**PROJECT A: A 28-DAY ORAL TOXICITY STUDY IN CYNOMOLGUS MONKEYS WITH A 28-DAY RECOVERY**

**11 SUMMARY**

This study was conducted for Mitobridge, Inc. to evaluate the toxicity of the test article, PROJECT A, in cynomolgus monkeys when administered daily via oral gavage for 28 days, to evaluate the plasma exposure to the test article in the first and last doses, and to evaluate the reversibility of any test article-related effects during a 28 day postdose observation period. Animals were assigned to the study as indicated in Table A.

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| **Table A. Study Design** | |
| **Dose Dose Group Dose Level Volume Concentration Number (mg/kg/day) (mL/kg) (mg/mL)** | **Number of Animals** |
| **Initial Terminal Recoverya** |
| **M F M F M F** |
| 1 0 5 0 5 5 3 3 2 2  2 10 5 2 3 3 3 3 - -  3 100 5 20 5 5 3 3 2 2  4 1000 5 200 5 5 3 3 2 2 | |
| M = Male F = Female  aAnimals remained on study for a 28 day recovery period. | |

In life, monkeys were observed for clinical signs of toxicity; findings detectable by ophthalmoscopic, physical, and electrocardiographic examinations; and effects on body weight and hematology, coagulation, clinical chemistry, and urinalysis parameters. Clinical chemistry parameters included troponin I, aldolase, creatine kinase (total and isozymes), lactate dehydrogenase, and cholesterol (total, HDL, LDL, and VLDL). Plasma samples were taken at intervals after the first and last doses to measure PROJECT A concentration and evaluate plasma exposure.

At necropsy, macroscopic pathologic findings were recorded; the whole animal and selected organs were weighed; bone marrow smears were made; samples of liver, heart, gastrocnemius muscle, and kidney were collected and stored refrigerated (2 to 8°C) for potential electron microscopic evaluation; samples of heart (left ventricular free wall), liver, gastrocnemius muscle, and quadriceps muscle were flash frozen in liquid nitrogen and liver samples will be shipped to SNBL Japan for potential exploratory analysis outside the scope of this study; and tissue samples were taken and fixed. Bone marrow smears were stained and examined for cytologic findings. All fixed tissue samples from all monkeys were processed and examined for histopathologic findings.

PROJECT A given daily over a 28-day period was well-tolerated by monkeys at all dose levels tested. The only findings considered to be related to PROJECT A were a greater incidence of soft and/or watery feces, slight decreases in red cell mass, and hepatocellular hypertrophy at 1000 mg/kg/day, none of which was considered adverse. These findings were shown to reverse after a 28-day recovery period.

The relationship between dose level and plasma exposure was similar in both sexes and did not change meaningfully with repeated daily dosing. Based on mean Cmax and AUC0-24h values for sexes combined, plasma exposure to PROJECT A tended to increase proportionally when dose level increased from 10 to 100 mg/kg/day but less than proportionally when dose level increased from 100 to 1000 mg/kg/day.

Based on these results, the 28-day no observed adverse effect level (NOAEL) is considered to be 1000 mg/kg/day. At the NOAEL on Day 28, the PROJECT A Cmax and AUC0-24h values for males were 4710 ng/mL and 22700 hr\*ng/mL, respectively, and for females were

5120 ng/mL and 28200 hr\*ng/mL, respectively.