INTESTINOTROPHIC EFFECTS OF GLEPAGLUTIDE FOLLOWING CHRONIC EXPOSURE IN RATS AND DOGS

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INTRODUCTION
Glucagon-like peptide-2 (GLP-2) is a 33-amino-acid endogenous peptide formed from the cleavage of pro-glucagon in enteroendocrine L cells of the intestine. Under normal conditions, GLP-2 is secreted in response to nutrient intake but is rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-IV). The GLP-2 receptor has been localized in the gastrointestinal tract, where GLP-2 induces significant growth of the intestinal epithelium via proliferation in the crypts and inhibition of apoptosis on the villi. Glepaglutide is a novel long-acting (effective half-life approx. 50 hours in man) GLP-2 analogue (39 amino acid peptide) currently under development for the treatment of patients with Short Bowel Syndrome (SBS). Nonclinical pharmacology studies in mice and rats have shown that glepaglutide is a potent and selective GLP-2 receptor agonist, producing a dose- and time-dependent intestinotrophic effect on small and large intestinal mass.

METHODS
Short-term study: Groups of 7 Wistar rats were dosed subcutaneously (SC) with vehicle, 0.1, 0.25, 1, 4 and 10 mg/kg glepaglutide on a daily basis for 7 days. The dose levels were selected in order to investigate a broad dose range to determine maximal effect. The weight of the small intestine was measured at necropsy as an indicator of intestinotrophic effects. Long-term studies: Wistar rats and Beagle dogs received daily SC doses of vehicle or glepaglutide for 26 and 39 weeks, respectively (Table 1). Furthermore, sub-groups were allowed a 6-week recovery period. The highest dose levels were selected based on an AUC multiple of 50 fold to human exposure (ICH M3(R2)).

RESULTS-1
Trophic effect in Wistar rats after short-term treatment

Table 1: Study design of long-term studies in rats and dogs.

During the studies, blood samples were collected for determination of the exposure profile. In addition to standard toxicology parameters measured during the studies (data not presented), the length and the weight of the small intestine were measured at necropsy as indicators of intestinotrophic effects and the intestinal tract was evaluated histologically.

RESULTS-2
Trophic effect in Beagle dogs after long-term treatment

Comparison of short- and long-term effects in Wistar rats

RESULTS-3
Pathology: At all dose levels in both species, macroscopic thickening of the duodenum, jejunum and ileum was present. Histologically, glepaglutide produced dose-related mucosal hyperplasia of the duodenum, jejunum and ileum, which was still present at the end of the 6-week recovery period. The trophic effect seen is in concordance with the changes seen in the phase 2 trial, indicating increased enteroocyte mass and intestinal absorptive surface area.

CONCLUSION
A significant dose-related intestinotrophic effect was seen following 7 days of glepaglutide dosing in rats. This response was similar to findings after 26 and 39 weeks of dosing in rats and dogs, respectively.

SUMMARY
These studies demonstrate that glepaglutide has a fast onset and long duration of action (intestinal trophic effects). The prolonged action can be explained by the protracted kinetic profile of glepaglutide observed in the chronic studies. A phase 3 trial testing efficacy and safety of once- and twice weekly glepaglutide dosing is ongoing.

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