**A 4-Week Oral Dose Toxicity Study of Project 7**

**in Dogs with a 4-Week Recovery Period**

1. **SUMMARY AND CONCLUSION**

This study was designed to investigate the potential toxicity of PROJECT 7 when administered orally to beagle dogs for 4 weeks at dose level of 10, 50 and 300 mg/kg and to determine the toxicokinetic profile of PROJECT 7. The 10 and 50 mg/kg groups consisted of 3 animals/sex/group and the 300 mg/kg group consisted of 6 animals/sex. The reversibility of any effects was assessed following a 4-week untreated recovery period using 3 animals/sex from the 300 mg/kg group. The doses are equivalent to 30, 150 and 900 mg/kg as Project 7 (PROJECT 7 : hydroxypropylmethylcellulose 2910 = 1:2), respectively. The dosing formulations were prepared by suspending Project 7 in water for injection. Control animals (3 animals/sex) received the vehicle, water for injection, in a similar manner.

For all animals, clinical observations and measurements of food consumption were conducted daily and body weight measurements, electrocardiography, ophthalmology, hematology, clinical chemistry and urinalysis were conducted at the scheduled intervals. The animals were sacrificed at termination of dosing or recovery for postmortem examinations including gross pathology, organ weight measurements and histopathology. In addition, blood samples were collected from all groups at 0.5, 1, 2, 4, 8 and 24 hours after dosing on Day 1 of dosing and prior to and at 0.5, 1, 2, 4, 8 and 24 hours after dosing on Days 14 and 28 of dosing to determine plasma PROJECT 7 concentrations.

All animals survived the duration of the study.

In the clinical observations, loose stools were observed in a female in the 50 mg/kg group and males and females in the 300 mg/kg group at a high frequency. Muddy or watery stools were also observed in the 300 mg/kg group. In addition, vomitus was noted in males and females in the 300 mg/kg group. Although salivation was observed in males and a female in the 300 mg/kg group, this sign was not considered to be toxicological significance since this sign was mainly observed shortly after dosing at a low frequency and no histopathological findings were noted in the salivary glands. Slight body weight loss and slightly decreased food consumption were noted in males in the 300 mg/kg group. Hematology evaluations revealed decreases in the red blood cell count in males and females and decreases in hemoglobin concentrations and hematocrit in females in the 300 mg/kg group. Increased liver weights were noted in males and females in the 300 mg/kg group. However, these changes were not considered to be toxicological significance since no related histopathological lesions or no related changes in clinical chemistry parameters were evident in the liver.

All of these changes were no longer evident following a 4-week untreated recovery period. No treatment-related effects were noted in electrocardiography, ophthalmology, clinical chemistry, urinalysis, gross pathology or histopathology.

In the TK analysis, plasma PROJECT 7 concentrations were determined in all treated groups. The Tmax values ranged from 0.50 hours to 1.00 hour in the 10 and 50 mg/kg groups and from 0.50 to 4.00 hours in the 300 mg/kg group. The Cmax and AUC0-24h values increased dose-dependently between 10 and 300 mg/kg. Following repeated dosing, the Cmax and AUC0-24h values did not appear to change in the 10 mg/kg group. However, the Cmax and AUC0-24h values tended to decrease from Day 1 to Day 14 of dosing in the 50 and 300 mg/kg groups. These values did not appear to change from Day 14 to Day 28 of dosing. There were no sex differences in the Cmax or AUC0-24h values at any dose level.

In conclusion, the no observed adverse effect levels (NOAELs) of PROJECT 7 were considered to be 10 mg/kg/day under the conditions of this study. All findings were reversible following the 4-week recovery period.