstrated ↓exacerbations OR 0.76 (0.68-0.84, I^2=68%), however, low quality of evidence due to attrition and inconsistency among trials; neutral exacerbations leading to hospital admission OR 0.79 (0.55-1.13, I^2=70%); and ↑ pneumonia OR 1.55 (1.2-2.01, I^2=22%).[10]
    - In a large (n=6 112) RCT, with relatively lower risk of bias (which was included in Cochrane meta-analysis), combination LABA+ICS vs LABA monotherapy demonstrated ↓ moderate-severe exacerbations (requiring systemic corticosteroids and/or antibiotics) ARR 0.28 P<0.001, ↓ severe exacerbations (requiring hospitalization) ARR 0.03 P=0.03, and ↑ pneumonia ARI 7.3 P<0.001.[11 TORCH]
- Given the potential side effects from long-term ICS, **FLAME** aimed to demonstrate that combination LABA+LAMA was **non-inferior** to combination LABA+ICS in preventing COPD exacerbations.

TRIAL BACKGROUND [1,12-14]

DESIGN: international (43 countries), multi-centre (356 sites), prospective, double-blind patients, caregiver, outcome assessors, data analysts, double-dummy, randomized controlled trial with a 4 week run-in period (patients received tiotropium 18 mcg daily). Non-inferiority analysis for primary efficacy outcome followed by superiority analysis. Random sequence generation and allocation concealment via interactive response technology. Funding: Novartis (Ultibro manufactuer). Enrollment period: July 2013-September 2015.

INTERVENTION: indacaterol+glycopyrronium 50+110 mcg once daily vs salmeterol+fluticasone 50+500 mcg BID x 52 weeks

- co-intervention: salbutamol 100 mcg PRN

INCLUSION: age ≥ 40 years, mMRC scale ≥ Grade 2, post-bronchodilator FEV_1 25-59%, FEV_1/FVC < 70%, current or ex-smoker with smoking history ≥ 10 pack-years, **COPD exacerbation during previous year requiring systemic glucocorticoids and/or antibiotics**.

EXCLUSION: T1DM, uncontrolled T2DM, asthma, α-1 anti-trypsin deficiency, O_2 therapy > 12 hours/day, history of long QT syndrome or QTc >450 msec, paroxysmal atrial fibrillation, narrow angle glaucoma, urinary retention, moderate to severe renal impairment (Scr or CrCl NR), symptomatic BPH not on stable treatment or bladder-neck obstruction, on any type of antipsychotic.

POPULATION randomized: n=3362; mITT: n=3354; PP: n=3084. Mean age ~65 years, ~75% ♂

- duration of COPD ~7 years, current smoker ~40%, post-bronchodilator FEV_1 44.1%, post-bronchodilator FEV_1/FVC 41.6%, SGRQ-C ~47, rescue medication use ~4 puffs/day, 1 COPD exacerbation in previous year 80.6%, ≥2 COPD exacerbations in previous year 19.3%, mMRC: Grade 2 71.7%, Grade 3 25.9%, Grade 4 2.2%, GOLD: Group A 0.1%, Group B 24.4%, Group C 0.1%, **Group D 74.8%**, ICS 56.3%, LAMA 60.6%, LABA 67.1
- HTN 47.9%, hyperlipidemia 21.3%, T2DM 12.3%

RESULTS [1,13] follow-up: 52 weeks

TABLE: EFFICACY & SAFETY

CLINICAL ENDPOINTS	INDACATEROL+ GLYCOPYRRONIUM 110/50 mcg ONCE DAILY n=1680	SALMETEROL+ FLUTICASONE 50/500 mcg BID n=1682	RR 95% CI	P VALUE	NNT/NNH* /1 YR OR ARR/ARI	COMMENTS
PRIMARY ENDPOINT						
All (mild, moderate, severe) exacerbations (rate/year) [PP analysis]	3.59	4.03	0.89 (0.83, 0.96)	**0.003**	ARR 0.44	Primary outcome met non-inferiority and superiority criteria.
All (mild, moderate, severe) exacerbations (rate/year) [mITT analysis]	3.59	4.09	0.88 (0.82, 0.94)	**<0.001**	ARR 0.50	
SECONARY ENDPOINTS						77% of patients in indacaterol+ glycopyrronium vs 82% of patients in salmeterol+ fluticasone had at least 1 exacerbation (any severity, p<0.001***), NNT= 20/1 YEAR (95% CI 13- 44/1 YEAR).
Mild exacerbation (rate/year)	2.46	2.72	0.91 (0.83, 0.99)	**0.030**	ARR 0.26	
Moderate exacerbation (rate/year)	0.81	0.98	0.83 (0.74, 0.92)	**<0.001**	ARR 0.17	
Severe exacerbation (rate/year)	0.15	0.17	0.87 (0.69, 1.09)	**0.231**	-	
Moderate or severe exacerbation (rate/year)	0.98	1.19	0.83 (0.75, 0.91)	**<0.001**	ARR 0.21	
Median time to 1st exacerbation, any (days)	71	51	0.84 (0.78, 0.91)	**<0.001**	-	
Time to moderate or severe exacerbation (days)**	127	87	0.78 (0.70, 0.86)	**<0.001**	-	Change in SGRQ-C and FEV_1 did not meet widely accepted MCID thresholds (i.e. average change of 4 units and 0.1-0.14 L respectively).[15-17]
Time to severe exacerbation (days)**	NR	NR	0.81 (0.66, 1.00)	**0.046**	-	
SGRQ-C @ 52 weeks (mean)	-3.1	-1.9	-1.3 (-2.1, -0.4)	**0.003**	-	
Patients with MCID 4 units on SGRQ-C (%)	49.2	43.7	1.30, 95% CI NR	**<0.001**	NNT 18 (95% CI 11, 47)	
Rescue medication use (puffs/day)	-1.01	-0.76	-0.25 (-0.38, -0.12)	**<0.001**	-	Although no consistent greater benefit among more severe subgroups (e.g., GOLD Group, airflow limitation, # COPD exacerbations in previous year), but majority of all randomized patients were severe.
Days with no rescue medication use (%)	13.0	8.3	4.7 (2.7, 6.7)	**<0.001**	-	
Change from baseline in pre-dose trough FEV_1 @ week 52 (L)	0.015	-0.048	0.062 (0.048, 0.077)	**<0.001**	-	
Death (%)	1.4	1.4	NR	NR	-	
CV Death (%)	0.5	0.7	NR	NR	-	
SAE (%)	18.4	19.9	NR	NR	-	
Discontinuation due to AE (%)	7.5	8.5	NR	NR	-	
≥ 1 AE (%)	86.9	89.2	NR	NR	-	No significant interaction between blood eosinophil count and exacerbation rates.
Pneumonia (%)	3.2	4.8	NR	**0.02**	ARR 1.6	
Influenza (%)***	2.1	3.3	NR	**0.026**	ARR 1.2	
Oral candidiasis(%)***	1.2	4.2	NR	**<0.001**	ARR 3.0	Pneumonia diagnosis required radiographic imaging; however, infiltrates not required.

