INTRODUCTION
Eliglustat is in development for oral treatment of the inherited metabolic disorder Gaucher Disease type 1 (GD1). This lysosomal storage disease results from a deficiency of the catabolic enzyme acid-(ß)-glucosidase leading to accumulation of glucosylceramide. The principal substrate of acid-(ß)-glucosidase is glucosylceramide (GL-1); eliglustat acts to reduce production of GL-1 by inhibition of glucosylceramide synthase. Since GD1 patients will require chronic treatment with eliglustat, carcinogenicity studies are needed. We have evaluated the potential carcinogenicity of eliglustat in a 3-week rat (4-year) lifetime study in which blood samples for toxicokinetic analysis of plasma samples from satellite animals were taken from study days 5/6, 85/86 and in week 13.

MATERIALS AND METHODS
Mouse study:
The dose-levels were based on the results of a 13-week dietary preliminary study, and were confirmed in consultation with the FDA CAC. The Swiss CD1 mice received eliglustat for 104 weeks by dietary administration. The dietary route was selected because of the very demonstrated systemic exposure to eliglustat. Serum levels of glucosylceramide (GL-1) were measured in all animals (both decedents and terminal kill animals). Blood samples for toxicokinetics were taken from satellite animals on study days 5/6, 85/86 and in week 13.

RESULTS AND DISCUSSION
Mouse study:
In the mouse study, treatment with eliglustat did not influence overall survival rates of treated mice at dose-levels up to 75 mg/kg/day. The terminal bodyweights of eliglustat treated mice were similar to controls. At histopathology, no treatment-related increases in tumour incidence were observed in any groups of eliglustat treated mice for any tumour type. Toxicokinetic analyses to confirm systemic exposure were uninformative, as most of the test item plasma concentrations were below the lower limit of quantification. Reduction of circulating GL-1 levels was proposed as a pharmacodynamic biomarker of exposure and GL-1 values were generally lower in both males and females treated at 10, 25 or 75 mg/kg/day when compared to controls, confirming systemic exposure in the eliglustat-treated mice.

Rat study:
Similarly, in the rat study there was no effect of eliglustat on the overall survival rates up to the high dose levels of 75 mg/kg/day (50 females) of eliglustat mg/kg/day. Reduced bodyweight gain in males at the high dose level indicated that the MTD had been achieved. At histopathology, no treatment-related increases in tumour incidence were observed in any groups of eliglustat treated rats for any tumour type. Toxicokinetic analysis of plasma samples from satellite animals demonstrated systemic exposure to eliglustat. At Week 13, over the range of doses studied, the mean AUCs varied from 129 to 1135 ng·h/ml for males and from 76 to 825 ng·h/ml for females. At the high dose, these represent about 4-fold and 3-fold multiples, respectively, of the mean AUC of 307 ng·h/ml.

CONCLUSION
Carcinogenicity studies in the mouse and rat were performed with eliglustat, a novel glucosylceramide synthase inhibitor that resembles the ceramide substrate for this enzyme. Survival over the two year period was good, and as a consequence long (mean) duration of exposure was achieved. No treatment-related increases in the incidence of any tumour types were observed in eliglustat treated mice and rats at any dose-level. It is concluded that eliglustat did not induce any tumours at any dose-level of lifetime exposure after oral administration at the maximum tolerated doses in rats and mice, resulting in prolonged and significant decreases in plasma GL-1 levels, revealed no novel or previously undetected effects, and provided no indication of any exaggerated pharmacology associated with eliglustat and glucosylceramide synthase inhibition.