**Final Report**

**Four-Week Repeated Dose Oral Toxicity Study of Project U in Beagle Dogs Followed by a 4-Week Recovery Period**

**11 SUMMARY**

Project U [PROJECT U · Hypromellose TC-5E (1:1)] suspended in water for injection was orally administered to 4 male and 4 female beagle dogs each in every dosage group at daily doses of 1, 10, 100 and 1000 mg/kg as PROJECT U for 4 weeks to investigate the toxicity of PROJECT U. The control animals received 100 mg/mL hypromellose solution. A recovery period of 4 weeks was established for the high-dose group (3 animals/sex) following completion of the administration period to investigate reversibility. Additionally, systemic exposure to PROJECT U was assessed. The results are summarized below.

The investigation items included clinical signs, body weight, food consumption, ophthalmology, electrocardiography, urinalysis, hematology, blood chemistry, necropsy, organ weight measurement, histopathology and toxicokinetics.

No death occurred during the administration or recovery period.

In the 1000 mg/kg group, loose stool, watery stool and mucous stool were frequently observed in both sexes throughout the administration period. These changes were observed mainly at the time 4 or 8 hours post dose. In addition, vomitus was frequently observed in both sexes in this group at 4 hours post dose. The loose stool and vomitus frequently contained unabsorbed test article.

No test article-related change was detected in the measurement of body weight or food consumption, ophthalmology, electrocardiography, urinalysis, hematology analysis, blood chemistry analysis, necropsy, organ weight measurement, or histopathological examination.

In the recovery study, all changes seen in the administration period disappeared, suggesting their reversibility.

In the TK analysis, Cmax and AUC24 values increased with the increasing dose level up to 1,000 mg/kg. tmax values showed a tendency to be constant regardless of the dose. Among dosing period, consistent sexual difference in Cmax and AUC24 was not observed at any doses.

There was no obvious repeated dose effect.

In conclusion, the no observed adverse effect level (NOAEL) of Project U was therefore 100 mg/kg/day as PROJECT U for both sexes under these study conditions.