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

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ABSTRACT
Congenital hyperinsulinism (CHI) is a rare genetic disorder characterized by hypoglycemia caused by excessive insulin secretion and is associated with significant morbidity and mortality. Therefore, the most potent therapeutic options, its utilization is limited due to poor solubility, limited stability, and adverse effects of side effects. Recently, to overcome these limitations, we developed a novel long-acting glucagon analog, HM15136, consisting of a glucagon analog conjugated to a long-acting glucagon receptor (G-Pump™) vehicle. We investigated the therapeutic potential of HM15136 in CHI by evaluating its pharmacological features and its potential as a new therapeutic option for CHI.

METHODS
To measure intracellular cyclic AMP level, CHO cells stably expressing either human or mouse GlucagonR was treated with HM15136 for 30 min. The accumulation of cAMP in the medium was determined by using in-house developed ELISA method. The cellular glucose production was measured using the LANCET™ Glucose assay kit (PerkinElmer).

RESULTS
In vitro properties of HM15136

Figure 2. Intracellular cAMP accumulation by HM15136
(a) Human GCG/RCHO cells
(b) Mouse GCG/RCHO cells

In conclusion, HM15136 shows prolonged glucagon-like action allowing the development of a novel once a weekly therapeutic option for CHI.

ORPHAN DRUG STATUS FOR CHI (FDA)

• Orphan drug status for CHI (FDA)

TREATMENT SCHEME

• Efficacy and convenience

In vitro properties of HM15136

Figure 3. Glucose production by HM15136 in rat primary hepatocytes

CONCLUSIONS
• HM15136 is a long-acting glucagon receptor agonist developed for the treatment of CHI
• HM15136 induces GlucagonR activation with full agonistic nature
• HM15136 not only induce glucagonesis, but also glycogenolysis and gluconeogenesis in rat primary hepatocytes
• 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

In conclusion, HM15136 shows prolonged glucagon-like action with improved physicochemical features which may allow the development of a novel therapeutic option for CHI for easy weekly use.

REFERENCES
Amass J.B et al., Orphanet J Rare Dis. 6, 13 (2011)

Figure 4. Plasma glucose after chronic administration of HM15136 in CHI rats (n=5)
(a) Experimental scheme
(b) Glucose concentration

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

Figure 6. Blood glucose after chronic administration of HM15136 in CHI rats (n=5)
(a) Experimental scheme
(b) Blood glucose concentration

When chronically administered, HM15136 sustainably increases BG in CHI mimetic rat, demonstrating its therapeutic potential in CHI.