Efficacy and Safety Outcomes in Patients with Probable or Proven vs. Possible Invasive Mould Disease from the Phase 3 SECURE Study, Evaluating Isavuconazole vs. Voriconazole for the Primary Treatment of Invasive Fungal Disease Caused by Aspergillus spp. or Other Filamentous Fungi

Johan A. Maertens1, Dominik Selleslag2, Werner J. Heinz3, Raoul Herbrelle4, Galia Rahavy5, Michael Giladi6, Mikeael Aoun7, Oliver C. Cornely8, Niekke Azië9, Rochelle M. Maher10, Achim Kaufhold11, Marc Engelhardt12, Mikael Saulay13, Andrew J. Ullmann14

1University of Maastricht: UMCU, Maastricht, Belgium; 2Astellas Pharma Global Development, Inc., Northbrook, Illinois, USA; 3Koseka Pharmaceutical International Ltd, Basel, Switzerland; 4ICON plc, Allschwil, Switzerland; 5Julius-Maximilians-University, Würzburg, Germany; 6Astellas Pharma International, U.K.; 7Astellas Pharma Global Development, Inc., Kyoto, Japan; 8German Centre for Infection Research, University of Cologne, Cologne, Germany; 9Astellas Pharma Global Development, Inc., Northbrook, Illinois, USA; 10Basilea Pharmaceutica International Ltd, Basel, Switzerland; 11ICON plc, Allschwil, Switzerland; 12Julius-Maximilians-University, Würzburg, Germany

ABSTRACT

Background: SECURE was a Phase 3 double-blind, randomised trial of isavuconazole (ISAV) vs. voriconazole (VRC) for primary treatment of invasive mould disease (IMD) caused by Aspergillus spp. or other filamentous fungi. The ITT population included all patients who received ≥1 dose of study drug. ISAV was non-inferior to VRC in overall (57% vs. 58%, P=0.20) and clinical (52% vs. 53%, P=0.56) success rates at the end of treatment (EOT) and was associated with significantly lower rates of severe adverse drug reactions (SADRs; 20% vs. 29%, P<0.01). Drug-related SADRs were reported in 29% (5% vs. 6% for ISAV vs. VRC; P=0.007) of patients with PROV/PROB-IMD and 48% in 60% (P=0.03) of patients with PSB-IMD (P=0.007).

METHODS

• The intent to treat (ITT) population included all patients who received ≥1 dose of study drug.
• Patients with PROV/PROB-IMD, as determined by the IRC, were included in the reported ITT (P) population.
• Patients with a single positive serum galactomannan (GM) value of ≥0.7 or ≥2 consecutive values ≥0.7 were considered to have GM-positive IMD.
• Patients with a single positive serum GM value between 0.5 and 0.7 or any positive bronchoalveolar lavage (BAL) GM were considered to have BAL-GM-positive IMD.

Efficacy assessments

• The primary endpoint was Day 42 ACM (95% CI) as assessed by an independent blinded data-review committee (DRC).
• A key secondary efficacy endpoint was overall success at end of treatment (EOT) and adverse drug reactions.

Safety assessments

• Treatment-emergent adverse events (TEAEs) were assessed throughout the study for patients who received ≥1 dose of study drug.

RESULTS

Table 1. Demographics of patients with PROV/PROB-IMD and patients with PSB-IMD

<table>
<thead>
<tr>
<th>Category</th>
<th>ISAV (n=129)</th>
<th>VRC (n=128)</th>
<th>Adjusted treatment difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60 (58–62)</td>
<td>61 (59–63)</td>
<td>0.8 (–0.9, 2.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>81 (64–88)</td>
<td>81 (64–88)</td>
<td>0.0 (–1.3, 1.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Race* (%)</td>
<td>11 (9–13)</td>
<td>15 (11–18)</td>
<td>2.9 (1.0, 4.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other* (%)</td>
<td>28 (24–32)</td>
<td>29 (26–33)</td>
<td>1.6 (–1.1, 4.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Neutropenia only (%)</td>
<td>116 (84–94)</td>
<td>122 (89–96)</td>
<td>1.7 (–0.3, 3.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diagnoses/clinical features (%)</td>
<td>60 (52–68)</td>
<td>59 (51–67)</td>
<td>1.0 (–2.6, 4.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Relapse (%)</td>
<td>54 (40–69)</td>
<td>59 (49–70)</td>
<td>5.4 (–2.0, 13.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Relapse (%)</td>
<td>35 (29–40)</td>
<td>39 (32–46)</td>
<td>4.1 (–0.8, 8.9)</td>
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• All-cause mortality was lower in possible IMD vs. proven or probable IMD (HR[95% CI]: 0.20[0.04–0.99], P=0.03). The adjusted treatment difference was calculated as ISAV-VRC.

• Drug-related TEAEs were reported in 29% (5% vs. 6% for ISAV vs. VRC; P=0.007) of patients with PROV/PROB-IMD and 48% in 60% (P=0.03) of patients with PSB-IMD (P=0.007).

• In the SECURE trial (ClinicalTrials.gov identifier: NCT01472952), patients with IMD were randomised 1:1 to receive 200 mg voriconazole (VRC) twice daily for 2 days and 200 mg orally (oral) or 200 mg intravenously (IV) 3 times daily for 2 days, then 4 mg/kg IV or 200 mg oral and IV on Day 3 or 2 days onwards.

• The intent to treat (ITT) population included all patients who received ≥1 dose of study drug.

• Patients with PROV/PROB-IMD, as determined by the IRC, were included in the reported ITT (P) population.

• Patients with a single positive serum galactomannan (GM) value of ≥0.7 or ≥2 consecutive values ≥0.7 were considered to have GM-positive IMD.

• Patients with a single positive serum GM value between 0.5 and 0.7 or any positive bronchoalveolar lavage GM were considered to have BAL-GM-positive IMD.

• The primary endpoint was Day 42 ACM (95% CI) as assessed by an independent blinded data-review committee (DRC).

• A key secondary efficacy endpoint was overall success at end of treatment (EOT) and adverse drug reactions.

• Treatment-emergent adverse events (TEAEs) were assessed throughout the study for patients who received ≥1 dose of study drug.

CONCLUSIONS

• All-cause mortality was lower in possible IMD vs. proven or probable IMD (HR[95% CI]: 0.20[0.04–0.99], P=0.03). The adjusted treatment difference was calculated as ISAV-VRC.

• Overall clinical success rates were significantly lower in patients with proven or probable IMD compared to those with possible IMD in both treatment arms.

• Although the superior results observed in the possible IMD group probably reflect a lower disease burden or lower proportion of IMD, it still supports the initiation of antifungal treatment prior to mycological confirmation.

• The incidence of drug-related TEAEs was significantly lower in ISAV-treated patients compared with VRC-treated patients with proven or probable IMD.

REFERENCES


Disclosures

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Contact information

Michael A. Menees, MD
Universities Zhejiang University, Shanghai,
Tel: +86 21 6367682
Email: michael.menees@astellas.com

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