**Four-Week Repeated Intravenous Dose Toxicity Study of PROJECT 14 in Cynomolgus Monkeys Followed by a 4-Week Recovery Period**

**11 SUMMARY**

PROJECT 14 was diluted with formulation buffer [20 mmol/L phosphate-buffered solution (pH 5.7) / 140 mmol/L arginine hydrochloride **/** 0.02% Polysorbate80] and administered intravenously once weekly for 4 weeks at dose levels of 0 (vehicle control), 3, 10, and 100 mg/kg to 4 male and 4 female cynomolgus monkeys per group in order to investigate its toxicity. The animals were sacrificed 7 days after the last dosing (4th dosing). Three males and three females were added to the 100 mg/kg group to assess the reversibility of toxicity during a subsequent 4-week recovery period. Systemic exposure of PROJECT 14 was also assessed. For the control group, formulation buffer was administered in the same manner as the test article. The following observations and examinations were performed: clinical signs, general behavior and neurobehavioral function, body weight, food consumption, ophthalmology, electrocardiography, body temperature, blood pressure, respiratory rate, urinalysis, hematology, blood chemistry, gross pathology, organ weights, histopathology, toxicokinetics, and anti-PROJECT 14 antibody analysis.

No test article-related death occurred in any group. At 100 mg/kg, 1 female was found dead on Day 20 of dosing (the day after 5 days after the 3rd dosing), and the cause of death was considered to be aspiration of vomit.

No test article-related changes were noted at 3 or 10 mg/kg.

At 100 mg/kg, occult blood in urinalysis was noted in males. In 1 male, low albumin, albumin ratio and albumin/globulin ratio, and high globulin and γ-globulin ratio were noted in blood chemistry, and perivascular inflammatory cell infiltration in the heart, submandibular glands, esophagus, stomach, duodenum, ileum, cecum, rectum, urinary bladder, sciatic nerve, femoral skeletal muscle, lungs, and pancreas was observed, and inflammatory cell infiltration in the alveoli and bronchioles was also observed.

During the recovery period, no test article-related changes were noted in any examination. Occult blood in urinalysis noted on Day 27 of dosing disappeared on Day 27 of recovery.

In anti-PROJECT 14 antibody analysis, 8 and 2 out of 8 animals were judged as positive at 3 and 10 mg/kg, respectively. One out of 14 animals at 100 mg/kg was transiently anti-PROJECT 14 antibody positive with an extremely low titer.

In toxicokinetics, the Cmax and AUC168 values increased with dose. The Cmax and AUC168 values on Day 22 of dosing were higher than those on Day 1 of dosing in some and all animals in the 10 and 100 mg/kg groups, respectively. The t1/2 and AUC168 values on Day 22 of dosing were lower than those on Day1 of dosing in all animals in the 3 mg/kg group. The decrease in t1/2 and AUC168 values after repeated dosing would be related to the production of anti-PROJECT 14 antibody. There were no apparent gender differences in the toxicokinetic parameters.

In conclusion, at 100 mg/kg in this study, occult blood was noted in the urine in males, and perivascular inflammatory cell infiltration (heart, submandibular gland, esophagus, stomach, duodenum, ileum, cecum, rectum, urinary bladder, sciatic nerve, femoral skeletal muscle, lungs, and pancreas) and inflammatory cell infiltration of the alveoli and bronchioles, which were associated with the changes in blood chemistry including high globulin and γ-globulin ratio, were noted in 1 male, and thus, the no-observed-adverse-effect level of PROJECT 14 was determined to be 10 mg/kg for males and 100 mg/kg for females. The production of ADA and possibly relevant decrease in t1/2 and AUC168 were prominently noted at 3 mg/kg.