**A 4-Week Repeated Oral Dose Toxicity Study of Project 5 in Cynomolgus Monkeys Followed by a 4-Week Recovery Period**

1. **SUMMARY AND CONCLUSION**

Project 5 was administered orally once daily for 4 weeks at dose levels of 0 (vehicle), 8, 15, 30, and 60 mg/kg (as PROJECT 5) 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 60 mg/kg groups in order to assess the reversibility of toxicity observed during the dosing period in the subsequent 4-week recovery period. Systemic exposure to the test article was also evaluated. The animals in the control group received 0.5 w/v% methylcellulose solution.

No animals died in any group during the dosing or recovery period.

In the 8 and 15 mg/kg groups, no test article-related changes were noted in any examination.

In the 30 mg/kg group, soft stool or diarrhea (watery stool) was observed in 2 males for 3 or 4 days. Food consumption decreased in 1 male from Day 9 to Day 14 and body weight decreased on Day 14, but recovered thereafter. In histopathology, slight atrophy of the thymus was observed in 2 males. A very slight increase in granulocytes in the sternal bone marrow was observed in the males.

In the 60 mg/kg group, vomiting was observed in 1 male for 6 day, immediately to 1 hour after dosing or 3 to 5 hours after dosing. Salivation was observed in 5 females for 1 to 22 days from Day 6, immediately after dosing. Soft stool or diarrhea (watery stool) was observed in 3 males and 3 females for 6 to 10 days. Food consumption decreased in 2 males and 2 females between Days 6 and 10, between Days 20 and 24, and on Days 26 and 28, between Days 26 and 28, and between Days 11 and 15, respectively. Body weight decreased in 1 male and 1 female on Day

28. In urinalysis, low pH, decreased chloride excretion, and cast in urinary sediment were noted in 1 male on Day 26. In hematology, decreased erythrocyte count, hematocrit value, and hemoglobin concentration were noted in 1 male and 1 female on Day 27. Conversely, increased erythrocyte count, hematocrit value, and hemoglobin concentration were noted in 1 male. Neutrophil count increased in 2 males and 1 female, and leukocyte count increased. In blood chemistry, increased creatinine in 1 male and 1 female, decreased albumin in 3 males, and decreased sodium and chloride decreased in 1 male were noted on Day 27. Increased chloride was noted in 4 males and 4 females, and was statistically significantly high in females. In histopathology, slight or moderate atrophy of the thymus in 1 male and 1 female, and an increase in granulocytes in the sternal bone marrow in 1 male and 1 female were observed. Although no test article-related changes were noted in troponin T, troponin I, or lactate dehydrogenase (LDH) isozyme, or in histopathology of any muscular tissue examined, increased LDH and creatine phosphokinase (CPK) activities were noted in 2 males in blood chemistry.

No test article-related changes were noted in ophthalmology, electrocardiography, gross pathology, or organ weights in any group during or at the end of the dosing period.