**A 2-Week Repeated Dose Oral Toxicity Study of Project 19 in Cynomolgus Monkeys Followed by a 2-Week Reversibility Study**

**11 SUMMARY**

Project 19 was repeatedly administered orally to cynomolgus monkeys, 3 males and 3 females at 10 and 100 mg/kg as PROJECT 19 (free form), and 6 males and 6 females at 0 (0.5% w/v% methylcellulose solution, control) and 1000 mg/kg as free form, once daily for 2 weeks to evaluate toxicity and systemic exposure. For evaluation of the reversibility of toxicity by a 2-week recovery period, 3 males and 3 females from the control group and 3 males and 2 females from the 1000 mg/kg group were used (3 males and 3 females were planned to be assigned, however, 1 female at 1000 mg/kg died during the dosing period).

One female in the 1000 mg/kg group died on Day 10 of dosing. Vomiting was observed on Days 1, 3, and 6 of dosing. In gross pathology and histopathology, systemic subcutaneous edema was observed.

During the dosing period, urinary glucose concentration and urinary glucose excretion increased in males and females in all test article groups.

No toxicological changes were noted in any examination in the 10 or 100 mg/kg group during the dosing period.

In animals that survived during the dosing period in the 1000 mg/kg group, vomiting was observed once, twice, or sporadically in 3 males and 2 females between Day 1 and Day 14. Soft stool or watery stool was observed sporadically in 5 males and all females between Day 2 and Day 14. A decrease in spontaneous activity was observed in 1 female on Day 10. Food consumption decreased from Day 7, body weight decreased from Day 8, and emaciation was observed from Day 12 to the end of the dosing period in this female. In hematology and blood chemistry in this female, erythrocyte count, hematocrit value and hemoglobin concentration and MCHC increased, and reticulocyte count and MCV decreased on Day 7 and/or 13. Total protein and albumin tended to increase, and triglycerides, BUN and creatinine increased on Day 7 and/or 13, and sodium and chloride decreased on Day 13.

No toxicological changes were noted in water consumption, ophthalmology, electrocardiography, auditory reflex, urinalysis, plasma glucose measurement, necropsy, organ weights, or histopathology in any male or female.

All changes noted in the 1000 mg/kg group during the dosing period disappeared or recovered by the end of the recovery period.

In toxicokinetics, Tmax values tended to delay with increasing dose. Cmax and AUC0-24h values increased almost dose-proportionally over the dose range of 10 to 100 mg/kg, but less than dose-proportionally at 1000 mg/kg. There were no large differences in TK parameters between sexes or dosing frequencies.

In conclusion, the no observed adverse effect level of PROJECT 19 when administered orally for 2-week was 100 mg/kg/day in male and female cynomolgus monkeys. Changes noted during the dosing period disappeared by the end of the 2-week recovery period.