**A 4-Week Repeated Oral Dose Toxicity Study of PROJECT I in Beagle Dogs Followed by a 4-Week Recovery Period**

**12 SUMMARY AND CONCLUSION**

PROJECT I was suspended in 0.5 w/v% methylcellulose solution and orally administered once daily for 4 weeks at dose levels of 0 (vehicle control), 3, 10, 30, and 100 mg/kg/day 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 100 mg/kg group to assess the reversibility of toxicity observed, and recovery period was set for 4 week.

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

No animal died or was euthanized due to moribundity at either dose level during the dosing or recovery period.

No test article-related changes were noted at 3, 10, or 30 mg/kg.

At 100 mg/kg, vomiting was observed in 1 male, and occult blood in urine was noted in 1 in female.

No test article-related changes were observed in body weight, food consumption, ophthalmology, electrocardiography, hematology, blood chemistry, troponin measurement, gross pathology, organ weights, or histopathology at any dose level. All changes observed at 100 mg/kg during the dosing period recovered during the 4-week recovery period.

In toxicokinetics, mean tmax tended to lengthen with increasing dose level. Mean Cmax values between 3 and 10 mg/kg increased almost dose-proportionally, while those values between 10 and 100 mg/kg increased less than dose-proportionally on Days 1, 14, and 28 of dosing. Mean AUC24 values between 3 and 100 mg/kg increased almost dose-proportionally on Days 1, 14, and 28 of dosing. Mean Cmax and AUC24 values were not influenced by the repeat dosing at any dose. No sex differences were observed at any dose.

It was concluded that, under the conditions of this study, the NOAEL was 30 mg/kg/day for males and females. The changes observed during the dosing period recovered during the 4-week recovery period.