**Four-Week Repeated Dose Intravenous Toxicity Study of PROJECT 10 in Cynomolgus Monkeys Followed by a 4-Week Recovery Period**

**11 SUMMARY**

The objective of this study was to investigate the toxicity and its reversibility of PROJECT 10 when administered intravenously to cynomolgus monkeys once weekly for 4 weeks. Systemic exposure to PROJECT 10 was also assessed.

PROJECT 10 at dose levels of 6, 20, and 60 mg/kg, which was formulated in 20 mM citrate solution (pH4.9) containing 240 mM D-sorbitol and 0.02 % (w/v) polysorbate 80, was intravenously administered once weekly for 4 weeks (a total of 4 injections) to male and female cynomolgus monkeys (4 and 7 animals/sex/group; 3 to 6 years of age). The administration (5 mL/kg) was done from the cephalic vein at a rate of 5 mL/minute. The vehicle was administered to control group animals (4 animals/sex) in the same manner. Four males and 4 females of each group were euthanized after the 4-week dosing period, and 3 males and 3 females of the 60 mg/kg group were euthanized after a 4-week recovery period. The following observations and examinations were performed: clinical signs, body weight, food consumption, ophthalmology, electrocardiography, body temperature, blood pressure, respiration rate, urinalysis, hematology, blood chemistry, gross pathology, organ weights, histopathology, toxicokinetics, and anti-PROJECT 10 antibody analysis.

No deaths occurred during the dosing or recovery period. There were no test article-related changes in clinical signs, body weight, food consumption, ophthalmology, electrocardiography, body temperature, blood pressure, respiration rate, urinalysis, hematology, blood chemistry, gross pathology, organ weights, or histopathology at up to 60 mg/kg.

C0 and AUC168 increased almost dose proportionally from 6 to 60 mg/kg and t1/2 was comparable among these dose levels in both sexes on Days 1 and 22 of dosing. Following repeated dosing, C0 and AUC168 were 1.5 to 2.1 times increased from Day 1 of dosing, although t1/2 was unchanged. No obvious sex differences in toxicokinetics were noted at any dose level.

PROJECT 10 at 6, 20, and 60 mg/kg was intravenously administered to cynomolgus monkeys for 4 weeks followed by a 4-week recovery period. Animals tolerated and there were neither effects on the cardiovascular and respiratory systems nor CNS clinical signs. No changes were noted in clinical pathology or histopathology at any dose. Therefore, the no-observed- adverse-effect level (NOAEL) was 60 mg/kg, the highest dose tested.