**A 4-week repeated dose oral toxicity study of Project 3 in beagle dogs with a recovery period of 4 weeks**

**11 SUMMARY**

Project 3 was administered orally to groups of male and female beagle dogs (HRA Beagle, Covance Research Products Inc.) once daily for 4 weeks at dose levels of 0 (0.5% methylcellulose solution), 1, 3, 30 and 300 mg/kg/day as PROJECT 3 to examine its toxicological effects, and plasma concentrations of PROJECT 3 were determined to evaluate systemic exposure of the animals. Each dosing group consisted of 3 males and 3 females. For the 300 mg/kg group, 3 males and 3 females were assigned to the recovery group to examine the reversibility of the changes induced by Project 3.

The results are summarized as follows:

No treatment-related findings were observed at 1 or 3 mg/kg.

At 30 mg/kg and above, vomiting, salivation that was observed soon after the administrations, abnormal stools (soft, mucous or watery), decreases in body weight, body weight gain and food consumption, low values for erythrocytes, hemoglobin, hematocrit and total protein, and extramedullary hematopoiesis in the spleen were noted as toxicologically significant changes. At 300 mg/kg, low values for reticulocytes (count and ratio), an increase in polychromatic erythroblasts ratio and a decrease in M/E ratio, low values for albumin, globulin and calcium, high values for urea nitrogen and creatinine without test article-related histopathological findings in the kidney, decrease in glycogen of hepatocyte in the liver in contrast to the increased liver weight, and an increase in the adrenal weight without test article-related histopathological findings in the adrenal were noted in addition to the above mentioned changes at 30 mg/kg.

Otherwise, microvesiculation of adipocytes was noted in the mesenteric white adipose tissue at 3, 30 and 300 mg/kg; however, the finding was considered not to be toxicologically significant since no degenerative or necrotic changes were observed in the white adipose tissue.

In the recovery period, abnormal stools, which were soft or contained test article-like material, were noted at 300 mg/kg (1 male and 1 female) on the first day of withdrawal; however, the findings were judged not to be toxicologically significant because they were probably due to excretion of unabsorbed test article of the final administration in the stools. Other findings observed in the dosing period disappeared during the recovery period.

Cmax and AUC0-24h values increased less than dose-proportionally over the dose range of 1 to 300 mg/kg. Tmax values showed a tendency to be delayed with increase of the dose.

Throughout dosing periods, no consistent sexual differences and no effects of the repeated dosing were observed in the Cmax and AUC0-24h at any doses.

From these results, all of the findings observed in the dosing period recovered after 4-week withdrawal. It was concluded that the no observable adverse effect level (NOAEL) under the conditions of this study was 3 mg/kg/day.