**A 4-Week (5-Dose) Study of PROJECT 12 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 12, a human anti‑NRP1 IgG4 S228P/kappa antibody, when given by intravenous infusion once weekly for 5 doses (Days 1, 8, 15, 22, and 29) to cynomolgus monkeys, and to evaluate the potential reversibility of any findings after a 4-week recovery period. In addition, the toxicokinetic characteristics and changes to the immunophenotype were monitored.

The study design was as follows:

Text Table   
Experimental Design

| **Group No.** | **Test Material** | **Dose Level (mg/kg/dose)** | **Dose Volume (mL/kg)** | **Dose Concentration (mg/mL)** | **No. of Animals** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Main Study** | | **Recovery Study** | |
| **Males** | **Females** | **Males** | **Females** |
| 1 | Control | 0 | 8 | 0 | 3 | 3 | 2 | 2 |
| 2 | PROJECT 12 | 20 | 8 | 2.5 | 3 | 3 | ‑ | ‑ |
| 3 | PROJECT 12 | 60 | 8 | 7.5 | 3 | 3 | ‑ | ‑ |
| 4 | PROJECT 12 | 200 | 8 | 25 | 3 | 3 | 2 | 2 |
| ‑ = not applicable.  a Dosing was stagger-started with a 3-day interval between dosing Set A (males) and Set B (females). Males were dosed initially, followed by the females. Animals were dosed by IV infusion (target 60 minutes) once weekly for 5 doses (Days 1, 8, 15, 22, and 29). The main study and recovery animals underwent necropsy on Day 30 and Day 57, respectively. | | | | | | | | |

The following parameters and end points were evaluated in this study: clinical signs, body weights, qualitative food evaluation, ophthalmology, electrocardiology, blood pressure, heart rate, respiratory rate, neurologic examinations, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), bioanalysis and toxicokinetic parameters, anti‑drug antibodies (ADA), immunophenotyping, cytokines, gross necropsy findings, organ weights, and histopathologic examinations.

There were no mortalities or PROJECT 12-related effects on clinical signs, body weights, qualitative food consumption, ophthalmology, electrocardiology, blood pressure, heart rate, respiratory rate, neurologic examinations, immunophenotyping, cytokines, or in hematology, coagulation, or urinalysis parameters. PROJECT 12‑related clinical chemistry changes included mildly decreased triglycerides at ≥ 20 mg/kg/dose, with no recovery by the end of the recovery phase (Day 57). In addition, minimally increased globulins and decreased albumin/globulin (A/G) ratio were noted at 200 mg/kg/dose, with complete recovery by Day 57 except for 1 male that exhibited partial recovery.

At the end of the dosing phase, on Day 30, and at the end of the recovery phase, on Day 57, there were no gross, organ weight, or microscopic findings related to PROJECT 12.

In conclusion, administration of PROJECT 12 by intravenous (IV) infusion once weekly for 5 doses was well tolerated in cynomolgus monkeys at levels of 20, 60, and 200 mg/kg/dose. There were no changes in any of the parameters evaluated that were considered toxicologically relevant. Based on these results, the no-observed-adverse-effect level (NOAEL) under the conditions of the study was considered to be 200 mg/kg/day.