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

**11 SUMMARY**

Project 4 was administered orally once daily for 4 weeks at dose levels of 0 (vehicle), 1, 3, 10, and 30 mg/kg (as PROJECT 4) 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 30 mg/kg group in order to assess the reversibility of toxicity during a subsequent 4-week recovery period. The animals in the control group received 0.5 w/v% methylcellulose solution. Systemic exposure to PROJECT 4 was also evaluated.

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

In the 1 and 3 mg/kg groups, no test article-related changes were noted in any examination.

In the 10 mg/kg group, symptoms were observed in all males and females. Ataxic gait was observed daily or almost daily from Day 1 or 2 in 2 males and 1 female, and was

accompanied frequently by decrease in spontaneous activity and/or incomplete eyelid opening. Ataxic gait was observed also in 1 male and 2 females, once, sporadically, or transiently in the middle of the dosing period. These symptoms were observed from 1 hour after dosing, and disappeared by 8 hours after dosing. Vomiting was observed in 2 females for 2 or 4 days from 1 or 4 hours after dosing. Food consumption was decreased in all males and 1 female for 2 to

9 days during the first 2 weeks, and statistically significantly low values were noted in males from Day 1 to Day 4. Body weight decreased transiently in 1 male. No test article-related changes were noted in other examinations.

In the 30 mg/kg group, symptoms were observed in all males and females. Ataxic gait was observed daily or almost daily from Day 1 in all animals, and was accompanied frequently by decrease in spontaneous activity and/or incomplete eyelid opening. Abnormal position (sitting, lateral, or prone position), suppressed response to stimulation, disappearance of touch response, somnolence, tremor, mydriasis, salivation, and/or vertical nystagmus were also observed frequently or sporadically in 5 males and 2 females. In 1 female, ataxic gait was the only sign observed for 11 days. These symptoms were observed from 1 hour after dosing, tended to be most severe around 1 to 2.5 hours after dosing, and subsided thereafter. Ataxic gait was the only one that sometimes remained 8 hours after dosing, but it had always disappeared by the next morning. Vomiting was observed in 3 males and 4 females for 1 to 6 days, mainly in the first week of dosing between 2.5 hours and 8 hours after dosing. Food consumption was decreased in 4 males and all females for 1 to 13 days during the first 2 weeks of the dosing period, and statistically significantly low values were noted in males on Day 3 and in females from Day 1 to Day 5. A decrease was also noted in 2 males and 1 female on Day 25. In 1 of these males, body weight decreased through the dosing period. In erectrocardiography, a statistically significantly decrease or decreased tendency was noted in heart rate in males and females 2 hours after dosing on Day 22, and individual heart rate markedly decreased in 2 males and 1 female. In hematology, decreased erythrocyte count, hematocrit value, and hemoglobin concentration were noted in 1 female on Day 26. In blood chemistry, decreased albumin and albumin/globulin ratio were noted in 1 female on Day 26.

No test article-related changes were noted in other examinations (ophthalmology, urinalysis, gross pathology, organ weight, and histopathology).

During the recovery period in the 30 mg/kg group, the decreased body weight noted in 1 male recovered by Day 7, and no test article-related changes were noted in any examination in the recovery period.

In toxicokinetics, Tmax showed no clear difference between doses. Cmax and AUC0-24h increased almost dose proportionally in both sexes. There was no apparent sex difference in any parameter. These parameters showed no clear change after repeated dosing.

In conclusion, the no-observed-adverse-effect-level was 3 mg/kg/day as PROJECT 4 in this 4- week repeated oral dose toxicity study of Project 4 in cynomolgus monkeys. No test article-related changes were noted during the recovery period.