Pharmacokinetics and Exposure–Response in Patients With Anemia Due to Low- or Intermediate-1-Risk Myelodysplastic Syndromes (MDS): Preliminary Results From Phase 2 Studies

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INTRODUCTION

• Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by ineffective erythropoiesis leading to anemia
• Luspatercept (JAK2 inhibitor) is a novel therapeutic option that acts as a farnesyl transferase inhibitor to block terminal erythropoiesis in the TGF-β superfamily

OBJECTIVE

• To characterize the pharmacokinetics of luspatercept and to explore the exposure–response relationship of luspatercept serum exposure in patients with IPSS-defined low-risk MDS, thereby informing selection of the starting dose in phase 3 studies of luspatercept in MDS

METHODS

StudY Design

• Pharmacokinetic, safety, and efficacy data were collected from two phase 2 studies (basic and extension); NCT01749514 and NCT02306380 (luspatercept for the treatment of anemia in patients with IPSS-defined low-risk MDS)

• Patients were categorized by baseline transfusion burden:
  - Patients requiring ≥ 4 red blood cell (RBC) units in the 3 weeks prior to study start and with baseline Hb < 10 g/dL were classified as low transfusion burden (LTB)
  - Patients requiring ≥ 4 RBC units in the 8 weeks prior to study start were classified as high transfusion burden (HTB)

TREATMENT

• In the basic study, luspatercept was administered by subcutaneous injection once every 2 weeks, for up to 5 doses, in sequential cohorts

The base study included:
  - A dose-escalation cohort, with fixed doses ranging from 0.150 mg/kg to 1.75 mg/kg
  - An expansion cohort, with a starting dose of 1.0 mg/kg followed by individual dose titration up to 1.75 mg/kg

• Patients comprising the base study were eligible to enroll in an extension study, where patients continued to receive luspatercept every 3 weeks for up to 1 year

• Patients who experienced treatment interruption for ≥ 3 months before enrolling

• The main exposure endpoint was area under the curve (AUC) of luspatercept serum concentration–time curve (AUC)

• Clinical endpoints included Hb level increase, transfusion reduction, and drug-related adverse events (DRAEs) in weeks 1–10

• Responders were defined as patients achieving erythroid hematopoietic improvement (HI) per International Working Group (IWG) criteria

• For LTB patients, an Hb increase of ≥ 1.5 g/dL, without transfusion

• For HTB patients, a transfusion reduction of ≥ 4 RBC units over 8 weeks

RESULTS

Table 1. Summary of Luspatercept Pharmacokinetic Parameters in the Basic Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LTB (n = 15)</th>
<th>HTB (n = 49)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hb change</td>
<td>1.7 (0.3)</td>
<td>2.0 (0.4)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Transfusion burden reduction</td>
<td>0.47 (0.05)</td>
<td>0.49 (0.05)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
| LTB, low transfusion burden; RBC, red blood cell.

Table 2. Predictors of RBC-TI ≥ 8 Weeks Among Patients With a Transfusion Burden ≥ 8 Weeks

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline transfusion burden</td>
<td>&gt; median AUC</td>
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Table 3. Predictors of RBC-Transfusion Independence

<table>
<thead>
<tr>
<th>Predictor</th>
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</thead>
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Figure 1. Serum Drug Exposure Versus Hb Increase in LTB Patients and RBC Transfusion Burden Reduction in HTB Patients by Baseline Hb Level

Figure 2. Response Rate by Exposure in Weeks 1–15 for LTB and HTB Patients

Figure 3. Overall Rate of RBC-4 Response Versus Luspatercept Serum Exposure

Figure 4. Relationship Between Drug-Related AEs and Luspatercept Serum Exposure

CONCLUSIONS

• Higher luspatercept serum exposure was found to correlate with greater rates of HI for both LTB and HTB patients
• LTB patients exhibited higher luspatercept serum exposure and lower frequency of drug-related adverse events compared to HTB patients

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DISCLOSURES