Pharmacological Evaluation of Once-weekly Combination Of A Long-acting Insulin Analog With A Long-acting Exendin-4 Analog In An Animal Model

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RESULTS

Weekly Potential of LAPS-Insulin 115 + LAPS-CA-Exendin-4 Combination

Table 1. In vitro pharmacologic activity of co-formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Activity vs. LAPS-Insulin 115</th>
<th>% Activity vs. LAPS-CA-Exendin-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAPS-Insulin 115</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>LAPS-CA-Exendin-4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Co-formulation (1:1)</td>
<td>101.2%</td>
<td>104.4%</td>
</tr>
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</table>

- The co-formulation showed no interference with the intrinsic activity of individual drugs.

Figure 2. Multiple dose PK of co-formulated LAPS-Insulin 115 and LAPS-CA-Exendin-4 in normal rats (ns, s, Q3D)

No PK and Pharmacologic Drug-Drug Interaction Between LAPS-Insulin 115 and LAPS-CA-Exendin-4 When Co-formulated

Figure 3. PK profile of co-formulation vs. individual drug in normal rats (ns, s, single)

Aims

- To evaluate the once-weekly potential of LAPS-Insulin 115 + LAPS-CA-Exendin-4 combination.
- To evaluate the beneficial effects of LAPS-Insulin 115 + LAPS-CA-Exendin-4 combination in in vivo disease models.

Methods

- In vitro pharmacologic study of single formulation
  
  - Reactor binding affinity of LAPS-Insulin 115 and LAPS-CA-Exendin-4 in co-formulation was determined by SPR (surface plasmon resonance) method. GLP-1RA and exendin-4 were available kit after 10% heteromultimer filter. HGLP-1RA and HGLP-4 were assayed by ELISA and MPM binding assay, respectively.

- PK study in db/db mice or DIO-STZ rats
  
  - Similar and prolonged PK profiles of LAPS-Insulin 115 and LAPS-CA-Exendin-4 were observed in SD rat and weekly human PK simulation.
  
  - Exendin-4: 3.75 nmol/kg was administrated on Q2D in SD rat, preclinical rat, and human.
  
  - Exendin-4: 0.36 nmol/kg was administrated on Q2D in SD rat (50U/day + 1.8 mg human HbA1c).

- Statistical analysis
  
  - The body weight changes by LAPS-Insulin 115 + LAPS-CA-Exendin-4, and their combination were analyzed using one-way ANOVA with Dunnett’s post test.

CONCLUSIONS

- LAPS-Insulin 115 and LAPS-CA-Exendin-4 showed well-harmonized and prolonged PK profiles compared to daily insulin and GLP-1RA.

- In a co-formulation of LAPS-Insulin 115 and LAPS-CA-Exendin-4 showed no PK profiles and intrinsic activity interferences.

- LAPS-Insulin 115 + LAPS-CA-Exendin-4 combination showed superior glycemic control and reduced body weight gain in db/db mice and DIO-STZ rats.

- Switching from daily basal insulin to weekly LAPS-Insulin 115 + LAPS-CA-Exendin-4 combination demonstrated improved glycemic and body weight control in db/db mice.

REFERENCES