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Pharmacokinetic Profile of FE 203799: A Novel Long Acting Peptide Agonist of Glucagon-Like Peptide-2 (GLP-2)

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Introduction

GLP-2 is a 33-amino acid peptide secreted by the intestinal L-cells in response to nutrition ingestion. It is known to stimulate intestinal growth, nutrient absorption and mesenteric blood-flow [1,2]. Native GLP-2 has a short elimination half-life (6.4 & 7.2 min in rats and humans, respectively) and high clearance (24.6 and 6.8 ml/kg/min in rats and humans, respectively), in part due to its susceptibility for the dipeptidyl peptidase-IV (DPP4) enzyme [3]. A DPP4 resistant analog of GLP2, teduglutide, has marginally lower clearance (9.9 and 2 ml/kg/min in rats and humans, respectively) than GLP-2 [4]. Herein, we describe the pharmacokinetics (PK) and in vivo efficacy of a novel GLP-2 agonist, FE 203799, which retains potency and selectivity at the hGLP-2 receptor but has a superior pharmacokinetic (PK) and pharmacological profile.

Methods

Peptide synthesis: Conducted using Fmoc solid phase method. The compounds were purified using reverse phase-HPLC.

Rat, Monkey and Minipig PK: In the *in vivo* PK experiments, the jugular vein was used for compound administration intravenously (IV) and the carotid artery was used for blood sampling. The dosing vehicle was 25 mM phosphate buffer, pH 7.4. The PK parameters were determined by non-compartmental analysis using PK Solutions software. (a) Rat: Drugs were administered subcutaneously (SC) or IV by bolus injection to catheterized male Sprague Dawley rats (~0.3 kg). Blood was collected at multiple time points post-injection up to 5 h (IV) and 103 h (SC). (b) Monkey: Drugs were administered SC or IV by bolus injection to male cynomologous monkeys (~5.4 kg). Blood was collected at multiple time points post-injection up to 6 h (IV) and 80 h (SC). (c) Minipig: Drugs were administered SC or IV by bolus injection to catheterized male Yucatan pigs (~67 kg). Blood was collected at multiple time points post-injection up to 10 h (IV) and 169 h (SC).

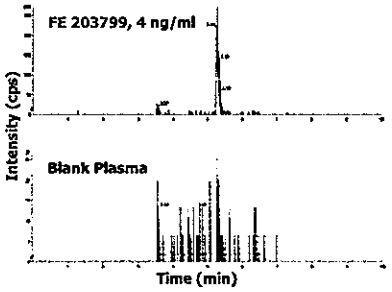

Fig. 1. LC/MS/MS chromatogram of FE 203799 and control in rat plasma.

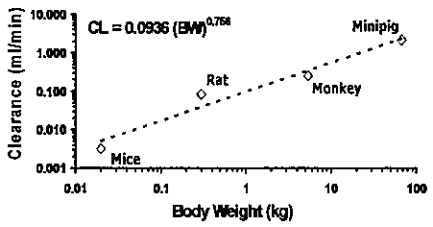

Fig. 2. Allometric scaling of clearance in multiple species.

Bioanalysis: Plasma was isolated from blood samples, flash frozen and stored at -20°C. The method involved protein precipitation extraction electrospray ionization LC/MS/MS (AB Sciex API4000 MS, Shimadzu Prominence HPLC (CBM-20A, SIL-20ACHT). The gradient HPLC method involved reverse-phase column (Phenomenex Jupiter 00B-4053-B0, C_{18}, 50x2.0mm, 5µm, 300Å) and mobile phase (A: 0.01% TFA, 1.0% Formic acid in water, B: 0.01% TFA, 1.0% Formic acid in 70% ACN) at a flow rate of 0.5 ml/min.

Rat PD (Small Intestine Growth): Compounds or vehicle were administered (dose-range 0.3-1000 nmol/kg) by SC injection to male Sprague Dawley rats. Compounds were dosed daily for five days, the rats euthanized, and small intestines were carefully dissected, cleaned, and weighed.

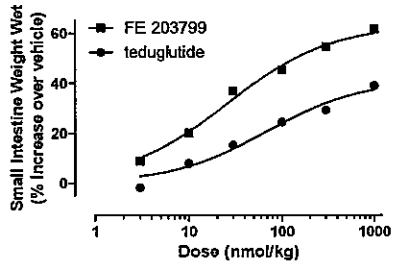

Fig. 3. Dose response curve of FE 203799 and teduglutide (QD, 5 d).

