**Final Report**

**A 5-Week Toxicity Study of PROJECT 13 by Intravenous Infusion in Cynomolgus Monkeys with a 4-Week Recovery Period**

**11 SUMMARY**

The objectives of this study were to determine the potential toxicity of PROJECT 13, when given by intravenous infusion to cynomolgus monkeys once weekly for 5 weeks and to evaluate the potential reversibility of any findings. In addition, 2 animals/sex/group in the control and high dose were allowed to recover for an additional 4 weeks following the completion of the main study. The toxicokinetic characteristics of PROJECT 13 were also determined and changes to the immunophenotype were monitored.

The study design was as follows:

The following parameters and end points were evaluated in this study: clinical signs, body weights, qualitative food evaluation, ophthalmology, qualitative electrocardiology, respiratory function, neurological assessments, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), laboratory parameters (immunophenotyping, anti-therapeutic antibody and cytokine analysis), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations.

All PROJECT 13-treated animals were exposed to the compound up to Day 30 postdose, with animals dosed at 200 mg/kg/dose exposed to compound up to the end of the recovery period (4 weeks following dosing completion). There was no test item present in control animals. Two animals dosed at 50 mg/kg/dose were positive for anti-drug antibody presence on Day 29. There was no mortality over the course of the study and there were no treatment-related clinical signs during the main and recovery phases of the study. Food intake and body weight were unaffected following weekly doses for 5 weeks and following a 4-week recovery. Ophthalmic, respiratory and neurological assessments evaluated during Week 4 were unaffected by PROJECT 13 up to doses of 200 mg/kg/dose. All clinical pathology parameters, including immunophenotyping were unchanged following the treatment and recovery periods. PROJECT 13 did not induce a pattern of cytokine upregulation following 5 weekly doses. Gross pathology, organ weights and microscopic evaluations were also unaffected by the administration of PROJECT 13.

In conclusion, the weekly intravenous administration of PROJECT 13 over 5 weeks was well tolerated in both male and female monkeys at levels up to 200 mg/kg/dose. There were no treatment-related changes in the parameters evaluated. Based on these results, the no-observed-adverse -effect level (NOAEL) was considered to be 200 mg/kg/dose (Cmax 7365 μg/mL and AUC(0-168h) 786000 hr∙μg/mL, gender combined).