Final Report

Study Title	Lu 02-648 (CEP-1347): 26 Week Oral (Gavage Administration) Toxicity Study in the Monkey
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SUMMARY

The objective of the study was to determine the potential toxicity of the test article, Lu 02-648 (CEP-1347), following daily oral (gavage) administration to the monkey for 26 weeks.

The following dose levels were selected:

Group number	Group description	Dose volume (mL/kg)	Dose level (mg/kg/day)	Animals/group	
				Male	Female
1	Vehicle control	4	0 (b.i.d.)	4	4
2	Low	4	25	4	4
3	Intermediate	4	50	4	4
4	High	4	100 (50 b.i.d#)	4	4

- 50 b.i.d – 50 mg/kg administered twice daily

There were no unscheduled deaths on the study and there were no treatment-related clinical signs.

Lu 02-648 was systemically absorbed following oral administration at all three doses investigated in male and female monkeys. Plasma concentrations in males and females were comparable.

In general, C_{max} and $AUC_{(0\text{-}24h)}$ values of Lu 02-648 (CEP-1347) increased with increasing dose between 25 and 100 mg/kg/day for both sexes at all occasions but were considerably lower in Weeks 4, 13 and 26 than on Day 1.

No sex-related differences were observed. In general the individual data were variable and therefore the observations made during the TK analysis must be evaluated in light of this variability.

Intermediate and high dose animals exhibited lower body weight gains over the first 13 weeks of treatment; thereafter they were similar to controls.

There was no effects of treatment on heart rates or blood pressures.

There were no effects of treatment on any of the haematology, clinical chemistry or urine analysis parameters.

At necropsy higher spleen weights were noted for high dose females, higher liver weights and lower pituitary weights for low and high dose females.

There were no macroscopic findings due to effects of the test article.

Microscopically, in treated animals there were more fine brown pigment granules in the cytoplasm of the tubular epithelial cells in the pars recta region of the proximal tubules in the kidneys compared with controls, but the extent was not dose related. The pigment was identified as lipofuscin. This change was not accompanied by evidence of tubule cell injury, funtional or clinical pathology indices of toxicity.

In conclusion, Lu 02-648 (CEP-1347) was very well tolerated by all the animals on the study. The only treatment-related finding, which was observed at microscopic examination, was an accumulation of yellow-brown pigment in the cytoplasm of proximal tubule cells in kidneys of both sexes. There was no evidence of cytoplasmic vacuolation or degeneration, single cell death or necrosis, and increased mitotic activity or tubule hyperplasia. Importantly, no functional or clinical pathology indices of renal toxicity were apparent in these monkeys.

Based on the absence of any indication of proximal tubule damage or functional change and the absence of deposition in any other tissue/organ, indicates the likely role of an adaptive metabolic process involving the kidney. The accumulation of lipofuscin itself is not considered to be toxic to the cell, and therefore is not considered to be toxicologically significant (Sohal, 1981).

Additionally there were mild effects on body weight in intermediate and high dose animals and on organ weights.

Based on these findings a no observed adverse effect level (NOAEL) was considered to be 100 mg/kg/day (50 mg b.i.d.).