Efficacy of one time per day, single-inhaler indacaterol/glycopyrronium/ mometasone in patients with inadequately controlled asthma: post hoc analysis of IRIDIUM study in Asian population

Hironori Sagara,1 Nathalie Barbier,2 Tsuyoshi Ishii,3 Hajime Yoshisue,3 Ivan Nikolaev,2 Motoi Hosoe,2 Yasuhiro Gom

ABSTRACT

Background and objective The 52-week IRIDIUM study demonstrated the efficacy of indacaterol acetate/glycopyrronium bromide/mometasone furoate (IND/GLY/ MF) versus IND/MF and salmeterol xinafoate/fluticasone propionate (SAL/FLU) in patients with symptomatic asthma, despite long-acting β₂-agonist/inhaled corticosteroids (LABA/ICS) medium-dose or high-dose, predicted forced expiratory volume in 1 s (FEV₁) <80% and at least one exacerbation in the previous year. Here, we present data from a post hoc analysis of the IRIDIUM study in the Asian subpopulation.

Methods This post hoc analysis evaluated improvements in lung function, asthma control and reduction in asthma exacerbations with IND/GLY/MF medium- (150/50/80 µg) and high-dose (150/50/160 µg) versus IND/MF medium- (150/160 µg) and high-dose (150/320 µg), all one time per day and SAL/FLU high-dose (50/500 µg) two times per day, in Asian patients from the IRIDIUM study.

Results In total, 258 patients (IND/GLY/MF medium-dose, 52; IND/GLY/MF high-dose, 52; IND/MF medium-dose, 51; IND/MF high-dose, 51; SAL/FLU high-dose, 52) were included. IND/GLY/MF medium- and high-dose showed greater improvement in trough FEV₁ at week 26 versus respective doses of IND/MF (Δ, 100 mL and 101 mL; both p<0.05, respectively), and SAL/FLU high-dose (Δ, 125 mL; p=0.0189, and 136 mL; p=0.0118, respectively), which were maintained over 52 weeks. Both doses of IND/GLY/ MF showed greater improvement in morning and evening peak expiratory flow versus respective doses of IND/ MF and SAL/FLU high-dose at week 52. The changes in Asthma Control Questionnaire-7 scores from baseline were comparable in all treatment groups. IND/GLY/MF medium- and high-dose showed greater reductions in severe (34%, 69%), moderate or severe (18%, 54%) and all exacerbations (21%, 34%) compared with SAL/FLU high-dose over 52 weeks.

Conclusion One time per day, single-inhaler IND/GLY/MF improved lung function, reduced asthma exacerbations and provided comparable asthma control versus IND/MF and SAL/FLU in Asian patients with inadequately controlled asthma despite LABA/ICS. The results of this analysis were consistent with the overall population in the IRIDIUM study.
or high-dose ICS is widely considered the preferred controller treatment option.\textsuperscript{5–8}

However, despite available therapeutic options for asthma, a significant number of patients receiving LABA/ICS treatment continue to experience poor disease control, increased emergency or hospital-based medical care and reduced quality of life and work productivity.\textsuperscript{9,10} Similar to the Global Initiative for Asthma report,\textsuperscript{5} the Japanese asthma guidelines\textsuperscript{6} and Korean asthma guidelines\textsuperscript{5} also recommend treatment with add-on long-acting muscarinic antagonist (LAMA, tiotropium) in patients with uncontrolled asthma with LABA/ICS therapy. The addition of LAMA to LABA/ICS has demonstrated improvement in lung function, asthma control and exacerbation reduction, with fewer non-serious adverse events, overall,\textsuperscript{11–14} as well as in the Asian population\textsuperscript{15} with uncontrolled asthma.

In the IRIDIUM study\textsuperscript{14} particularly, one time per day fixed-dose combination of indacaterol acetate/glycopyrronium bromide/mometasone furoate (IND/GLY/MF) demonstrated improvements in lung function and reductions in asthma exacerbations with comparable asthma control versus IND/MF one time per day and salmeterol xinafoate/fluticasone propionate (SAL/FLU) two times per day in patients with asthma inadequately controlled with LABA/ICS medium- and high-dose. In a study including healthy subjects, there were no ethnic differences (Asian vs Caucasian patients) found in the pharmacokinetics of IND, GLY and MF.\textsuperscript{16} However, racial and ethnic differences in asthma epidemiology, biology and medical care have been discussed previously,\textsuperscript{17,18} and therefore, it is important to evaluate whether these may result in different response of Asian patients to inhaled asthma treatments compared with patients from other regions.

Here, we report a post hoc analysis of the IRIDIUM study to evaluate the efficacy of IND/GLY/MF medium- and high-dose versus respective doses of IND/MF and SAL/FLU high-dose in the Asian subpopulation and to understand whether there is an ethnic difference with the overall study population.

METHODS

Study design
This is a post hoc analysis of data from the IRIDIUM study\textsuperscript{14} in patients from Asian countries (Japan, China, Philippines, Vietnam and Thailand). IRIDIUM was a 52-week, randomised, double-blind, parallel-group, active-controlled study (ClinicalTrials.gov no. NCT02571777) in patients with inadequately controlled asthma. Patients were randomised (1:1:1:1) to IND/GLY/MF medium-dose (150/50/80 µg); IND/ GLY/MF high-dose (150/50/160 µg); IND/MF medium-dose (150/160 µg); IND/MF high-dose (150/320 µg); all one time per day or SAL/FLU high-dose (50/500 µg) two times per day. Both IND/GLY/MF and IND/MF were delivered via Breezhaler in the evening, and SAL/FLU was delivered via Diskus in the morning and the evening. Details of the study design and methodology of the IRIDIUM study are described in the original manuscript.\textsuperscript{14}

Statistical analysis
Trough FEV\textsubscript{1} and ACQ-7 score at week 26 were analysed in the full analysis set (FAS) population using a mixed model for repeated measures. The FAS included all patients who were assigned a randomisation number and received at least one dose of study medication for all analyses. This model contained treatment, visit and treatment-interaction as fixed effects, with baseline FEV\textsubscript{1}/ACQ-7 measurement, baseline-by-visit interaction, FEV\textsubscript{1} prior to inhalation and FEV\textsubscript{1} within 15–30 min post-inhalation of salbutamol/
Table 1  Baseline demographics and clinical characteristics (randomised set)

<table>
<thead>
<tr>
<th></th>
<th>IND/GLY/MF medium-dose N=52</th>
<th>IND/GLY/MF high-dose N=52</th>
<th>IND/MF medium-dose N=51</th>
<th>IND/MF high-dose N=51</th>
<th>SAL/FLU high-dose N=52</th>
<th>Total N=258</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>52.4±11.57</td>
<td>49.4±11.72</td>
<td>50.9±12.50</td>
<td>52.4±10.52</td>
<td>51.9±12.30</td>
<td>51.4±11.71</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>28 (53.8)</td>
<td>37 (71.2)</td>
<td>37 (72.5)</td>
<td>34 (66.7)</td>
<td>36 (69.2)</td>
<td>172 (66.7)</td>
</tr>
<tr>
<td><strong>Number of asthma exacerbations that required treatment in the 12 months prior to start of study, n (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>39 (75.0)</td>
<td>41 (78.8)</td>
<td>34 (66.7)</td>
<td>31 (60.8)</td>
<td>41 (78.8)</td>
<td>186 (72.1)</td>
</tr>
<tr>
<td>2</td>
<td>10 (19.2)</td>
<td>10 (19.2)</td>
<td>16 (31.4)</td>
<td>12 (23.5)</td>
<td>8 (15.4)</td>
<td>56 (21.7)</td>
</tr>
<tr>
<td>3</td>
<td>3 (5.8)</td>
<td>0</td>
<td>0</td>
<td>3 (5.9)</td>
<td>0</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>≥4</td>
<td>0</td>
<td>1 (1.9)</td>
<td>1 (2.0)</td>
<td>5 (9.8)</td>
<td>3 (5.8)</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td><strong>Never smoked, n (%)</strong></td>
<td>44 (84.6)</td>
<td>48 (92.3)</td>
<td>47 (92.2)</td>
<td>45 (88.2)</td>
<td>45 (86.5)</td>
<td>229 (88.8)</td>
</tr>
<tr>
<td><strong>Baseline ACQ-7 score</strong></td>
<td>2.2±0.46</td>
<td>2.3±0.67</td>
<td>2.3±0.45</td>
<td>2.4±0.52</td>
<td>2.3±0.40</td>
<td>2.3±0.51</td>
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<tr>
<td><strong>Pre-bronchodilator FEV₁, % predicted</strong></td>
<td>55.6±14.80</td>
<td>57.1±13.65</td>
<td>56.4±11.50</td>
<td>53.6±14.33</td>
<td>54.3±13.59</td>
<td>55.4±13.58</td>
</tr>
<tr>
<td><strong>FEV₁ reversibility after salbutamol inhalation, % increase</strong></td>
<td>26.0±15.13</td>
<td>28.2±12.23</td>
<td>27.0±13.26</td>
<td>29.2±13.59</td>
<td>26.7±13.44</td>
<td>27.4±13.50</td>
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<td><strong>Prior asthma treatment, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LABA/ICS medium-dose</td>
<td>32 (61.5)</td>
<td>32 (61.5)</td>
<td>35 (68.6)</td>
<td>36 (70.6)</td>
<td>29 (55.8)</td>
<td>164 (63.6)</td>
</tr>
<tr>
<td>LABA/ICS high-dose</td>
<td>19 (36.5)</td>
<td>19 (36.5)</td>
<td>15 (29.4)</td>
<td>15 (29.4)</td>
<td>23 (44.2)</td>
<td>91 (35.3)</td>
</tr>
</tbody>
</table>

IND/GLY/MF medium-dose, IND/GLY/MF 150/50/80µg one time per day; IND/GLY/MF high-dose, IND/GLY/MF 150/50/160µg one time per day; IND/MF medium-dose, IND/MF 150/160µg one time per day; IND/MF high-dose, IND/MF 150/320µg one time per day; SAL/FLU high-dose, SAL/FLU 50/500µg two times per day. Data presented as mean±SD, unless otherwise specified.

*The baseline ACQ-7 score was reported at screening, or if missing, at the last visit from run-in.

†FEV₁ reversibility was calculated as increase of FEV₁ value after inhalation of bronchodilator (400µg salbutamol/360µg albuterol, or equivalent dose) relative to FEV₁ value before inhalation of bronchodilator.

ACQ, Asthma Control Questionnaire; eCRF, electronic case report form; FEV₁, forced expiratory volume in 1 s; IND/GLY/MF, indacaterol acetate/glycopyrronium bromide/mometasone furoate; IND/MF, indacaterol acetate/mometasone furoate; LABA/ICS, long-acting β₂-agonist/inhaled corticosteroid; SAL/FLU, salmeterol xinafoate/fluticasone propionate.
albuterol (components of short-acting β₂-agonist reversibility) as covariates and centre as a random effect. Mean morning and evening PEF was analysed using an analysis of covariance (ANCOVA) model. The annualised rates of asthma exacerbations were analysed using a generalised linear model assuming the negative binomial distribution. All analyses were performed using SAS V.9.4. Due to the post hoc nature of the analysis, all treatment comparisons assessed in this analysis were descriptive and not powered to claim significance. All p values are nominal.

RESULTS
Baseline demographics and clinical characteristics
This post hoc analysis of Asian population included 258 randomised patients, 8.3% of overall randomised population of IRIDIUM study (IND/GLY/MF medium-dose, n=52; IND/GLY/MF high-dose one time per day, n=51; IND/MF high-dose one time per day, n=51; SAL/FLU high-dose two times per day, n=52). Baseline demographics and clinical characteristics were comparable across the treatment groups (table 1) and in line with the overall population of the IRIDIUM study.¹⁴

Lung function
IND/GLY/MF medium- and high-dose one time per day showed greater improvements in trough FEV₁ at week 26 versus respective IND/MF medium-dose one time per day (least squares mean treatment difference (Δ), 100mL; 95% CI 2 to 198mL; p=0.0463) and IND/GLY/MF high-dose one time per day (Δ, 101mL; 95% CI 3 to 200mL; p=0.0443) (figure 1A). The improvement in trough FEV₁ was greater with IND/GLY/MF medium- and high-dose versus SAL/FLU high-dose two times per day at week 26 (Δ, 125mL; 95% CI 21 to 230mL; p=0.0189 and Δ, 136mL; 95% CI 30 to 243mL; p=0.0119) (figure 1B). These improvements in trough FEV₁ with IND/GLY/MF versus IND/MF and SAL/FLU were sustained up to week 52 (figure 1B).

