**A 4-Week Repeated Oral Dose Toxicity Study of Project H in Cynomolgus Monkeys Followed by a 4-Week Reversibility Study**

**12 SUMMARY AND CONCLUSION**

Project H was administered once daily for 4 weeks at dose levels of 0 (vehicle), 3, 10, and 20 mg/kg/day to 4 male and 4 female cynomolgus monkeys per group in order to investigate its toxicity. Three males and three females were added to the 20 mg/kg/day group to assess the reversibility of toxicity during a subsequent 4-week recovery period. Systemic exposure to PROJECT H was also assessed.

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

No animal died or was euthanized due to moribundity, and no test article-related changes were observed in ophthalmology, blood pressure, gross pathology, or histopathology.

At 3 mg/kg, no test article-related changes were observed.

At 10 mg/kg and greater, a decrease or a tendency toward a decrease in body weight (in 1 male and 1 female at 10 mg/kg and 1 male and 4 females at 20 mg/kg) or food consumption (2 males at 10 mg/kg and 3 males and 4 females at 20 mg/kg) was observed. Globulin increased (each 1 male at 10 and 20 mg/kg) and A/G decreased (1 male at 10 mg/kg and each 1 male and female at 20 mg/kg).

At 20 mg/kg, a slight decrease in spontaneous activity in 3 males, vomiting in all males and 4 females, and salivation in 1 female were observed. QRS duration prolonged in 3 males and 2 females on Day 9 or 23 of dosing, PR interval prolonged in 1 male on Day 9 of dosing, and body temperature decreased in 2 males on Day 11 of dosing. In hematology, erythrocyte count, hemoglobin concentration, and hematocrit value decreased and reticulocyte ratio increased in 1 male. Platelet count increased in 2 males and 2 females and eosinophil count and large unstained cell count increased in 2 females. In blood chemistry, albumin decreased in 1 male. In organ weights, a statistically significantly high relative liver weight was observed in both sexes.

In toxicokinetics, mean tmax values ranged from 1.5 to 6.6 hours in males and 2.0 to 5.5 hours in females. Mean Cmax and AUC24 values increased with increasing dose level except for those values in males at a dose level of 20 mg/kg on Day 14 of dosing, which were almost equal to those values at a dose level of 10 mg/kg. Mean Cmax and AUC24 values on Day 14 of dosing increased compared with those values on Day 1 of dosing by repeated dose. However, means of the Cmax and AUC24 values on Day 28 of dosing were almost equal to those on Day 14 of dosing except for those in males at 3 mg/kg, which were lower than those on Day 14 of dosing.

After the 4-week recovery period, the toxic changes noted during the dosing period were not observed.

It was concluded that, under the conditions of this study, the no-observed-adverse-effect level (NOAEL) was 3 mg/kg/day for males and females, since decreases in food consumption, body weight, and A/G and increase in globulin were observed at 10 mg/kg and greater. These changes observed during or after the dosing period at 20 mg/kg disappeared after the 4-week recovery period.