FLAME: Indacaterol+Glycopyrronium versus Salmeterol+Fluticasone for COPD

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 a 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.
- 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. 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 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 LABA+ICS demonstrated no clinically significant difference FEV1 or statistically significant difference in SGRQ, symptoms (TDI), or adverse events (AE).
- 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 Canadian Thoracic Society 2007, 1B graded 9 Gold 2016), LABA+ICS (Level of evidence A9 Gold 2016, Grade 1A CHEST/CTS 2015), or LAMA (Level of evidence B9 Gold 2016, Grade 1A CHEST/CTS 2015). Combination LABA+LAMA is recommended as a second-line alternative (after combination LABA+ICS) (Level of evidence B9 Gold 2016), however, until now, it has not been seen vs combination LABA+LAMA 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, I²=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, I²=70%); and ↑ pneumonia OR 1.55 (1.2-2.01, I²=22%).
  - 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 ARR 1.1/0.001.5 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

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 manufacturer). 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 FEV1 25-59%, FEV1/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, α1- anti-trypsin deficiency, O2 therapy > 12 hours/day, history of long QT syndrome or QTc >450 msec, paradoxymal 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% male.

- duration of COPD ~7 years, current smoker ~40%, post-bronchodilator FEV1 44.1%, post-bronchodilator FEV1/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

#### TABLE: EFFICACY & SAFETY

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>INDACATEROL+ GLYCOPRYSRONIUM 110/50 mcg ONCE DAILY n=1680</th>
<th>SALMETEROL+ FLUTICASENONE 50/500 mcg BID n=1682</th>
<th>RR 95% CI</th>
<th>P VALUE</th>
<th>NNT/NNH* /1 YR OR ARR/ARI</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (mild, moderate, severe) exacerbations [rate/year] [PP analysis]</td>
<td>3.59</td>
<td>4.03</td>
<td>0.89 (0.83, 0.96)</td>
<td>0.003</td>
<td>ARR 0.44</td>
<td>Primary outcome met non-inferiority and superiority criteria.</td>
</tr>
<tr>
<td>All (mild, moderate, severe) exacerbations [rate/year] [mITT analysis]</td>
<td>3.59</td>
<td>4.09</td>
<td>0.88 (0.82, 0.94)</td>
<td>&lt;0.001</td>
<td>ARR 0.50</td>
<td>77% of patients in indacaterol+glycopyrronium vs 82% of patients in salmeterol+fluticasone had at least 1 exacerbation (any severity, p&lt;0.001***), NNT= 20/1 year (95% CI 13-44/1 year).</td>
</tr>
<tr>
<td>SECONDES ENDPOINTS</td>
<td>Mild exacerbation (rate/year)</td>
<td>2.46</td>
<td>2.72</td>
<td>0.91 (0.83, 0.99)</td>
<td>0.030</td>
<td>ARR 0.26</td>
</tr>
<tr>
<td>Moderate exacerbation (rate/year)</td>
<td>0.81</td>
<td>0.98</td>
<td>0.83 (0.74, 0.92)</td>
<td>&lt;0.001</td>
<td>ARR 0.17</td>
<td></td>
</tr>
<tr>
<td>Severe exacerbation (rate/year)</td>
<td>0.15</td>
<td>0.17</td>
<td>0.87 (0.69, 1.09)</td>
<td>0.231</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe exacerbation (rate/year)</td>
<td>0.98</td>
<td>1.19</td>
<td>0.83 (0.75, 0.91)</td>
<td>&lt;0.001</td>
<td>ARR 0.21</td>
<td></td>
</tr>
<tr>
<td>Median time to 1st exacerbation, any (days)</td>
<td>71</td>
<td>51</td>
<td>0.84 (0.78, 0.91)</td>
<td>&lt;0.001</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Time to moderate or severe exacerbation (days)**</td>
<td>127</td>
<td>87</td>
<td>0.78 (0.70, 0.86)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>Change in SGRQ-C and FEV1 did not meet widely accepted MCID thresholds (i.e. average change of 4 units and 0.1-0.14 L respectively).15-17</td>
</tr>
<tr>
<td>Time to severe exacerbation (days)**</td>
<td>NR</td>
<td>NR</td>
<td>0.81 (0.66, 1.00)</td>
<td>0.046</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SGRQ-C @ 2 weeks (mean)</td>
<td>-3.1</td>
<td>-1.9</td>
<td>-1.3 (-2.1, -0.4)</td>
<td>0.003</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Patients with MCID 4 units on SGRQ-C (%)</td>
<td>49.2</td>
<td>43.7</td>
<td>1.30, 95 CI NR</td>
<td>&lt;0.001</td>
<td>NNT 18 (95% CI 11, 47)</td>
<td></td>
</tr>
<tr>
<td>Rescue medication use (puffs/day)</td>
<td>-1.01</td>
<td>-0.76</td>
<td>-0.25 (-0.38, -0.12)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>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.</td>
</tr>
<tr>
<td>Days with no rescue medication use (%)</td>
<td>13.0</td>
<td>8.3</td>
<td>4.7 (2.7, 6.7)</td>
<td>&lt;0.001</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Change from baseline in pre-dose trough FEV1, @ week 52 (L)</td>
<td>0.015</td>
<td>-0.048</td>
<td>0.062 (0.048, 0.077)</td>
<td>&lt;0.001</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>1.4</td>
<td>1.4</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>No significant interaction between blood eosinophil count and exacerbation rates.</td>
</tr>
<tr>
<td>CV Death (%)</td>
<td>0.5</td>
<td>0.7</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SAE (%)</td>
<td>18.4</td>
<td>19.9</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to AE (%)</td>
<td>7.5</td>
<td>8.5</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>≥ 1 AE (%)</td>
<td>86.9</td>
<td>89.2</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>3.2</td>
<td>4.8</td>
<td>NR</td>
<td>0.02</td>
<td>ARR 1.6</td>
<td></td>
</tr>
<tr>
<td>Influenza (%)***</td>
<td>2.1</td>
<td>3.3</td>
<td>NR</td>
<td>0.026</td>
<td>ARR 1.2</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis(%)****</td>
<td>1.2</td>
<td>4.2</td>
<td>NR</td>
<td>&lt;0.001</td>
<td>ARR 3.0</td>
<td>Pneumonia diagnosis required radiographic imaging; however, infiltrates not required.</td>
</tr>
</tbody>
</table>

* 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.14
**< 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.

**UNCERTAINTIES:**
- ? clinical importance of ψ in exacerbation due to small ARR (0.5 less exacerbations/1 year [any severity]).
- Risk of unblinding due to ψ 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 reflect chronic, progressive disease.
- Longest assessment of indacaterol+glycopyrronium is 15 months.7
- ? relative benefit of combination LABA+LAMA compared to LAMA monotherapy in reduction of severe exacerbations.14
- Indacaterol+glycopyrronium has not been assessed as part of a “triple therapy” regimen in combination with ICS.

**COST:**
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References:


