**Final Report**

**A 4-Week Repeated Oral Dose Toxicity Study of Project P in Beagle Dogs Followed by a 4-Week Reversibility Study**

**11 SUMMARY**

Project P suspended in 0.5 w/v% methylcellulose solution was administered orally once daily for 4 weeks at dose levels of 0 (vehicle), 20, 100, and 1000 mg/kg (as PROJECT P) to 4 male and 4 female beagle dogs per group in order to investigate its toxicity. Three males and three females were added to the 1000 mg/kg group in order to assess the reversibility of toxicity observed during the dosing period in a subsequent 4-week recovery period. Animals in the control group received 0.5 w/v% methylcellulose solution.

The following observations and examinations were performed in this study: clinical signs, body weight, food consumption, ophthalmology, electrocardiography, urinalysis, hematology, blood chemistry, gross pathology, organ weights, histopathology, and toxicokinetics.

No animal died or was sacrificed due to moribundity in any group during the dosing or recovery period.

In the 20 mg/kg group, no test article-related changes were noted.

In the 100 mg/kg group, vacuolation of the epithelium in the gallbladder was observed in males.

In the 1000 mg/kg group, vomiting was observed in all males and females mainly approximately 1 or 4 hours after dosing on 21 to 27 days frequently during the dosing period. Salivation was observed in all males and females immediately after dosing and/or approximately 1 hour after dosing on 5 to 22 days from Day 6 of dosing, and was observed in 4 males and 2 females among these animals almost every day from Day 6, 10, 11, 12, or 15 of dosing. Abnormal stool color (yellowish white) was observed in all males and females on 9 to 18 days sporadically during the dosing period. Decreased body weight was noted in males from Day 14 to Day 28 of dosing. A high platelet count in both sexes, and high leukocyte count, monocyte count, and neutrophil count and ratio, and a low lymphocyte ratio in males were noted on Day 27 of dosing. High total bilirubin and low total protein, albumin, globulin, and total cholesterol were noted in both sexes on Day 27 of dosing. High blood urea nitrogen, inorganic phosphorus, and sodium, and low calcium in both sexes, and high chloride in males were noted on Day 27 of dosing. In urinalysis, low sodium excretion in males and low chloride excretion in females were noted on Day 26 of dosing. Vacuolation of the epithelium in the gallbladder was observed in both sexes, and vacuolation of the hepatocytes in males, and vacuolation of the epithelium in the duodenum, jejunum, and ileum in females was observed. The vacuoles of the hepatocytes and of the epithelium in the gallbladder, duodenum, jejunum, and ileum were positive for oil red O stain.

No toxicological changes were noted in food consumption, ophthalmology, electrocardiography, gross pathology, or organ weights in any group during the dosing or recovery periods.

The changes noted during the dosing period were not noted after the 4-week recovery period.

In toxicokinetics, mean Cmax increased dose dependently at 20 and 100 mg/kg, and increased less than the dose ratio at 100 and 1000 mg/kg. Mean AUC24 increased greater than the dose ratio at 20 and 100 mg/kg, and increased less than the dose ratio at 100 and 1000 mg/kg. Cmax and AUC24 did not change with repeated dosing at any dose level. Mean Cmax and AUC24 were comparable between males and females in all dose groups and at all sampling days.

It was concluded that, under the conditions of this study, the no-observed-adverse-effect levels of Project P were 20 mg/kg/day for males and 100 mg/kg/day for females as PROJECT P because vacuolation of the epithelium in the gallbladder was observed in males at 100 mg/kg and above and in females at 1000 mg/kg, vacuolation of the hepatocytes in males and vacuolation of the epithelium in the duodenum, jejunum, and ileum in females were observed at 1000 mg/kg, and vomiting in both sexes, decreased body weight in males, low sodium excretion in males, low chloride excretion in females, high platelet count in both sexes, high total bilirubin, blood urea nitrogen, inorganic phosphorus, and sodium in both sexes, low total protein, albumin, globulin, total cholesterol, and calcium in both sexes, and high chloride in males were noted in the 1000 mg/kg group. The changes noted during the dosing period were not noted after the 4-week recovery period.