IND/GLY/MF medium- and high-dose showed greater improvements in post-dose PEF compared with respective doses of IND/MF and SAL/FLU as early as 5 min after the study drug administration and up to 1 hour on day 1 (online supplemental material, figure S1).

Both doses of IND/GLY/MF showed greater improvement in morning and evening PEF from baseline to week 52 compared with respective doses of IND/MF and SAL/FLU high-dose (figure 2).
Asthma control

At week 26, the improvements in ACQ-7 scores were comparable for IND/GLY/MF medium- and high-dose versus the respective doses of IND/MF and SAL/FLU high-dose, such that there were no notable differences observed between the treatment groups in terms of change of ACQ-7 scores from baseline (figure 3A). A similar trend was observed in the changes in ACQ-7 score with all treatments from baseline to week 52 (online supplemental material, figure S2). Approximately 69%–78% of patients across all treatment arms achieved the minimum clinically important difference (MCID ≥ 0.5 decrease in ACQ-7 score) change from baseline at week 26 (figure 3B). Similarly, 70.2% of patients in IND/GLY/MF medium-dose, 88.6% of patients in IND/GLY/MF high-dose, 81.4% and 89.1% of patients, respectively, for IND/MF medium- and high-dose and 83.3% of patients in SAL/FLU high-dose achieved MCID in ACQ-7 score at week 52.

Asthma exacerbations

Over 52 weeks, IND/GLY/MF medium- and high-dose reduced the rate of severe exacerbations by 32% and 36% versus respective doses of IND/MF. Comparable reductions in moderate or severe, and all exacerbations, were observed between IND/GLY/MF medium- and high-dose versus respective doses of IND/MF (figure 4A). IND/GLY/MF medium- and high-dose showed reductions of 34% and 69% in the rate of severe exacerbations versus SAL/FLU high-dose, respectively. The reduction in the rate of moderate or severe exacerbations was 18% with IND/GLY/MF medium-dose and 54% with IND/GLY/MF high-dose versus SAL/FLU high-dose. IND/GLY/MF medium- and high-dose showed 21% reductions and 34% reductions in the rate of all exacerbations versus SAL/FLU high-dose, respectively (figure 4B).

DISCUSSION

This post hoc analysis of the IRIDIUM study assessed lung function, asthma control and asthma exacerbations with IND/GLY/MF medium- (150/50/80µg) and high-dose (150/50/160µg) compared with respective doses of IND/MF (150/160µg and 150/320µg) and SAL/FLU high-dose (50/500µg) in Asian patients with inadequately controlled asthma despite LABA/ICS medium-dose or high-dose therapy. The results showed greater...
improvements in lung function and exacerbation reduction and comparable asthma control with IND/GLY/MF versus IND/MF and SAL/FLU over 52 weeks of treatment.

Baseline and clinical characteristics were comparable between the Asian patients included in this post hoc analysis and the overall population in the IRIDIUM study. In this analysis, there were more female patients than male patients, similar to that observed in the overall population. In the Asian subgroup, 14.3% patients were aged ≥65 years versus 18.4% in the overall population; those with one asthma exacerbation during the previous year were 72.1% versus 80.3%. Patients who had prior treatment with LABA/ICS medium-dose and high-dose in Asian subgroup were 63.6% and 35.3%, compared with 62.4% and 37%, respectively, in the overall population in the IRIDIUM study.

