**A 4-Week Repeated Oral Dose Toxicity Study of Project 1 in Cynomolgus Monkeys Followed by a 4-Week Recovery Period**

1. **SUMMARY AND CONCLUSION**

Project 1 was administered orally once daily for 4 weeks at dose levels of 0 (vehicle), 10, 30, 100, and 800 mg/kg to 3 male and 3 female cynomolgus monkeys per group in order to investigate its toxicity. Three males and three females were added to the 800 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.

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

In the 10, 30, and 100 mg/kg groups, no toxicologically significant changes were noted in any examination during the dosing period.

In the 800 mg/kg group, vomiting was observed in males and females on 1 to 5 days mainly at Weeks 1 and 2 of dosing. Salivation was observed in males and females immediately after dosing during the dosing period. Decreased body weight was noted in males and females during the dosing period. Low erythrocyte count, hematocrit value, and hemoglobin concentration were noted in 1 male and 1 female on Day 27 of dosing. High triglycerides were noted in males and females on Days 14 and/or 27 of dosing, and high glucose was noted in 1 male on Days 14 and 27 of dosing. High relative liver weight in males and low absolute and relative adrenal weights in 1 female were noted at the end of the dosing period.

In toxicokinetics, Tmax was between 0.5 and 4 hours after dosing. Cmax increased with dose in both males and females, except for females at 100 mg/kg on Day 28 of dosing. Cmax in females at 100 mg/kg on Day 28 of dosing was lower than that at 30 mg/kg on Day 28 of dosing. The degree of the increase was almost dose proportional in males and females between 10 and 100 mg/kg, and was greater than the dose increase between 100 and 800 mg/kg. AUC0-24h increased with dose in both males and females. The degree of the increase was almost dose proportional in males and females between 10 and 30 mg/kg, and was greater than the dose increase between 30 and 800 mg/kg. No apparent gender difference was noted in any TK parameter. There were no marked differences in any TK parameter after repeated dosing.

The changes noted during the dosing period recovered during the 4-week recovery period. From these results it was concluded that, the no-observed-adverse-effect level of Project 1 (as PROJECT 1) when administered orally to monkeys for 4 weeks was 100 mg/kg/day for males and females. The changes noted during the dosing period recovered during the 4-week recovery period.