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

**12 SUMMARY AND CONCLUSION**

PROJECT W was administered orally once daily for 4 weeks at dose levels of 0 (vehicle), 0.3, 1, 5, and 30 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 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 W was also evaluated. The following observations and examinations were performed in this study: clinical signs, body weight, food consumption, ophthalmology, electrocardiography, body temperature, urinalysis, hematology, blood chemistry, gross pathology, organ weights, and histopathology.

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

In the 0.3, 1, and 5 mg/kg groups, no test article-related changes were noted.

In the 30 mg/kg group, palpebral ptosis and/or decreased spontaneous activity were observed in 5 males and 4 females, mainly in the first 2 weeks of the dosing period. Decreased food consumption was noted in 2 males and 4 females for 1 to 4 days at the beginning of the dosing period. Hypothermia was noted in 3 males and 1 female at 4 and/or 8 hours on Day 1. Decreased heart rate was noted in 1 male at 8 hours after dosing at Week 4.

During the 4-week recovery period, no test article-related changes were noted in the 30 mg/kg

group in any examination.

Cmax and AUC0-24h increased with dose level and the increase was greater than dose proportional. Tmax tended to be delayed with dose increase. No clear sex difference was noted in any parameter. Throughout the 4-week dosing period, no clear change was noted in any parameter.

It was concluded that, under the conditions of this study, the no-observed-adverse-effect level (NOAEL) was 5 mg/kg/day for males and females. No test article effects were noted during the 4-week recovery period.