**A 13-week repeated oral dose toxicity study of PROJECT V in cynomolgus monkeys followed by a 4-week reversibility study**

**11 SUMMARY**

A toxicity study in which PROJECT V was repeatedly administered orally by gavage at 0 (vehicle: 0.5 w/v% methylcellulose solution), 10, 30, 100 or 1000 mg/kg/day (dose volume: 5 mL/kg) for 13 weeks to male and female cynomolgus monkeys was conducted. The number of animals used was 3 males and 3 females each for the 0, 10, 30 and 100 mg/kg groups and 6 males and 6 females for the 1000 mg/kg group. For 3 males and 3 females in the 1000 mg/kg group, a 4-week withdrawal period was provided to examine reversibility of the toxic changes.

In this study, animals were observed for clinical signs, body weight, food consumption, ophthalmological examination, electrocardiogram, urinalysis, hematological examination, blood chemistry examination, necropsy, organ weight, histopathological examination and hormone measurement. The concentration of PROJECT V in plasma was measured to confirm systemic exposure to the test article.

1) No deaths occurred and there were no animals that were sacrificed moribund during the 13-week administration period or the 4-week recovery period.

2) In clinical observation, abnormal stool color (black, negative occult blood reaction) were observed in males and females in the 100 and 1000 mg/kg groups and vomitus in females in the 1000 mg/kg group.

3) In blood chemistry, a high value in triglyceride was recorded in females in the 1000 mg/kg group in Week 13 of administration, and a high value in phospholipid in males and females in the 100 mg/kg group and females in the 1000 mg/kg group in Weeks 7 and 13 or in Week 13 of administration.

4) There were no test article-related effects in body weight, food consumption, ophthalmological examination, electrocardiogram, urinalysis, hematological examination, necropsy, organ weight, histopathological examination or hormone measurement.

5) In the analysis of PROJECT V concentration in plasma, both Cmax and AUC24 increased with the increase in the dose level for both males and females on Day 1 and in Week 7 and Week 13 of administration, but the increases were slightly saturated in the 1000 mg/kg group. For Cmax and AUC24, values were comparable on Day 1 and in Week 7 and Week 13 of administration. tmax was 1.7-3.7 hours and there were no clear differences among dose groups in males or females. There were no sex differences in any TK parameter.

6) During the 4-week recovery period, the clinical signs and the changes in blood chemistry examination that were observed during the administration period were no longer observed. Therefore, reversibility of the changes was suggested.

Based on the results described above, it was judged that the no observed adverse effect level of PROJECT V was judged to be 30 mg/kg for both males and females.