**ABSTRACT**

Efpeglenatide is composed of CA-Ex4 homolog 4 peptide linked to a non-peptidic linker. Efpeglenatide has an extended pharmacokinetic (PK) profile with enhanced pharmacodynamic properties over the GLP-1 receptor. The absorption and excretion profiles of Efpeglenatide were evaluated in rats, monkeys, and dogs following intravenous (IV) or subcutaneous (SC) administration of radiolabeled at a dose of 24 nmol/kg in rats and 1.7 mg/kg in dogs. The excretion profiles were qualitatively similar with a fast initial elimination phase and a slower elimination phase, as evidenced by urinary and fecal recovery of labeled IgG4. The radioactivity in the feces was above 60% and in the urine above 20% in all groups.

**STUDY OBJECTIVE**

To evaluate the pharmacokinetic and excretion profiles of differently radiolabeled Efpeglenatide in vivo.

**METHODS**

Three differently labeled Efpeglenatide molecules were used in this study. The labeled sites were as follows: [125I]-radiolabeled on CA-Ex4 and IgG4 fragment and [14C]-radiolabeled on the non-peptidic linker PEG. The level of radioactivity in serum and excreta was determined by liquid scintillation counting (LSC), and the clearance route of urinary and gastrointestinal excretion was calculated by radioactivity of IgG radioactivity in the excreta.

**BACKGROUND**

Efpeglenatide is a long-acting glucagon-like peptide-1 receptor agonist under development for the treatment of type 2 diabetes. Efpeglenatide is the site-specific compound for IGFI, and the Ex4 and the constant region of human immunoglobulin G4 fragment linked via a non-peptidic 3.4 kDa PEG linker which is based on a novel strategy LAPSCOVERY.

**RESULTS**

**Pharmacokinetic profile of Efpeglenatide**

- *High bioavailability, a long half-life and high stability in the system were observed*

**EXPRESSION OF ABSTRACT**

Efpeglenatide is composed of CA-Ex4 homolog 4 peptide linked to a non-peptidic linker. Efpeglenatide has an extended pharmacokinetic (PK) profile with enhanced pharmacodynamic properties over the GLP-1 receptor. The absorption and excretion profiles of Efpeglenatide were evaluated in rats, monkeys, and dogs following intravenous (IV) or subcutaneous (SC) administration of radiolabeled at a dose of 24 nmol/kg in rats and 1.7 mg/kg in dogs. The excretion profiles were qualitatively similar with a fast initial elimination phase and a slower elimination phase, as evidenced by urinary and fecal recovery of labeled IgG4. The radioactivity in the feces was above 60% and in the urine above 20% in all groups.

The absorption and excretion profiles of Efpeglenatide were evaluated in rats, monkeys, and dogs following intravenous (IV) or subcutaneous (SC) administration of radiolabeled at a dose of 24 nmol/kg in rats and 1.7 mg/kg in dogs. The excretion profiles were qualitatively similar with a fast initial elimination phase and a slower elimination phase, as evidenced by urinary and fecal recovery of labeled IgG4. The radioactivity in the feces was above 60% and in the urine above 20% in all groups.

**CONCLUSION**

- When differently labeled on three comprising moieties, the absorption and elimination profiles were well characterized and comparable indicating that the compound is stable in the body.
- Fragments of Efpeglenatide were cleared from the urine via the urinary excretion was the major route of elimination.
- In conclusion, this study demonstrated that Efpeglenatide has favorable pharmacokinetic properties with a high bioavailability and a long half-life ensuring the prolonged PDE effect and a satisfactory elimination profile.

**REFERENCES**


**EXPERIMENTAL DESIGN**

**Figure 1. Pharmacokinetic parameters following IV and SC administration at a dose of 24 nmol/kg in rats (n=3)**

**Table 1. Pharmacokinetic parameters following IV and SC administration at a dose of 24 nmol/kg in rats (n=3)**

- *Fragments of [125I-CA-Ex4] Efpeglenatide and [14C-PEG] Efpeglenatide were mainly excreted by urine (95.9%) and the range of total recovery of radioactive doses was 96.9% in terms of fragments of [125I-PEG] Efpeglenatide, the amount of radioactivity excreted was 81-85% in urine and 22% in feces. The total recovery was 91-93% of the administered doses.*
Underlying Superagonistic Mechanisms of Efpeglenatide in Glycaemic Control and Weight Loss Potency

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ABSTRACT
Efpeglenatide is a long-acting GLP-1 receptor (GLP-1R) agonist developed for the treatment of type 2 diabetes and is considered an extension of and human β-propeptide covalently conjugated to efpeglenatide. As previously reported, efpeglenatide possesses a superagonistic property compared to GLP-1 in terms of GLP-1R binding and cell signaling, leading to more significant improvements in metabolic parameters compared to GLP-1. This study introduces cyclic AMP (cAMP) accumulation and body weight loss in obese mice using efpeglenatide. Efpeglenatide showed greater efficacy in improving glycemic control, weight loss, and cAMP accumulation in vehicle-treated obese mice. It was also reported that efpeglenatide was superior to dulaglutide in improving cAMP accumulation in INS-1E cells. By comparing efpeglenatide to dulaglutide in human insulinoma cell lines and in vivo assays, the following results were observed:

METHODS

- In vitro: Cyclic AMP (cAMP) and insulin release were measured in a 1 h treatment with efpeglenatide in 24-wk-old C57BL/6J mice
- In vivo: Cyclic AMP and body weight were measured in vehicle-treated db/db mice

RESULTS

- Efpeglenatide induced significantly greater GLP-1R internalization compared to dulaglutide
- Efpeglenatide showed superior glucose control and weight loss compared to other long-acting GLP-1R agonists

CONCLUSIONS

- Efpeglenatide possesses superagonistic properties compared to other long-acting GLP-1R agonists, which are derived from a fast receptor agonist
- Efpeglenatide leads to significantly less GLP-1R internalization and consequently can maintain signaling in contrast to dulaglutide and degludec in human insulinoma cell lines
- The superagonistic property of efpeglenatide was translated into more potent glucose lowering with greater weight loss in db/db mice and DIO mice

REFERENCES


FURTHER INFORMATION

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