Cross-Species Pharmacokinetic Comparison and Human PK Prediction of HM15275, A Novel Long-Acting GLP1/GIP/GLUCAGON Triple Agonist for Treatment of Obesity

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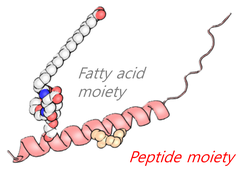
Introduction

HM15275 is a long-acting triple agonist peptide consisting of 39 amino acids, functioning as a GLP-1, GIP and glucagon receptor agonist. It has demonstrated significant body weight loss and improved blood glycemic control in preclinical studies. In First-in-human Phase 1 clinical study [HM-OBCT-101], HM15275 was generally safe and well tolerated, exhibiting a safety profile consistent with incretin-based therapies. HM15275 is currently being evaluated in a Phase 2 clinical study [HM-OBCT-201] involving adults with obesity (BMI ≥30 kg/m² and ≤50 kg/m²) or overweight (BMI ≥27 kg/m²) without type 2 diabetes mellitus. The objective of this study is to compare the pharmacokinetic properties of HM15275 across the species, and to predict the human pharmacokinetic (PK) or toxicokinetic (TK) data from mice, rats, and monkeys following subcutaneous administration.

Structure & Mechanism of Actions



GLP-1
GIP
- Weight loss by appetite regulation
- Indirect effect from BW loss and BG control for CVRM benefits

Glucagon
- Weight loss by energy expenditure
- Direct tissue effect for CVRM benefits

Methods

- **Plasma protein binding (PPB)**
  : The binding affinity of HM15275 with plasma isolated from various species was evaluated by using surface plasmon resonance (SPR). The affinity constant (K_D) was calculated based on the affinity (steady-state) sensorgram on a 1:1 binding model. The percentage unbound in plasma ($f_{u,p}$%) was calculated using K_D values of HM15275 for mouse, rat, dog, monkey and human plasma.

- **Animal PK/TK studies**
  : CD-1 (ICR) mice, SD rats, beagle dogs and cynomolgus monkeys were administered single or multiple doses of HM15275 *via* intravenous (I.V.) or subcutaneous (S.C.) route. The plasma concentrations of HM15275 were analyzed using validated LC-MS/MS bioanalytical methods.

- **Human PK prediction**
  : The human PK of HM15275 in healthy subject (70 kg) was predicted using PK/TK data from three animal species (mouse, rat and monkeys). The PK in obese patients (100 kg, BMI 35 kg/m²) was scaled from the predicted PK in healthy subject by applying the approach used in other incretin drug[1]. The allometric scaling and C_{ss}-MRT method[2] were applied to predict human PK parameters and profiles, respectively.

Parameter Prediction

- **SS_{monkey}**
  : single-species scaling (SS) using monkey with fixed exponent 0.8 (CL/F)[3] and 1.0 (V_{ss}/F)[4]
- **SS_{avg}**
  : average of single-species scaling for mouse, rat and monkey

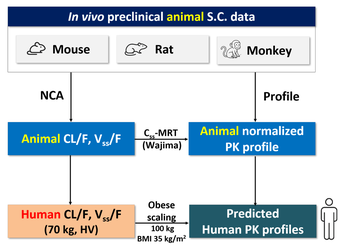
$$Parameter_{human} = Parameter_{animal} \times \left(\frac{BW_{human}}{BW_{animal}}\right)^{0.8\ or\ 1.0}$$

- **SA-ROE or SA**
  : CL/F - simple allometry with the rule of exponent for protein drugs[5]
  - if b < 1 → simple allometry ; b ≥ 1 → correction by brain weight
  : V_{ss}/F – simple allometry

$$Parameter = a \times BW^{b}$$

* Note : V_{ss}/F (= CL/F x MRT_{INF}) did not represent the actual V_{ss}/F value. Instead, it was used as a scaling factor related to the V_d to predict human PK profiles.

Figure 1. Flow chart for prospective human PK prediction of HM15275



Preclinical PK Results

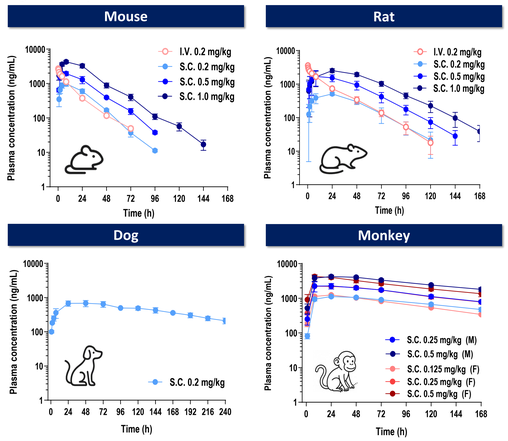
- **Plasma protein binding (PPB)**
  : The PPB in equilibrium state was greater than 99% across all tested species, indicating that the acylated linker of HM15275 binds to albumin, the predominant plasma protein, contributing to its long-acting property.

Table 1. PPB of HM15275 across species

Species	K_D (μM)	% unbound in plasma ($f_{u,p}$)
Mouse	2.21 ± 0.30	0.37
Rat	0.55 ± 0.03	0.09
Dog	2.46 ± 0.31	0.41
Monkey	3.43 ± 0.27	0.57
Human	1.23 ± 0.81	0.20

- **Animal PK/TK**
  : In rodents, HM15275 exhibited low clearance (CL; 3.5 – 6.1 mL/h/kg) and low volume of distribution (V_{ss}; 85.2 – 132.8 mL/kg), indicating limited extravascular distribution consistent with high plasma protein binding. In all tested species, prolonged $t_{1/2}$ values were observed in mice (12.4 – 16.3 h), rats (17.5 – 18.8 h), dogs (91.9 h) and monkeys (76.0 – 108.2 h). The absolute bioavailability (BA) following subcutaneous administration was high in mice (79.8 – 92.6%) and rats (47.8 – 64.4%).

