In vitro characterization of a novel long-acting glucagon analog (HM15136) and its potential effect in animal models of chronic hypoglycemic diseases

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ABSTRACT

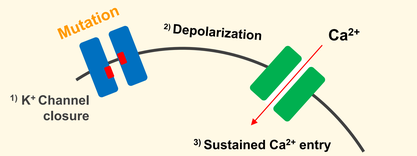
Glucagon plays an essential role in glucose homeostasis, and has been used to treat acute hypoglycemia in diabetic patients. However, due to poor solubility and stability at physiological pH as well as short duration of action, its utility was hampered when managing chronic hypoglycemic diseases. One such example is congenital hyperinsulinism (CHI). CHI is a rare genetic disorder characterized by unregulated insulin secretion which leads to severe hypoglycemia especially during fasting condition. Another example is post-bariatric hypoglycemia (PBH) which can also lead to postprandial neuroglycopenia. Despite this life-threatening condition, no drugs are approved for CHI and/or PBH, and available glucagon therapies are very inefficient and inconvenient due to abovementioned limitations. Thus, to provide more optimal therapy for these chronic hypoglycemic diseases, a novel long-acting glucagon analog (HM15136) was developed. Here, we evaluated HM15136's 1) solubility and stability at physiologic pH, 2) *in vitro* properties, and 3) potential therapeutic effect in animal models of CHI or PBH.

First, we demonstrated improved solubility of HM15136 (≥150 *vs.* 0.03 mg/mL) at pH 7.0 and stability at day 20, compared to those of native glucagon. Next, *in vitro* cAMP assay was performed in CHO cells expressing human glucagon receptor (hGCGR), and HM15136 selectively activated hGCGR as a full agonist (EC_{50} = 0.024 *vs.* 0.003 nM; relative activity = ca.12.7%). In line with this, HM15136 promoted glycogenolysis and gluconeogenesis in rat primary hepatocytes in a dose dependent manner (relative potency = ca. 20%), confirming glucose producing nature of HM15136. To investigate *in vivo* therapeutic effect on CHI and PBH, chronic hypoglycemia rats induced by SC infusion of insulin (CHI rats) and postprandial hypoglycemia rats induced by vertical sleeve gastrectomy (VSG rats) were established, respectively. Notably, HM15136 treatment significantly restored FBG by 37.3 ~ 69.7% ($p<0.05$ ~ 0.001) in CHI rats. Consistently, HM15136 treatment significantly prevented a massive BG reduction during MMTT in VSG rats (ΔBG between 0 and 45 min = +21 *vs.* -30 mg/dL, $p<0.001$). Furthermore, weekly dosing potential and BG elevation effect of HM15136 were also demonstrated in healthy human subjects[1].

Based on these results, HM15136 could be a potential therapeutic option for chronic hypoglycemic diseases including CHI and PBH. Phase 2 clinical study in CHI subjects is on-going to assess the clinical relevance of these findings.

BACKGROUND

In CHI patients' pancreatic β-cell…

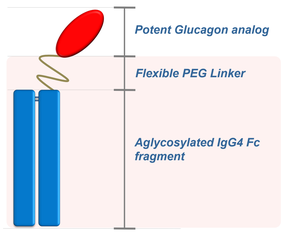


→ Enhanced/sustained INS secretion, leading to chronic and life-threatening hypoglycemia

- **Congenital hyperinsulinism (CHI)**
  - Inappropriate insulin secretion lead to hypoglycemia
  - ***Incidence : 1/25,000 ~ 1/50,000 (Orphan disease)***
- **To date, diazoxide was the only approved drug although ca. 60% of CHI patient was unresponsive to this drug**
- **Although glucagon could be a ideal therapeutic option, its 1) very short half-life and 2) highly insoluble and unstable properties at neutral pH hamper its long-term application to manage chronic hypoglycemia such as CHI**

HM15136 is a novel long-acting Glucagon analog conjugated with a human IgG4 Fc *via* flexible PEG linker

By improving physicochemical properties and extending PK, HM15136 could be a novel therapeutic option for chronic hypoglycemic diseases of unmet medical needs such as congenital hyperinsulinism (CHI)



LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

[General profile]
- **Ready-to-inject** with soluble formulation
  At pH 7.0, solubility of HM15136 ≥ 150 mg/mL (vs. 0.03 mg/mL for native glucagon)
- **Extended half-life allows once-weekly dosing in human**
- **Preferentially distributed to the liver, the main target organ of glucagon**

[Clinical aspects]
- **2 Phase 1 SAD** (KR), **MAD** (US) **studies completed**
  - Well-tolerated and Once-weekly potential was confirmed
  - Dose-dependent BG elevation was demonstrated in healthy obese population
- **Phase 2 study on-going for CHI subjects** (US, UK, DE and IL)
- **ODD for CHI** (US, EU, KR) **granted, RPD for CHI** (US) **and PIP approved** (EU)
- **Indication expansion** (e.g. PBH) **being considered**