One time per day, single-inhaler IND/GLY/MF medium- and high-dose showed greater improvement in trough FEV$_1$ at week 26 compared with respective IND/MF medium- and high-dose (100mL and 101mL) and SAL/FLU high-dose (125mL and 136mL). A slightly greater improvement in trough FEV$_1$ was observed in the Asian population when compared with the results of the IRIDIUM study for the overall population. IND/GLY/MF medium- and high-dose achieved numerically greater improvement in FEV$_1$ versus the respective doses of IND/MF (76mL and 65mL at week 26, both p<0.001), and SAL/FLU high-dose (99mL and 119mL at week 26, both p<0.001) in the overall population. A faster onset of action with IND/GLY/MF medium- and high-dose was observed compared with the respective doses of IND/MF and SAL/FLU high-dose on day 1, which was maintained up to week 52. This is in line with the overall population.

IND/GLY/MF medium- and high-dose revealed considerable improvements in terms of morning and evening PEF over 52 weeks, compared with the respective doses of IND/MF (10.4–24.2L/min) and SAL/FLU high-dose (29.0–39.3L/min). The PEF results of this analysis can be considered clinically relevant based on the clinically

Figure 3  (A) Change from baseline in ACQ-7 score with IND/GLY/MF versus IND/MF and SAL/FLU at week 26 and (B) proportion of patients achieving MCID in ACQ-7 score with IND/GLY/MF versus IND/MF and SAL/FLU at week 26 (full analysis set). IND/Glycyrroman bromide/mometasone furoate; IND/MF, indacaterol acetate/glycopyrronium bromide/mometasone furoate; IND/MF, indacaterol acetate/mometasone furoate; LS, least squares; SAL/FLU, salmeterol xinafoate/fluticasone propionate.
important differences reported in the previous publications.\textsuperscript{23,24} Compared with the PEF results in the overall population in the IRIDIUM\textsuperscript{14} study, both doses of IND/GLY/MF showed slightly greater improvements in PEF versus SAL/FLU high-dose. Overall, in Asian patients with inadequately controlled asthma, IND/GLY/MF medium- and high-dose showed greater lung function benefits (improvement in trough FEV\textsubscript{1}, fast onset of action in post-dose FEV\textsubscript{1}, and increase in PEF) compared with respective doses of IND/MF and SAL/FLU high-dose. This was in line with improvements observed with IND/GLY/MF medium- and high-dose in the overall population of the IRIDIUM trial.\textsuperscript{14}

IND/GLY/MF medium- and high-dose provided comparable change from baseline to week 26 in ACQ-7 score versus the respective dose of IND/MF and SAL/FLU high-dose in Asian patients. More than 70% of patients in all treatment groups achieved the MCID at the end of study. In this post hoc analysis, more patients receiving IND/GLY/MF high-dose achieved MCID in ACQ-7 score compared with SAL/FLU high-dose at week 26. The proportion of patients achieving MCID in ACQ-7 score with IND/GLY/MF, IND/MF and SAL/FLU in this analysis was comparable with the overall population in the IRIDIUM study at week 26.\textsuperscript{14}

There were no differences among any treatment groups regarding change from baseline in ACQ-7 scores, which is consistent with outcomes in the overall population in the IRIDIUM study.\textsuperscript{14} The validity of ACQ-7 scores has been assessed in placebo-controlled trials with milder or treatment-naïve patients. Studies evaluating the add-on treatment of bronchodilators to an established effective regimen in patients with severe asthma showed lack of treatment difference in ACQ-7 scores.\textsuperscript{25}

In this post hoc analysis, IND/GLY/MF medium- and high-dose showed greater reductions in severe exacerbations (>30%) and similar reductions in moderate or severe and all exacerbations versus respective IND/MF doses over 52 weeks. On the other hand, greater reductions in asthma exacerbations (moderate or severe, from 18% to 54%; severe, from 34% to 69%; all, from 21% to 34%) were observed with both doses of IND/GLY/MF versus SAL/FLU high-dose in Asian patients. These results are in alignment with the results of the IRIDIUM study in the overall population\textsuperscript{14} and revealed that the reductions in asthma exacerbations with both doses of

