A novel long-acting glucagon analog (HM15136) offers favorable stability, PK/PD, and therapeutic potentials in CHI (congenital hyperinsulinism) animal model

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RESULTS

Improved solubility and physical stability of HM15136

Table 1. Solubility of HM15136

<table>
<thead>
<tr>
<th>Test article</th>
<th>Solubility at pH 7.0</th>
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<tbody>
<tr>
<td>Glucagon</td>
<td>0.03 mg/mL</td>
</tr>
<tr>
<td>HM15136</td>
<td>≥ 150 mg/mL</td>
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</table>

Figure 1. Physical stability of HM15136 in PBS (pH 7.0) at 25°C

HM15136 shows improved solubility and physical stability at physiological pH compared to the native glucagon.

In vitro properties of HM15136

Table 2. cAMP accumulation by glucagon receptor (GCGR)

<table>
<thead>
<tr>
<th>Test articles</th>
<th>% Activity vs native GCG</th>
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</thead>
<tbody>
<tr>
<td>Human GCGR</td>
<td>Glucagon 100%</td>
</tr>
<tr>
<td></td>
<td>HM15136 11.83 ± 4.42%</td>
</tr>
<tr>
<td>Mouse GCGR</td>
<td>Glucagon 100%</td>
</tr>
<tr>
<td></td>
<td>HM15136 28.67 ± 8.22%</td>
</tr>
</tbody>
</table>

Figure 3. Glucose production by HM15136 in rat primary hepatocytes

(a) Glucose production by HM15136

(b) Glycogenolysis

(c) Gluconeogenesis

PK and short-term PD (reversal of acute hypoglycemia)

Figure 4. PK in normal mice (n=3/time point)

(a) For glucagon (Glucagon*)

(b) For HM15136

Figure 5. Reversal of acute hypoglycemia in normal rats (n=5)

(a) Time-course BG profiles

(b) BG AUC

Sustained BG increasing efficacy in hyperinsulinemia-induced chronic hypoglycemic rats

Figure 6. Blood glucose after chronic administration of HM15136 in CHI model rats (n=9)

(a) Experimental scheme

(b) Blood glucose change

CONCLUSIONS

- HM15136 is a long-acting glucagon receptor agonist developed for the treatment of CHI
- HM15136 induces GCGR activation with full agonistic nature
- HM15136 not only induce glucagon-like effect, but also gluconeogenesis in rat primary hepatocytes, indicating its glucose producing potential
- PK results demonstrate its prolonged half-life and improved BA, indicating weekly and self injection potential
- Intravenous administration of HM15136 could reverse acute hypoglycemia-induced by insulin challenge
- When chronically administered, HM15136 sustainably increases BG in CHI mimetic rats, demonstrating its therapeutic potential in CHI

REFERENCES

- Amos JB et al., Orphanet J Rare Dis. 6, 63 (2011)