Study Title	DU 127090: Maximum Tolerated Dose Study (Gavage and Intravenous Administration) in the Monkey
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Covance Report Number	65/55-D6154
Sponsor Number	H.154.484.
Report Issued	February 2002
Page Number	1 of 68
Solvay Internal doc.no:	56352/166/98

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SUMMARY

The objective of the study were as follows: to establish a maximum tolerable dose by oral gavage dosing, suitable for repeated dosing, to establish a maximum tolerable dose by intravenous dosing, to establish pharmacokinetic parameters in plasma at various incremental dose levels and at the MTD (both oral and IV).

Two male (1M and 2M) and two female (3F and 4F) monkeys were treated stepwise increasing oral doses of DU 127090. After an oral dose level of 150 mg/kg/day had been reached, and after a wash-out period of three weeks one of the males (2M) and one of the females (4F) received increasing doses of DU 127090 via the intravenous route until a maximal tolerated dose was reached.

The only death was animal number 3F on Day 52. This animal was killed *in extremes* after 3 doses at 400 mg/kg/day. In contrast, animal number 1M was killed as scheduled in good health after 11 doses of 400 mg/kg/day. The dose could not be increased further due to formulation constraints.

Other clinical observations during the oral administration phase were restricted to a short period of subdued behaviour, which was noted in one male animal after the second dose at 2.5 mg/kg/day. This sign was not noted again at any of the dose levels used. No clinical observations were noted after the intravenous administration until a dose of 8 mg/kg/day when dosing was stopped after the second administration, when CNS observations including an apparent inability to judge distance, uncoordination and subdued behaviour were noted.

On oral dosing, there was a large variation in exposure in terms of both AUC and Cmax between the four animals, by up to a factor of 10. However the rank order of exposure between the four animals was more or less constant, indicating that the intra-individual variation is much smaller than the inter-individual variation in exposure.

On incremental dosing, the observed increase in AUC was roughly proportional to dose. In the present study, the exposure in females was much higher than in males. This probably explains why the males were unaffected after multiple doses of 400 mg/kg/day, whereas one of the females had to be killed in extremes at this dose level. It should be realised however, that due to the small group size in this study it is unclear whether this apparent sex-difference reflects a real sex difference, or simply inter-individual differences in exposure.

With respect to the MTD after multiple oral dosing it can be concluded that for animals with high exposure to DU 127090, the MTD is lower than 400 mg/kg/day. In animals with low exposure, the MTD is higher than 400 mg/kg. The actual MTD in the latter animals could not be established due to formulation constraints.

On intravenous dosing, half-life appeared to increase with dose. The clearance of DU 127090 was low compared to the liver blood flow in monkeys. In the same animals there was a smaller inter-individual variation in exposure after iv dosing than after oral dosing. The bioavailability was variable, between 6.8 and 25 %.

The MTD after intravenous dosing was reached at a dose of 8 mg/kg/day. At this dose level uncoordination and subdued behaviour were observed.

In conclusion, due to large inter-individual differences in exposure after oral dosing and formulation constraints limiting the top dose, it was not possible to determine a clear-cut MTD after oral dosing. Probably the MTD will vary for every individual animal. In high exposure animals it will be below 400 mg/kg, in low exposure animals above 400 mg/kg. The MTD after intravenous dosing of DU 127090 was 8 mg/kg. The kinetics of DU 127090 were roughly proportional to dose, the clearance was low and the bioavailability was variable, between 6.8 and 25%.

observation. Therefore it was considered to be a reflux action related to the volume administered rather than any test article related response.

No clinical observations were noted after the intravenous administrations until a dose level of 8 mg/kg/day was given. Both the male and female animals appeared subdued, mildly uncoordinated, having difficulty in perching, judging distance and moving around the pen. Both animals slowly improved and appeared essentially normal about 5 hours post dose. Similar effects were noted after a second dose at 8 mg/kg/day was given on the following day in order to collect plasma samples. After this dose a decision was taken that the intravenous MTD had been reached.

Body weight (Figures 1& 2, Appendix 4)

There were no effects on body weight or weight gain during the gavage phase. During the IV phase (with a raising dose scheme from 2 to 8 mg/kg) the male lost 12% and the female 7% of their body weights. It should be noted, however, that the animals had a small weight loss in the week preceding the IV phase. In addition, the weight loss is calculated on one measurement per animal only. It is therefore difficult to assess whether the observed weight loss was drug-related.

Food consumption (Appendix 5)

The food consumption of all the animals was variable over the treatment period. However the majority of the fluctuations were with in the range measured pre-dose, with only one animal, 1M, having a slight initial reduction in food consumption, probably related to the initial stress associated with gavage administration.

Necropsy (Appendix 6)

At necropsy the findings were consistent with animals of this strain and age.

DISCUSSION AND CONCLUSION

On oral dosing, there was a large variation in exposure in terms of both AUC and C_{max} between the four animals, by up to a factor of 10. However the rank order of exposure between the four animals was more or less constant, indicating that the intra-individual variation is much smaller than the inter-individual variation in exposure.

On incremental dosing, the observed increase in AUC was roughly proportional to dose. In the present study, the exposure in females was much higher than in males. This probably explains why 1M was unaffected after multiple doses of 400 mg/kg/day, whereas 3F had to be killed in extremis at this dose level. It should be realised however, that due to the small group size in this study it is unclear whether this apparent sex-difference reflects a sex difference, or simply inter-individual differences in exposure.

With respect to the MTD after multiple oral dosing it can be concluded that for animals with high exposure, the MTD is lower than 400 mg/kg/day. In animals with low exposure, the MTD is higher than 400 mg/kg. The actual MTD in the latter animals could not be established due to formulation constraints.

On intravenous dosing, half-life appeared to increase with dose. The clearance of DU 127090 was low compared to the liver blood flow in monkeys. In the same animals there was a smaller inter-individual variation in exposure after IV dosing than after oral dosing. The bioavailability was variable, between 6.8 and 25 %.

The MTD after intravenous dosing was reached at a dose of 8 mg/kg. At this dose level uncoordination and subdued behaviour were observed.

In conclusion, due to large inter-individual differences in exposure after oral dosing and formulation constraints limiting the top dose, it was not possible to determine a clear-cut MTD after oral dosing. The MTD after intravenous dosing of DU 127090 was 8 mg/kg. The kinetics of DU 127090 were roughly proportional to dose, the clearance was low and the bioavailability was variable, between 6.8 and 25%.