Improved pharmacokinetics and bleeding efficacy of recombinant Factor IX Fc-XTEN in hemophilia-B mice

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INTRODUCTION

• Prophylactic treatment for severe hemophilia B patients is considered the optimal therapy to reduce bleeding frequency and prevent joint damage.
• Alprolix (rFIXFc) is the first of a new generation of long acting (LA) rFIX replacement products generated to improve patient care by reducing the frequency of infusions1. All rFIX preparations are administered by intravenous dosing, which can be particularly challenging for young patients and patients with limited venous access.
• We are using XTEN recombinant protein technology2, in combination with rFIXFc in order to develop LA rFIXFc molecules that are suitable for prophylactic, subcutaneous dosing in hemophilia B.
• XTEN are unstructured polypeptide sequences that consist of a limited set of natural amino acids (Pro, Ala, Gly, Glu, Ser, Thr).

Figure 1. Molecular design of rFIXFc-XTEN

Table 1. Relative specific activity of FIXFc-XTEN

<table>
<thead>
<tr>
<th>Molecule</th>
<th>IU/mg</th>
<th>Serum (aPTT)</th>
<th>γ-carboxylated</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIX</td>
<td>220</td>
<td>10</td>
<td>95%</td>
</tr>
<tr>
<td>FIXFc</td>
<td>1227</td>
<td>57</td>
<td>88%</td>
</tr>
<tr>
<td>FIXFc-XTEN</td>
<td>109-176</td>
<td>12-19</td>
<td>94%</td>
</tr>
</tbody>
</table>

• Higher specific activity at molar basis of FIXFc-XTEN compared to FIX as measured by aPTT compared to WHO standard.

Figure 2. rFIXFc-XTEN greatly improves efficacy and bioavailability for subcutaneous dosing

• rFIXFc-XTEN shows a 19-fold improved AUC/D and a 3.5-fold improved bioavailability compared to rFIX for subcutaneous dosing.
• Subcutaneously dosed rFIXFc-XTEN shows better AUC/D than intravenously dosed rFIXFc.

CONCLUSIONS

• rFIXFc-XTEN has a higher specific activity than rFIX.
• When compared to IV administered rFIXFc, preclinical subcutaneous dosing data in hemophilia B mice suggest the potential of once weekly or less frequent prophylactic subcutaneous dosing of rFIXFc-XTEN in patients.
• rFIXFc-XTEN shows acute efficacy in the HemB mouse tail bleeding model.
• Studies are ongoing to address in vivo efficacy and allometric scaling in preclinical animal models.

References

Disclosures
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