**A 4-Week Toxicity Study of Project 17-5 Administered by Intravenous Injection to Cynomolgus Monkeys, with a 6-Week Recovery Period**

1. **SUMMARY AND CONCLUSION**

The objectives of this study were to determine the potential toxicity and toxicokinetic profiles of Project 17-5 when administered once every week for a total of 4 doses by intravenous injection to cynomolgus monkeys, and to evaluate recovery from any effects over a dose-free period of 6 weeks. The test article, Project 17-5, and the control article, 20 mM histidine-HCL pH 5.2, 10% trehalose (w/v), were supplied by the Sponsor as bulk drug-crystalline powder and aqueous solution, respectively. Dosing formulation was prepared by dissolving the bulk powder in 0.01N hydrochloric acid (HCL) and further dilution of the stock formulation with control article to the desired concentration and sterile filtered. Formulations were prepared fresh on the day of dose administration.

Fifty experimentally naive cynomolgus monkeys (25 males and 25 females) were assigned to dose groups as shown in the table below.

All animals were dosed via intravenous injection once every week for a total of 4 doses (i.e., on Days 1, 8, 15, and 22).

The following parameters were evaluated: clinical signs, food consumption, detailed clinical observations, body weight, post dose observations, physical and ophthalmic examinations, electrocardiograms, blood pressure, serum chemistry, hematology, coagulation, urinalysis, and toxicokinetics at various time points as described in the subsequent sections of this report. Thirty animals (3/sex/group) were euthanized on Day 23. The remaining 20 animals (2/sex/group) were continued on study without further dosing and were terminated on Day 65.

At termination, a full necropsy was conducted on all animals, and tissues were collected, preserved, processed, and examined microscopically by a veterinary pathologist certified by the American College of Veterinary Pathologists.

The administration of Project 17-5 at 0.05, 0.2, 0.3, and 0.5 mg/kg via intravenous injection every week for a total of 4 doses was well tolerated in cynomolgus monkeys. All animals survived to the scheduled necropsy time points at Days 23 and 65. There were no changes in clinical signs, food consumption, detailed clinical observations, post dose observations, body weight, electrocardiograms, blood pressure, physical or ophthalmic exams, or clinical pathology parameters (including clinical chemistry, hematology, coagulation, and urinalysis) that were attributed to Project 17-5 administration.

In addition, there were no gross, organ weight or organ weight ratio, or histopathologic changes attributed to Project 17-5 administration.

Toxicokinetic data indicated that Project 17-5 exposure is linear with dose over the range tested in the study. Maximum serum Project 17-5 concentration (Cmax) increased proportionally to dose and area under the concentration time curve [AUC(0-∞)] showed proportional increases with dose over the dose range of 0.05 mg/kg to 0.5 mg/kg. Peak serum Project 17-5 concentrations were attained immediately post intravenous (IV) injection. Tmax was at the first TK collection time (5 minutes). No significant difference in Project 17-5 toxicokinetics was found between male and female monkeys.

Under the conditions of this study, 0.5 mg/kg/week dose of Project 17-5 was considered the no-observed-adverse-effect level (NOAEL).