**A 4-week repeated dose oral toxicity study of Project 6 in beagle dogs followed by a 4-week reversibility study**

1. **SUMMARY AND CONCLUSION**

Project 6 at dose levels of 0.3, 1, 3 and 30 mg/kg (as PROJECT 6 free form , dose volume: 5 mL/kg) was administered orally to groups of beagle dogs each consisting of 3 males and 3 females (6 males and 6 females for the 30 mg/kg group) at 8 months of age for 4 weeks. For 3 males and 3 females in the 30 mg/kg group, administration was withdrawn for 4 weeks after the end of the administration period to examine reversibility of the toxic effects that occurred during the 4-week administration period. Animals in the control group received 0.5 w/v% methylcellulose solution in the same manner. Plasma concentrations of PROJECT 6 were determined to detect systemic exposure to the test article.

1) Clinical Signs

Test article-related effects were a series of behavioral changes that reflect the pharmacological effect of the test article on the central nervous system. In the 3 mg/kg group, excitement and/or restlessness were observed in 2 males and 1 female mostly during the first 5 days of treatment. In the 30 mg/kg group, restlessness, excitement, tonic convulsion, staggering gait, aggressive behavior (aggression) and a decrease in spontaneous movement were observed simultaneously every day for several days after the start of treatment. They diminished thereafter to occasional occurrence.

2) Blood Chemistry

A high value for ALT was recorded for females in the 30 mg/kg group.

3) Organ Weight

A high value for relative kidney weight was recorded for males in the 30 mg/kg group.

4) Body Weight, Food Consumption, Ophthalmology, Electrocardiogram, Urinalysis, Hematology, Necropsy and Histopathology

No test article-related effects were recorded in any observation or examination.

5) Observation and examination of the recovery group

No noticeable findings were obtained.

6) Tokicokinetic

Cmax and AUC0-24 hr increased with the increasing dose of PROJECT 6 administrated in each administration. AUC0-24 hr tended to be smaller after repeated dosing at all doses except for 0.3 mg/kg. Tmax in most animals dosed at 0.3, 1 and 3 mg/kg was 0.5 or 1 hour, though that in most animals dosed at 30 mg/kg was 1 or 2 hours. In the control group, all determined concentrations were below the lower limit of quantification.

In conclusion, the no observed adverse effect level of Project 6 in beagle dogs was judged to be 3 mg/kg under the conditions of this study.