Pharmacological characterization of FE 203799, a novel long acting peptide analog of glucagon-like peptide-2 (GLP-2)


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# 1. Introduction

Glucagon-Like-Peptide-2 (GLP-2) is a 33 amino acid peptide derived from posttranslational processing of proglucagon in the intestine. GLP-2 is released by the enteroendocrine L cells that line the small intestine in response to nutrient ingestion and plays a physiological role in the regulation of normal digestive function and the maintenance of gut integrity.

Several GLP-2 analogs have been developed which produce therapeutic potential in gastrointestinal diseases. However, GLP-2 analogs have several limitations: low oral bioavailability and short half-life leading to development as a therapeutic agent.

Unique GLP-2 analog possessed a slow absorption and a short half-life, leading to development as a therapeutic agent. A dose dependent effect on increase of hGLP-2 (95% CI: 0.03-0.11) with variable observed maximum effect of FE 203799 is in clinical.

Through chemistry, we identified GLP-2 analogs with low clearance resulting in longer half-life and greater duration of action. These analogs retain the characteristics of GLP-2, such as the ability to stimulate intestinal growth and beneficial effects to promote healing and gastrointestinal tract integrity.

In the current study, we report on the characterization of FE 203799, a novel peptide analog of GLP-2 possessing unique PK profile of very low clearance contributing to an unprecedented prolonged half-life.

# 2. Experimental Methods

**Peptide Synthesis:**

Peptides were synthesized by solid phase peptide synthesis and purified by reverse phase HPLC.

**In Vitro Receptor Assay:**

Activity of peptides at the hGLP-2 receptor and selectivity vs. GLP-1 and glucagon (GCGR) receptors were determined using cell-based functional assays. HEK-293 cells transiently or stably co-transfected with human hGLP-2, hGLP-1 or GCGR receptor and a reporter plasmid containing a luciferase gene under the control of cAMP responsive elements were incubated with compounds for 5 hours. Followed by cell lysis and determination of luciferase activity.

**Rat Pharmacodynamics (Small Intestine Growth):**

The effects of FE 203799 were assessed in Sprague-Dawley rats (8-10 weeks old) treated orally for 7 days. Intestinal growth and body weight were monitored. The compounds were tested at doses (0.3-1000 nmol/kg) to generate a complete dose-response curve. The maximum possible effect (MPE) was calculated as the mean EC50 (95% CI) and efficacy (Max% vs. GLP-2). Selectivity ratio vs. GLP-1 was calculated using the mean EC50 (95% CI). Values are mean ± SEM, n = 3-15.

**Dosing protocols:**

Rats dosed SC, Once Daily

**Internalized PK Profile:**

Dose interval: 24h, 48h, 72h, 96h

**Safety and Conclusions:**

• Novel peptide analog of GLP-2.
• Selectivity and sensitivity of the hGLP-2 receptor comparable to the native ligand (NGL-2).
• Unique PK profile of very low clearance contributing to an unprecedented prolonged half-life.
• Slower in vivo recovery and sustained duration of action to achieve pharmacodynamic efficacy for stimulation of intestinal growth in rats compared to teduglutide.
• These properties of FE 203799 may confer a superior therapeutic profile for the treatment of gastrointestinal diseases.