**Final Report**

**A 4-week repeated oral dose toxicity study of PROJECT Z in dogs followed by a 4-week reversibility study**

**11 SUMMARY**

PROJECT Z was administered orally to groups of male and female beagle dogs (3 or 6 males and females per group) once daily for 4 weeks at dose levels of 0 (control), 30, 100, 300 and 1000 mg/kg/day to examine its toxicological effects, and plasma concentrations of PROJECT Z were determined to evaluate systemic exposure to the test article of the animals. For 3 males and 3 females each in the 1000 mg/kg group, a 4-week recovery period was provided following the end of the administration period to examine reversibility of possible test article-related changes.

The results are summarized as follows:

No treatment-related findings were observed at 300 mg/kg/day or below.

At 1000 mg/kg/day, soft or mucous stool were observed throughout the dosing period, but it recovered after a 3-day recovery period. Decrease in body weight were also noted, but recovered after a 4-week recovery period

No treatment-related changes were observed in food consumption, ophthalmology, electrocardiography, fecal occult blood test, urinalysis, hematology, blood chemistry or pathology in the present study.

In toxicokinetics, Cmax and AUC0-24h values increased less than dose-proportionally at all sampling period and both sexes. Tmax values showed a tendency to be constant regardless increase of the dose. Among dosing periods, consistent sexual difference in Cmax and AUC0-24h was not observed at any doses. Systemic exposure was increased less than dose proportionally over the dose range of 30 to 1000 mg/kg/day.

As described above, no observable adverse effect level (NOAEL) under the conditions of this study was 300 mg/kg/day.

The findings recorded during the dosing period were recovered during the 4-week withdrawal.