Safety, tolerability, pharmacokinetics and pharmacodynamics of the oral HIF stabilizer molidustat in pre-dialysis patients with renal anemia

Iain C Macdougall1, Silvia Lentini2, Anja Schmidt2, Michael Boettcher2, Dorina van der Mey3, Andreas Kaiser3, Dagmar Kubitza2, Georg Wensing2

1 King’s College London, London, UK; Clinical Sciences, Bayer Pharma AG, Wuppertal, Germany; 2 Research and Clinical Science Statistics, Bayer Pharma AG, Berlin, Germany

Disclosures
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BACKGROUND
Failing kidneys produce inadequately low amounts of erythropoietin (EPO) resulting in renal anemia in patients with chronic kidney disease (CKD). EPO gene transcription is regulated by the hypoxia inducible factor (HIF). Inhibition of PHD by molidustat mimics hypoxia.

OBJECTIVES
To investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of molidustat in pre-dialysis patients with renal anemia and stage 3–4 CKD.

METHODS
This randomized, placebo-controlled, combined single/multiple-dose escalation study took place in 7 centers in Germany and 1 in the UK.

RESULTS
44 patients (mean age [range]: 66.1 [39-81] years) were randomized to receive molidustat (n = 34) or placebo (n = 10). For demographic characteristics see Table 1.

Table 1. Demographics in the placebo and molidustat groups (N = 44).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Molidustat 5 mg</th>
<th>Molidustat 25 mg</th>
<th>Molidustat 75 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.9 (61-68)</td>
<td>66.1 (60-81)</td>
<td>65.9 (60-79)</td>
<td>65.3 (60-80)</td>
<td>65.6 (60-81)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
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<td>5:5</td>
<td>5:5</td>
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<tr>
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<td>9</td>
<td>9</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>10 (100)</td>
<td>5 (100)</td>
<td>5 (100)</td>
<td>8 (89)</td>
<td>11 (25)</td>
</tr>
</tbody>
</table>

Pharmacokinetics
Molidustat exposure increased in a dose-dependent manner in the dose range of 5 to 75 mg (Table 3). The PK was linear over time and no relevant accumulation was observed after once-daily dosing. Mean elimination half-life ranged from 7 to 13 hours. Urinary elimination of molidustat accounted for placebo.

CONCLUSIONS
Molidustat was well tolerated in pre-dialysis patients with renal anemia. The PK of molidustat was linear over time, with no relevant accumulation after once-daily administration. Mean EPO Cmax and AUC increased dose-dependently with a trend towards higher EPO response on Day 14 compared to Day 1. Indicators of stimulation of erythropoiesis were an increase in reticulocytes and a trend towards decreases in ferritin and hepcidin values. Owing to the short treatment duration, no significant increase in hemoglobin was observed. VEGF (like EPO a HIF target gene) expression was not increased by molidustat treatment.

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REFERENCES