* NNT not calculated for COPD exacerbation outcomes (with the exception of the outcome which includes patients with at least 1 COPD exacerbation) as may exaggerate effect, see reference.[18]
**< 50% of patients in the indacaterol+glycopyrronium had an exacerbation, the time by which ≥ 25% of patients had a 1st exacerbation was calculated.
*** p-values not reported in published trial documents and calculated with descriptive statistics calculator.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- First large, RCT assessing combination LABA+LAMA vs combination LABA+ICS in severe COPD patients.
- Well-designed (properly randomized, registered, appropriately powered, independent adjudication of safety outcomes).
- Similar discontinuation rates between treatment arms: indacaterol+glycopyrronium 16.6% (of which 46% had AE) vs salmeterol+fluticasone 19.0% (of which 45% had an AE).
- Analysis of exacerbations utilized negative binomial model (assumes each individual has their own underlying rate of exacerbations) for statistical analysis of exacerbations; however, robustness of results using different models (e.g., Poisson approach [assumes single exacerbation for all patients with a correction factor]) was not tested in sensitivity analysis.[19]

LIMITATIONS:

- Four week run-in phase (32% of patients discontinued therapy) may introduce selection bias (selecting compliant patients etc.) and limit generalizability; however, only 4.2% discontinued due to an AE (note: tiotropium [LAMA] given to all patients during run-in).
- Patient self-report of rescue medication use and symptoms may over/under-estimate true rate due to recall bias.
- Superiority statistical analysis conducted with mITT population; however, included ≥99% of all randomized patients.
- Risk estimates, 95% CI and/or p-values not reported for all outcomes.
- Industry involvement in trial monitoring, result verification, and reporting.

UNCERTAINITIES:

- ? clinical importance of ↓ in exacerbation due to small ARR (0.5 less exacerbations/1 year [any severity]).
- Risk of unblinding due to ↑ pneumonia, influenza, and oral candidiasis in salmeterol+fluticasone arm.
- Typical anticholinergic AE not reported (e.g., dry mouth) and patients at high risk were excluded (e.g., BPH, urinary retention).
- Trial duration of 1 year limits seasonal variation in exacerbation rates; however, effect may not be proportional year-to-year (e.g., COPD is a chronic, progressive disease). Longest assessment of indacaterol+glycopyrronium is 15 months.[2]
- ? relative benefit of combination LABA+LAMA compared to LAMA monotherapy in reduction of severe exacerbations.[3,4]
- Indacaterol+glycopyrronium has not been assessed as part of a "triple therapy" regimen in combination with ICS.

COST: Glycopyrronium 50mcg cap daily (Seebri Breezhaler ☎ ✆) $68/month.
Indacaterol 75 mcg cap daily (Onbrez Breezhaler ☎ ✆) $61/month.
Indacaterol+glycopyrronium 50+110 mcg DPI daily (Ultibro Breezhaler ☎ ✆) $98/month.
Salmeterol+fluticasone 50+500 mcg DPI twice daily (Advair Diskus ☎ ✆)$162/month.

RxFILES RELATED LINKS

- RxFiles COPD Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-COPD-Tx.pdf

☎=Exceptional Drug Status in SK ✆ Prior approval required by NIHB ♂=male **AE**=adverse event **BPH**=benign prostatic hypertrophy **BID**=twice daily **COPD**=chronic obstructive pulmonary disorder **CTS**=Canadian Thoracic Society **ED**=emergency department **FEV_1**=forced expiratory volume in 1 second **FVC**= forced vital capacity **GOLD**=Global Initiative for Chronic Obstructive Lung Disease **HTN**=hypertension **ICS**=inhaled corticosteroid **LABA**=long-acting beta-agonist **LAMA**=long-acting muscarinic agent **MCID**=minimum clinically important difference **mITT**=modified intention to treat **mMRC**=modified Medical Research Council **NR**=not reported **PP**=per-protocol **SAE**=serious adverse event **SGRQ-C**=St George's Respiratory Questionnaire C **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TDI**=transitional dyspnea index

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