Results and Discussion

The bioanalytical method was precise, sensitive (Figure 1) and reliable. Multispecies PK experiments showed that FE 203799 possesses a favorable PK profile with long terminal half-lives and low systemic clearance (Table 1, Figure 2,4), possibly due to high plasma protein binding (>99%, data not shown). The unique properties of FE 203799 include: (1) Potency and selectivity at the hGLP-2 receptor comparable to native hGLP-2 (2) unique PK profile with low clearance and unprecedented SC half-life (flip-flop PK, possibly due to solubility limiting SC absorption) (3) a greater *in vivo* potency for stimulation of intestinal growth in rats compared to teduglutide. The above properties may confer to FE 203799 a superior therapeutic profile in the treatment of GI diseases.

Table 1. PK parameters of GLP2 analogs in rat, monkey and minipig

Peptide	Rat				Monkey				Minipig			
	IV Dose		SC Dose		IV Dose		SC Dose		IV Dose		SC Dose	
	Elim. half-life	CL	Terminal half-life	F	Elim. half-life	CL	Terminal half-life	F	Elim. half-life	CL	Terminal half-life	F
	min	ml/kg/min	min	%	min	ml/kg/min	min	%	min	ml/kg/min	min	%
Dose (mg/kg)	0.2	0.2	5	5	0.1	0.1	0.25	0.25	0.025	0.025	0.15	0.15
FE 203799	159	0.27	1349	54	474	0.046	1941	32	782	0.032	1808	43
teduglutide	18.7	9.9	31.3	74	43	2.4	56	77	88*	0.99*	164	53
hGLP-2	6.4*	24.6*	21.4*	27.5*	Not Determined							

* hGLP-2 dose: IV 1 mg/kg, SC 2 mg/kg; tedulgutide IV dose: 0.1 mg/kg

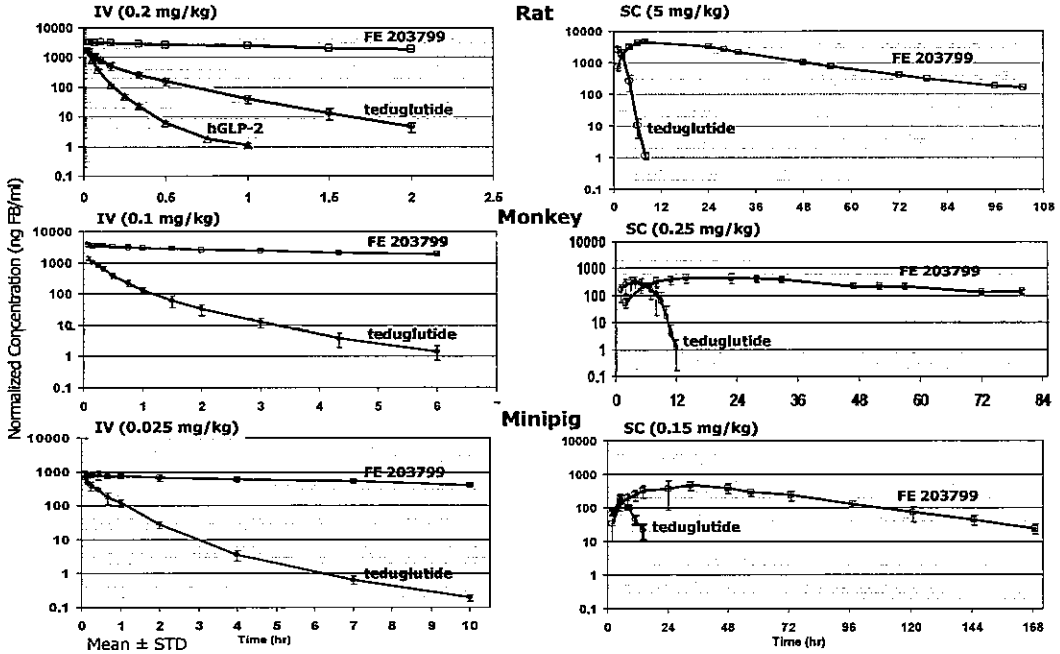

Fig. 4. PK profiles of GLP2 analogs in rat, monkey, and minipig (IV and SC dose).

References

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4. Marier, J.F., et al. *J. Clin. Pharmacol.* **48**(11), 1289-99 (2008).