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**Figure 4** Annualised rate of exacerbations with IND/GLY/MF versus (A) IND/MF and (B) SAL/FLU at week 52 in patients with inadequately controlled asthma (full analysis set). IND/GLY/MF medium-dose, IND/GLY/MF 150/50/80 µg one time per day; IND/GLY/MF high-dose, IND/GLY/MF 150/160/80 µg one time per day; IND/GLY/MF medium-dose, IND/GLY/MF 150/160/80 µg one time per day; IND/GLY/MF high-dose, IND/GLY/MF 150/320/160 µg one time per day; SAL/FLU high-dose, SAL/FLU 50/500 µg two times per day. Data presented as annualised rate (95% CI); error bars represent CI values. IND/GLY/MF, indacaterol/ glycopyrronium bromide/mometasone furoate; IND/MF, indacaterol acetate/mometasone furoate; SAL/FLU, salmeterol xinafoate/fluticasone propionate.
IND/GLY/MF versus SAL/FLU high-dose in the Asian populations are slightly better than the overall population in the IRIDIUM study. In the overall population, IND/GLY/MF medium- and high-dose resulted in a 7%–22% reduction in annualised rate of exacerbations (severe, moderate or severe and all) versus respective doses of IND/MF and 16%–42% reduction versus SAL/FLU highdose over 52 weeks of treatment.14

This analysis of the Asian subpopulation in the IRIDIUM study has the commonly recognised limitations of a post hoc analysis of a subpopulation from a larger study. This analysis included a small number of patients and did not conform to the population or the randomisation model of statistical inference. Due to its post hoc nature, all treatment comparisons assessed in this analysis were descriptive and not powered to claim significance.

CONCLUSION

In Asian patients with inadequately controlled asthma, single-inhaler, one time per day IND/GLY/ MF showed greater improvements in lung function and reduction in exacerbations, compared with respective doses of IND/MF and SAL/FLU, a standard-of-care. The change in ACQ-7 score from baseline was comparable with all treatments. The improvements in lung function, asthma control and exacerbation outcomes observed with IND/ GLY/MF in the Asian population are consistent with the results in the overall population of the IRIDIUM study.

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Competing interests

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Data availability statement

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Novartis is committed to sharing access to patient-level data and supporting documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Supplemental material

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REFERENCES


Efficacy of once-daily, single-inhaler indacaterol/glycopyrronium/mometasone in patients with inadequately controlled asthma: Post hoc analysis of IRIDIUM study in Asian population

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**Figure S1: Change from baseline in post-dose FEV<sub>1</sub> (5 min–1 h) with IND/GLY/MF, IND/MF and SAL/FLU at different time points on Day 1 (full analysis set)**


Data presented as LS mean

Δ, treatment difference; b.i.d., twice-daily; FEV<sub>1</sub>, forced expiratory volume in 1 second;

IND/MF, indacaterol acetate/mometasone furoate; IND/GLY/MF, indacaterol acetate/glycopyrronium bromide/mometasone furoate; LS, least square; o.d., once-daily; SAL/FLU, salmeterol xinafoate/fluticasone propionate
Figure S2: Change from baseline in ACQ-7 score with IND/GLY/MF versus IND/MF and SAL/FLU at Week 52 (full analysis set)


Data presented as LS mean ± SE, error bars represent SE values.

Δ, treatment difference; ACQ, Asthma Control Questionnaire; b.i.d., twice-daily; IND/MF, indacaterol acetate/mometasone furoate; IND/GLY/MF, indacaterol acetate/glycopyrronium bromide/mometasone furoate; LS, least square; o.d., once-daily; SAL/FLU, salmeterol xinafoate/fluticasone propionate
Supplemental material

Colour image_Supplementary Figures S1.tif

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**Figure Legend**

- **IND/GLY/MF medium-dose** vs **SAL/FLU high-dose**
  - Δ 107 mL (56 to 157 mL), P < 0.001
  - Δ 71 mL (20 to 122 mL), P < 0.001
  - Δ 105 mL (54 to 155 mL), P < 0.001
  - Δ 104 mL (54 to 155 mL), P < 0.001

- **IND/GLY/MF high-dose** vs **SAL/FLU high-dose**
  - Δ 76 mL (25 to 126 mL), P < 0.003
  - Δ 102 mL (51 to 152 mL), P < 0.001
  - Δ 88 mL (38 to 139 mL), P < 0.001
  - Δ 124 mL (73 to 174 mL), P < 0.001

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