Pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate following once-daily inhalation as a fixed-dose combination in healthy subjects

Hanns-Christian Tillmann1, Brian Ethel2, Nasri Abdallah2, Surendra Machineni2, Anton Drollmann3, Stephanie Last4, Michael Hahn5, Rajkumar Radhakrishnan2, Stanislav Ignatenko4, Soniya Valdyj2

1Novartis Institutes for Biomedical Research, Basel, Switzerland; 2Novartis Institutes for Biomedical Research, Cambridge, MA, United States; 3Novartis Healthcare Pvt. Ltd., Hyderabad, India; 4Charité Research Organisation GmbH, Berlin, Germany

Introduction

• Asthma is a chronic inflammatory disease of the airways characterised by respiratory symptoms and variable airflow obstruction.
• There is increasing evidence that in patients controlled on conventional and highdose inhaled corticosteroids, once-daily fixed-dose combinations (FDCs) including longacting muscarinic antagonists (LAMAs) and/or corticosteroids can provide additional benefits.6

IND/GLY/MF is a combination of indacaterol acetate (IND, a LAMA), glycopyrronium bromide (GLY, a LAMA), and mometasone furoate (MF, an ICS) being developed as a once-daily FDC delivered o.d. via the Breezhaler® inhaler. The Breezhaler® inhaler is a single-dose inhaler with a dry powder inhaler platform and a multidose valve, allowing the delivery of the active ingredients as individual powders with identical particle size and distribution, while also delivering a consistent dose of inhaled medication into the lungs to achieve a uniform therapeutic effect.8

Methods

Study design

• This was an international, open-label, four-sequence, four-period, crossover, randomised study in healthy men and women (Figure 1). Subjects were randomised to receive one of the treatment sequences in the order of 1-1-1-1.

Figure 1. Study design

Patients

• Key inclusion criteria: healthy men and women aged 18 to 65 years
• Subjects who weighed ≥50 kg having a body mass index (BMI) within the range of 18–32 kg/m²
• Subjects who had normal or corrected-to-normal vision as determined by Snellen chart
• Subjects with normal colour vision
• Subjects who signed an informed consent

Objectives

• To assess the safety, tolerability and efficacy of multiple inhaled doses of IND/GLY and MF when administered alone or as a combination (IND/GLY/MF) via Breezhaler® inhaler

Statistical analysis

• The safety analysis set included all subjects who received any study drug.
• The efficacy analysis set comprised all subjects who used the study inhaler and had at least one post-dose sample for any PK parameter.

Results

Treatment: IND/GLY/MF 150/50/160 µg (N = 34)

• No serious adverse events were reported during the study.
• The most common adverse events were respiratory in nature. The most common adverse events were nasopharyngitis, headache, oropharyngeal pain, cough, and nasopharyngeal pain.

Safety

• No subject discontinued due to a drug-related adverse event.

Conclusions

• IND/GLY/MF is a novel, fixed-dose combination of IND, GLY and MF, providing sustained bronchodilation and improved asthma control.

References

4. Charité Research Organisation GmbH, Berlin, Germany
5. Novartis Institutes for Biomedical Research, Basel, Switzerland
6. Novartis Institutes for Biomedical Research, Cambridge, MA, United States
7. Novartis Healthcare Pvt. Ltd., Hyderabad, India
8. Charité Research Organisation GmbH, Berlin, Germany

Table 1. Baseline demographics (safety analysis set)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male: 19, Female: 15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median: 34, Range: 18–65</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>Median: 25.2, Range: 18–32</td>
</tr>
</tbody>
</table>

Table 2. Summary statistics of plasma PK parameters of IND, GLY, MF on Day 14

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IND</th>
<th>GLY</th>
<th>MF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax,ss (ng/mL)</td>
<td>100</td>
<td>300</td>
<td>350</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>0.80</td>
<td>0.90</td>
<td>1.01</td>
</tr>
<tr>
<td>AUC0–24h,ss (h*ng/mL)</td>
<td>1.10</td>
<td>1.21</td>
<td>1.30</td>
</tr>
</tbody>
</table>

Figure 2. Plasma concentration-time profiles for IND on Day 14 from IND/GLY/MF combination and GLY monotherapy

Figure 3. Plasma concentration-time profiles for GLY were comparable on Day 14 when administered as IND/GLY/MF combination and monotherapy (geometric mean ratios)

Figure 4. Plasma concentration-time profiles for GLY on Day 14 from IND/GLY/MF combination and GLY monotherapy

Figure 5. Plasma concentration-time profiles for MF on Day 14 from IND/GLY/MF combination and MF monotherapy

Figure 6. Comparison of AUC0–24h (％) and Cmax (％) for IND/GLY/MF combination versus monotherapy

Figure 7. Mean AUC0–24h and Cmax of IND, GLY, MF on Day 14 following administration as IND/GLY/MF combination and monotherapy (geometric mean ratios and 90% confidence intervals for the IND/GLY/MF combination versus monotherapy)