**Final Report**

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

**11 SUMMARY**

PROJECT T was administered orally to groups of male and female beagle dogs (4/sex/group for a main group, 3/sex/group for a recovery group) once or twice daily for 4 weeks at dose levels of 0 (10 w/v% Cremophor solution, b.i.d.), 1000 (q.d.) and 2000 (1000 mg/kg, b.i.d.) mg/kg to examine its toxicological effects at higher dose levels, and plasma concentrations of PROJECT T and its metabolite AS2780148-00 were determined to evaluate systemic exposure of the animals to the PROJECT T. For 3 males and 3 females in the 2000 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. Study evaluation was performed for clinical signs, body weight, food consumption, ophthalmology, electrocardiogram, urinalysis, hematology, blood chemistry, pathology and toxicokinetics.

The results are summarized as follows:

In the clinical observation, soft stool (containing whitish test article-like material) was observed in animals in the 2000 mg/kg/day groups, and the change was considered to be of low toxicological significance.

Stool containing whitish test article-like material was observed frequently in all animals in the 1000 and 2000 mg/kg/day groups, and the change was judged to have no toxicological significance, because they were probably due to excretion of unabsorbed test article into stools. A high value for the relative weight of adrenal in the organ weight was noted in females in the 2000 mg/kg/day group; however, the change was judged to have no toxicological significance since it was statistically significant only in the relative weight, and there was no relevant histopathological evidence. No treatment-related changes were noted for body weights, food consumption, ophthalmology, electrocardiography, urinalysis, hematology, blood chemistry, organ weights, necropsy or histopathological examination at any dose.

In toxicokinetics, the Cmax values for PROJECT T and AS2780148-00 were almost comparable between 1000 and 2000 mg/kg/day groups. The AUC24 values for PROJECT T and AS2780148-00 increased with increasing dose levels. The tmax values for PROJECT T were 1.00 to 1.50 h and 1.79 to 5.57 h at 1000 and 2000 mg/kg/day, respectively, and those for AS2780148-00 were 1.50 to 2.00 h and 4.43 to 5.86 h, respectively, on all dosing days. For all dosing groups and days, no remarkable sex differences were observed in the TK parameters of PROJECT T or AS2780148-00. TK parameters of PROJECT T and AS2780148-00 showed no influence of repeat dosing for any dosing groups.

As described above, when PROJECT T was administered orally for 4 weeks to beagle dogs, soft stool was observed at 2000 mg/kg/day. Therefore, it was concluded that the non-toxic dose level under the conditions of this study was 1000 mg/kg/day in both sexes.