DISCUSSION

The administration of A358 to beagle dogs at dose levels of 25 mg/kg/day for 3 days followed by 50 mg/kg/day for 3 days resulted in decreased food consumption and slight bodyweight loss. Following administration of 100 mg/kg/day for 7 days, both animals showed evidence of bodyweight loss and one or more of liquid faeces, splayed hindlimbs, salivation or head shaking. Both animals were killed for humane reasons on Day 7.

In the escalating dose phase, lower food consumption and bodyweight loss were reported in both animals during the treatment period, and although a slight recovery was observed over the three days following dosing, the animals were necropsied to assess whether there was any evidence of damage to the gastrointestinal tract. The necropsy and subsequent histopathology investigations revealed evidence of minor effects on the gastrointestinal tract but not of systemic toxicity. It was therefore considered probable that most of the in-life observations were secondary to the low food consumption seen and of non-specific stress.

During the fixed dose phase at 100 mg/kg/day food consumption in the male animal, enhanced by a combination of pair housing with the female and the offering of food supplements, was similar to pre-dose values. Food consumption in the female declined daily up to Day 5 however a slight recovery was observed on Days 6 and 7 when food supplements were offered. Bodyweight losses were evident in both animals. Clinical pathology investigations on Day 7 revealed a few slight changes in the cellular, clotting and chemical composition of the blood however only isolated parameters were affected and in the absence of any histopathological examination the significance of these findings is unclear. At necropsy, findings comprised reddening of the mucosal surface of the gastrointestinal tract. On histopathological examination, these corresponded with areas of mucosal congestion with mineralisation and in the female, slight microthrombus formation in the jejunum. There was no evidence of mucosal erosion or ulceration.

Plasma levels of A358 in both dogs dosed with 100 mg/kg/day in the fixed dose phase were high and sustained. Levels of A358 were still raising 24 hours after the first dose and by Day 7, one hour after dosing, levels were approximately 18 to 20 fold greater than those on Day 1.

CONCLUSION

The administration of A358 to beagle dogs at dose levels of 25 mg/kg/day for 3 days followed by 50 mg/kg/day for 3 days resulted in decreased food consumption and slight bodyweight loss. Following administration of 100 mg/kg/day for 7 days, both animals showed evidence of bodyweight loss and one or more of liquid faeces, splayed hindlimbs, salivation or head shaking. Both animals were killed for humane reasons on Day 7.

Plasma levels of A358 were high and increased with time but there was no evidence in the limited number of organs examined of target organ toxicity. It is concluded therefore that the deterioration in the clinical condition of the animals was probably the consequence of inanition and stress.