**A 4-week repeated oral dose toxicity study of Project S in beagle dogs followed by a 4-week reversibility study**

**11 SUMMARY**

Project S was administered orally to groups of male and female beagle dogs once daily for 4 weeks at dose levels of 0 (control), 1, 3, 10 and 30 mg/kg/day as PROJECT S to examine its toxicological effects, and plasma concentrations of PROJECT S were determined to evaluate systemic exposure of the animals. Each dosing group consisted of 3 males and 3 females. For the 30 mg/kg group, 3 males and 3 females were assigned to the recovery group to examine the reversibility of the changes induced by Project S.

The results are summarized as follows:

No treatment-related changes were observed at 1, 3, or 10 mg/kg.

At 30 mg/kg, staggering gait in 2 males and 2 females (1 or 4 days/4 weeks), decrease in locomotor activity in 1 male and 2 females (1 or 3 days/4 weeks), ananastasia in 1 male and 1 female (1 day/4 week), tonic convulsion in 1 female (2 days/4 weeks), vomiting in all males and 5 females (5 to 23 days/4 weeks) and salivation in 4 males and 3 females (1 to 25 days/4 weeks) were noted within 1 hour after dosing on each day. In the electrocardiogram, prolongations of QT interval and QTc and an extension of QRS were noted in one female at pre-dosing and/or 1hour after dosing in Week 4.

The findings observed in the dosing period disappeared during the recovery period.

In the toxicokinetics, Cmax and AUC0-24h values increased more than dose-proportionally at all sampling points in both sexes, except the 3 mg/kg dosing group. In the 3 mg/kg dosing group, those values increased almost dose-proportionally. Tmax values showed a tendency to be constant. There was no appreciable sex difference. TK parameters were almost constant regardless of the frequency of administration. Systemic exposure, with AUC0-24h values as an index, increased more than dose-proportionally over the dose range of 1 to 30 mg/kg.

From these results, it was concluded that the no observable adverse effect level (NOAEL) under the conditions of this study was 10 mg/kg/day.