Introduction

Several groups are developing fully integrated dual-hormone artificial pancreas systems, which deliver insulin and glucagon in response to changes in glucose to maintain euglycemia. These systems hold the potential to transform management of type 1 diabetes, but in order to be realized these systems require a stable in-situ glucagon analog suitable for chronic use. Dasiglucagon is a stable glucagon analog comprised of 29 amino acids, with 7 amino acid substitutions compared to native glucagon. Dasiglucagon has been specifically designed to overcome the problems with fibril formation and instability in solution seen with marketed glucagon products.

Methods

Rats and dogs were dosed s.c. daily for 26 and 39 weeks, respectively, in 4 groups of 20 rats with 0 (vehicle), 0.5, 2, or 8 mg/kg/day, 4 groups of 4 beagle dogs with 0.02, 0.1, or 0.3 mg/kg/day. Delayed toxicity and recovery for any findings noted within the treatment period was evaluated following a 4-week treatment-free period in both studies.

Assessment of toxicity was based on clinical observations, food consumption, body weight measurements, ophthalmic observations, ECG measurements (dogs only), hematology, clinical chemistry, urinalysis, macroscopic pathology and histopathology. Blood samples were collected for exposure evaluations in Week 1 and Week 39 of the dosing phase and for ADA evaluations in Week 1 and Week 39 of the dosing phase and Week 4 of the recovery phase. Samples for analysis of plasma glucose and insulin concentrations were taken post dose in Week 26/39.

Findings

The principal effect of glucagon is to increase blood glucose through increased glycogenolysis and gluconeogenesis in the liver. Glucagon also has known physiological effects on other organ systems (see figure below). All findings in the chronic toxicity studies with dasiglucagon can be explained from these physiological effects. Dasiglucagon is therefore considered a specific glucagon receptor (GCGR) agonist with no observed off-target effects.

Heart weight in rats/dogs (≤ 25%)

Liver weight in rats/dogs (≤ 25%)

Pancreas weight in rats/dogs (≤ 25%)

Kidney weight in rats/dogs (≤ 25%)

Hearing absences: a sleep-like state with slow movement was noted in rats, body weight gain in dogs (≥ 10%)

Rat specific findings, not relevant for humans

1. Hyaline droplets in cortical tubules is a male rat specific finding caused by accumulation of α2µ globulin.
2. Chronic progressive nephropathy is a robust specific age-related finding.

Clinical implications

The chronic toxicity studies in rats and dogs do not raise any safety concerns for long-term clinical use of dasiglucagon. The physiological effects on heart, kidney, intestinal and liver function can be monitored via standard biomarkers in clinical trials.

Discussion of Findings

Chronic administration of dasiglucagon to rats and dogs was not associated with organ toxicity. The findings are consistent with exaggerated pharmacological effects.

1. Diarrhea in dogs: diarrhea is not a prominent finding in humans administered glucagon or dasiglucagon.
2. Increased heart/kidney weight – caused by increased work load following an increase in heart rate and GFR.
3. Unlike to be of clinical relevance at the doses administered with a dual-hormone AP system.
4. Increased glucagon content in the liver – found after administration of glucagon to normoglycemic animals.

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Conclusions

- Chronic administration of dasiglucagon was well tolerated with exposure at NOAEL exceeding human exposure (AUC) at the expected maximum daily dose of 0.6 mg/day by 22 and 3 in rats and dogs, respectively.
- All findings were consistent with the known physiological effects of glucagon.
- All findings showed full or partial recovery following a 4-week treatment free period.
- These findings support long-term human testing of dasiglucagon in dual-hormonal artificial pancreas systems.