The ultra-long acting LAPs GLP/GCG dual agonist, HM12525A, demonstrated safety and prolonged pharmacokinetics in healthy volunteers: a phase 1 first-in-human study

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) or glucagon-like peptide-2 (GLP-2) analogs may have the potential to treat diabetes and obesity by activating both GLP-1 and GCG receptors. The once-weekly, APA GLP/GCG dual agonist, HM12525A, is allosterically conjugated by LAPS/TEAL® technology for sustained duration of activity. By combining the synergistic GLP-1/GCG effects, this long-acting platform, HM12525A, may improve patient compliance and thereby treat diabetes and obesity further. This First-in-Humans Phase randomized, double-blind, placebo-controlled single ascending dose study evaluated the safety, tolerability, PK and PD of HM12525A in healthy volunteers.

BACKGROUND

Potential beneficial effects of GLP-1/GCG dual agonist

- Decrease food intake and increase glucose-dependent insulin secretion through GLP-1 receptor stimulation
- Energy expenditure and lipolysis increased by GCG activity

Overview of HM12525A

HM12525A is a novel ultra-long-acting dual agonist which consists of a chemically synthesized GLP-1 analog and GCG, conjugated with a human IgG Fc fragment to form PECLs. HM12525A exhibits a well balanced agonism at the GLP-1 receptor and the glucagon receptor (1:1 ratio).

STUDY DESIGN

Figure 1. Study Design

STUDY OBJECTIVES

- Primary objective: To evaluate safety and tolerability of HM12525A in healthy volunteers after single administration of HM12525A
- Secondary objectives:
  - To assess pharmacokinetic(PK) profile of HM12525A
  - To assess effects of HM12525A on glucose metabolic profiles

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>28.2 (1.6)</th>
<th>28.3 (2.2)</th>
</tr>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>64.4 (5.2)</td>
<td>65.1 (7.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.8 (5.4)</td>
<td>171.5 (4.1)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.1 (2.1)</td>
<td>23.7 (1.2)</td>
</tr>
<tr>
<td>Male</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

RESULTS

Figure 2. Serum PK exposure of HM12525 (linear scale)

Figure 3. 24hr ambulatory monitoring: systolic/diastolic blood pressure and heart rate at peak PK concentration

Figure 4. Incidence of gastrointestinal events

Table 2. Summary of gastrointestinal events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>HM12525A 6.5 x placebo or placebo</th>
<th>HM12525A 6.5 x placebo</th>
<th>HM12525A 6.040 (20.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (3.0)</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3.0)</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

Table 3. Summary of immunogenicity

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroconversion</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

The confirmed long half life after a single dose supports the potential use of HM12525A for weekly or longer injection intervals. Heart rate elevation was observed with increasing dose levels, while no clinically relevant changes in BP during 24hr ABP monitoring at peak concentration were observed. Low incidence of treatment emergent adverse events and no neutralizing antibodies were observed. Further clinical trials to investigate the efficacy and the safety in the disease population.

REFERENCES

Potent weight loss mechanism and improvement of NASH by the long-acting GLP-1/Glucagon receptor dual agonist HM1252A

**Background**
Dual agonists activating the GLP-1 receptor (GLP-1R) and the glucagon receptor (GGR) may represent a new therapeutic approach for obesity with the potential for enhanced weight loss beyond those of GLP-1R agonists. Onglyzomodulin, a human gut hormone with agonism to the GGLR and the GGR, causes a significant reduction in weight by regulating both appetite and energy expenditure, however its clinical application is limited due to a short half-life. HM1252A is a long-acting GLP-1/glucagon receptor dual agonist for once-weekly injection. It consists of a GLP-1 receptor glucagon receptor dual agonist conjugated via non-peptidyl linker to a non-glycosylated human Fc fragment. The aim of this development is to increase body weight loss efficacy compared to GLP-1R agonists while extending the half-life.

**Aims**
- To investigate the mechanism for potent anti-obesity efficacy by HM1252A
- To investigate the effect on nonalcoholic steatohepatitis (NASH) by HM1252A

**Anti-Obesity efficacy beyond GLP-1RAs**
- Powerful weight loss efficacy is observed in DM-12525A vs. GLP-1RAs
- Decrease food intake by GLP-1 activity
- Increase EE and lipolysis by glucagon activity

**Methods**
- Animal study
  - DIO rats were treated (i.c.) with HM1252A QOD and insulinoglu BID for 3 weeks. Reciprocated controls were given a daily food allotment equal to that consumed by a drug-treated group. The body weight and food intake was monitored daily.
  - DIO mice were treated (i.c.) with HM1252A QW and insulinoglu QD for 4 weeks. The body weight, fat mass, and lean mass were measured.

**Gene expression in adipocytes and myocytes**
- STS-L1 adipocytes and C2C12 myocytes were differentiated for 2 and 3 days, respectively. Cells were treated with glucagon, HM1252A or insulinoglu for 24 hours. qPCR, Nrf1, and UCP gene expression were evaluated by quantitative real-time PCR analysis.

**Confocal microscopic analysis for mitochondrial biogenesis**
- STS-L1 adipocytes and C2C12 myocytes were differentiated for 2 and 3 days, respectively. Cells were treated with glucagon, HM1252A or insulinoglu for 24 hours. Confocal microscopic analysis for mitochondrial biogenesis was performed.

**RESULTS**

**Figure 1. Body weight loss in DIO rats (n=7, 3weeks)**
(a) Body weight change
(b) Cumulative Food Intake

**Figure 2. In vivo increase of EE specific marker gene expression**
(a) STS-L1 adipocytes
(b) C2C12 myocytes

**Figure 3. In vitro induction of mitochondrial biogenesis**
(a) Mitochondria staining
(b) Relative intensity

**Figure 4. Body composition change in DIO mice (n=10, 4 weeks)**
(a) Body weight
(b) Body fat mass
(c) Lean body mass

**Figure 6. Therapeutic potential in MCD mice (n=7, 4 weeks)**
(a) TNFα mRNA
(b) Collagen-1 mRNA
(c) NAFLD activity score

**Figure 7. Clinical development milestone**

**CONCLUSIONS**
- In DIO rats, HM1252A showed superior body weight loss compared with liraglutide and the potent SWL, effect of HM1252A is twice than pair-fed groups indicating increase of EE.
- HM1252A induces the expression of EE specific marker genes (i.e. PGC1α, Nrf1, and UCP) and mitochondrial biogenesis as an action of glucagon in adipocytes and myocytes.
- HM1252A induced SWL and fat mass without a change in lean body mass supporting that increasing EE may be the driving force for the potent SWL.
- In NASH animal models, HM1252A reduces hepatic TG, inflammation, fibrosis marker, and histological scores.
- Our results suggest that the novel GLP-1/glucagon receptor dual agonist HM1252A may have clinical potential for the treatment of obesity and obesity-related liver diseases.

**REFERENCES**