RESULTS

In vitro characterization of HM15136

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

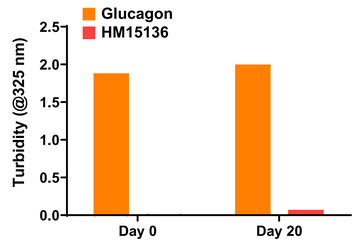
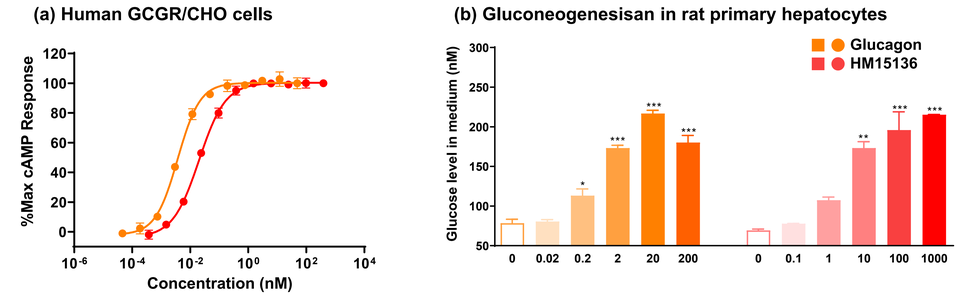


Figure 2. Intracellular cAMP accumulation (a) and glucose production (b) by HM15136



➢ HM15136 showed improved solubility and stability at physiological pH compared to native glucagon. Conjugation of IgG FC fragment didn't affect full-agonistic nature of HM15136 for GCGR activation and consequential glucose production by HM15136

In vivo effect of HM15136 in animal models of chronic hypoglycemia diseases

Figure 2. The effect of HM15136 on FBG change in CHI rats

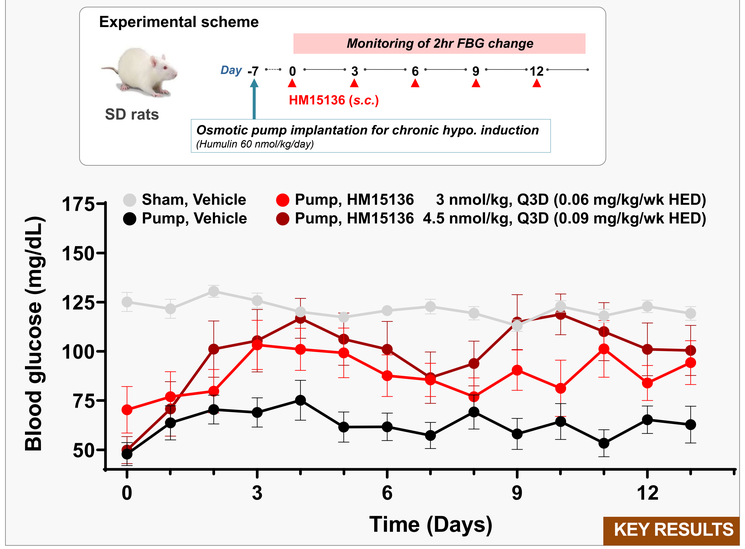
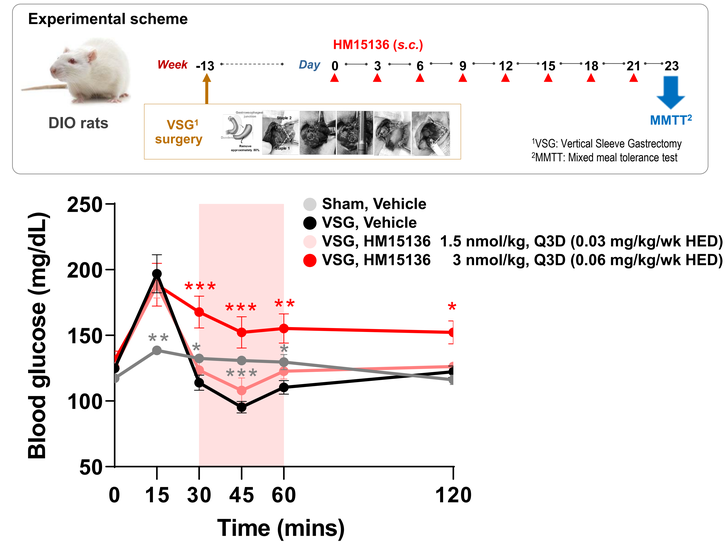


Figure 3. The effect of HM15136 on BG during MMTT in PBH rats



➢ Chronic treatment of HM15136 was associated with BG normalization in animal models of CHI and PBH

CONCLUSIONS

- **HM15135 is a novel long-acting glucagon analog with improved physicochemical properties and PK.**
- ***in vitro*/*in vivo* results support therapeutic potential of HM15136 for the management of chronic hypoglycemia diseases such as CHI and PBH**
- **P2 study is on-going in CHI patients to assess the clinical relevance of these findings**

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