**A 4-Week Repeated Oral Dose Toxicity Study of Project X in Cynomolgus Monkeys Followed by a 4-Week Reversibility Study**

**11 SUMMARY**

Project X was administered orally once daily for 4 weeks at dose levels of 0 (vehicle), 0.01, 0.1, 1, and 10 mg/kg (as PROJECT X) to 3 male and 3 female cynomolgus monkeys per group in order to investigate its toxicity. Three males and three females were added to the 10 mg/kg group in order to assess the reversibility of toxicity during a subsequent 4-week recovery period. The animals in the control group received 0.5 w/v% methylcellulose solution. Systemic exposure to PROJECT X was also evaluated.

The following observations and examinations were performed in this study: clinical signs, body weight, food consumption, ophthalmology (including fluorescein fundus angiography), electrocardiography, urinalysis, hematology, immunophenotyping, blood chemistry, gross pathology, organ weights, histopathology, and toxicokinetics.

No animal died in any group during the dosing or recovery period.

At 0.01 and 0.1 mg/kg, no toxic changes were noted in any examination. At 1 mg/kg, increased lung weight was noted in 1 male.

At 10 mg/kg, total protein, albumin, and globulin decreased in 1 male and 2 females. Increased lung weight was noted in all males and 1 female.

As the pharmacological action of the test article, the following changes were noted in dose- dependent manner: decreases in lymphocyte count, and atrophy of the germinal center, atrophy of the periarterial lymphoid sheath, and/or widening of marginal zone in the spleen in males and females at 0.1 mg/kg and greater. Immunophenotyping analysis gave the following results: CD3+CD4+ (helper T) cell and CD3+CD8+ (suppressor/ killer T) cell counts [due to CD28+CD95- (naïve) cell and CD28+CD95+ (central memory) cell counts], and CD3-CD20+

(B) cell count in males and females at 0.1 mg/kg and greater; decreases in CD28-CD95+ (effecter memory) cell counts in both CD3+CD4+ and CD3+CD8+ lymphocytes in males and females at 1 mg/kg and greater.

In toxicokinetics, on Day 1, Tmax did not differ between dose levels. Cmax and AUC0-24h increased almost proportionally, except for 10 mg/kg males that showed a lesser increase. No clear sex difference was noted in any TK parameter. On Days 14 and 28, no clear changes were noted in any TK parameter compared with that on Day 1.

After the 4-week recovery period, the changes noted in the 10 mg/kg group during the dosing period recovered or tended to recover.

It was concluded that, under the conditions of this study, the no-observed-adverse-effect level was 0.1 mg/kg/day as PROJECT X for males and 1 mg/kg/day for females, because high lung weight was noted in males at 1 mg/kg and greater and in females at 10 mg/kg. Reversibility of test article effects was confirmed after the 4-week recovery period.