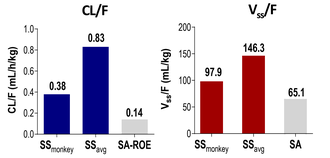
Figure 2. PK profiles of HM15275 in preclinical species



Human PK Prediction (I)

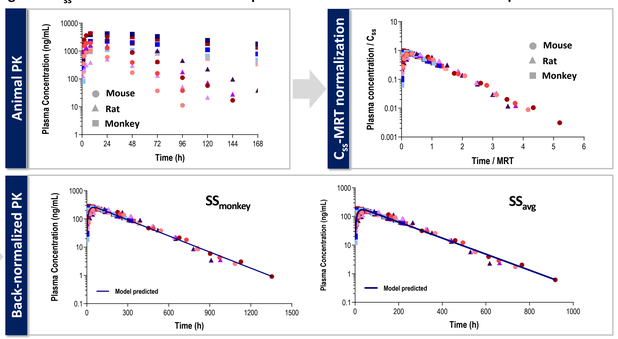
- **Prediction of human PK parameters**
  : For human PK simulation, SS_{monkey} was selected due to commonly used approach for human PK prediction of biotherapeutics, considering human relevance. SS_{avg} was also selected because it incorporates data from all three species. SA-ROE was excluded due to relatively low correlation. V_{ss}/F was predicted using the same approaches as CL/F.

Figure 3. Predicted human CL/F and V_{ss}/F



- **Prediction of human PK profiles**
  : The C_{ss}-MRT normalized profiles were superimposable across the species. Then, back-normalized human PK profiles were obtained using predicted human CL/F and V_{ss}/F values. Following single and multiple S.C. administration (0.5-16 mg), the predicted $t_{1/2}$ values were 107.7-159.1 h in healthy subject and 97.2-143.6 h in obese patient. Compared to healthy subject, obese patient was expected to exhibit slightly lower systemic exposure (16 – 17% for $AUC_{\tau,ss}$) and similar half-life.

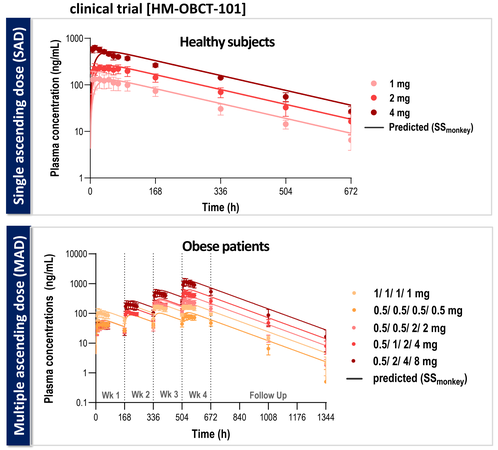
Figure 4. C_{ss}-MRT normalized animal PK profiles and back-normalized human PK profiles



Human PK prediction (II)

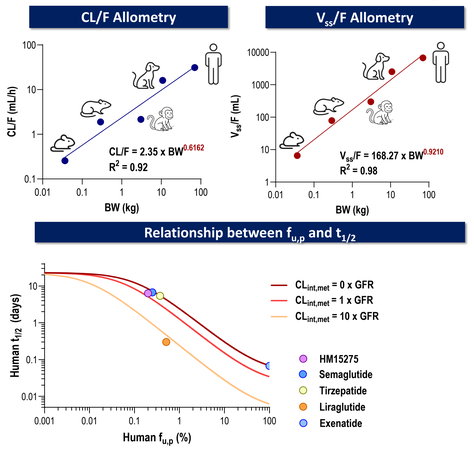
- **Comparison with clinical PK profiles [HM-OBCT-101]**
  : The predicted human PK profiles using SS_{monkey} exhibited high predictive accuracy, with predicted AUC, C_{max} and $t_{1/2}$ values within 1.4 and 1.5-fold of the observed values in the SAD and MAD studies, respectively. SS_{avg} also provided good predictions within 2.0-fold of observed values.

Figure 5. Observed and predicted human PK profiles of HM15275 in FIH clinical trial [HM-OBCT-101]



- **Allometry across species and comparison with other peptide drugs**
  : Observed animal and human PK were well described by interspecies allometry, with exponents for CL/F (0.62) and V_{ss}/F (0.92) within reported peptide ranges (CL/F: 0.58–0.88; V_{ss}/F: 0.89–1.1). In addition, HM15275 exhibited comparable plasma unbound fraction ($f_{u,p}$), $t_{1/2}$ and metabolic intrinsic CL (0 -1 x GFR) with those of semaglutide and tirzepatide based on human $f_{u,p}$– $t_{1/2}$ relationship[6].

Figure 6. Cross-species allometry and Relationship between human $f_{u,p}$ and $t_{1/2}$



Concluding remarks & Discussions

1. **HM15275, a fatty acid-acylated GLP-1/GIP/glucagon triple agonist, exhibited high plasma protein binding and long-acting PK characteristics across preclinical species.**
2. **The predicted human PK using preclinical data showed good agreement with observed clinical PK, indicating the translational predictability of HM15275. CL/F and V_{ss}/F of HM15275 followed interspecies allometric relationships across species including humans, with allometric exponents falling within the reported ranges for peptide drugs.**
3. **These findings support the application of translational PK approaches for human PK prediction of acylated peptide therapeutics.**

References

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