**A 28-DAY ORAL CAPSULE TOXICITY STUDY OF PROJECT 8 IN DOGS**

**11 SUMMARY**

The objective of this study was to evaluate the potential subchronic toxicity of the test article, PROJECT 8, in dogs when administered via capsule for a total of 8 doses (4 days apart), with a 13-day recovery observed in select control and high dose animals.

Oral administration of PROJECT 8 up to 10 mg/kg/dose for a total of 8 doses (four days apart), followed by a 13-day recovery was without effect on mortality, and did not produce any changes in body weights, food consumption, ophthalmology examination findings, ECG parameters, hematology, clinical chemistry, coagulation , urinalysis, organ weights, or macroscopic and microscopic pathology.

Oral administration of PROJECT 8 at 1 and 10 mg/kg/dose for a total of 8 doses (4 days apart) caused mild to moderate changes in clinical findings within feces (mucoid, soft, watery). These findings tended to reduce and/or resolve by the end of the recovery period.

Oral administration of PROJECT 8 at 50 mg/kg/dose for a total of 8 doses (four days apart), followed by a 13-day recovery did not produce any adverse changes in body weights, or any changes in food consumption, ophthalmology examination findings, ECG parameters, hematology, clinical chemistry, coagulation, urinalysis, or macroscopic and microscopic pathology.

Oral administration of PROJECT 8 at 50 mg/kg/dose for a total for 8 doses (4 days apart) caused changes in clinical findings within feces (mucoid, soft, watery). Hind limb weakness was also observed in six animals within this dose group over the course of this study. One animal was observed to be recumbent and was unable to recover enough to stand, therefore it was considered moribund and was euthanized *in extremis*. These findings were mostly resolved observed during the recovery period but due to the number of animals affected this is related to administration of PROJECT 8 at 50 mg/kg/dose using the above referenced dosing regimen.

Potential test article-related changes occurred for the thymus of males and females of the terminal phase. For males, mean thymus weights and ratios (thymus-to-body weight and thymus-to-brain weight ratios) were decreased at all doses in a dose-related manner. For females, mean thymus weights and ratios were decreased at 50 mg/kg/dose, only. These reductions in weights/ratios did not achieve statistical significance at any dose, there were no microscopic correlates for these reductions, and these were not observed in recovery animals, this is not considered adverse.

Based on these observations, the no-adverse-observed-effect-level (NOAEL) following repeat dosing with PROJECT 8 for 8 doses (4 days apart) with a 13-day recovery period. is 10 mg/kg/dose.