

**Halichondrin Analog E7389 Toxicology Summary**  
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National Cancer Institute

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Preclinical toxicology studies for E7389, a Halichondrin B analog (NSC-707389), were conducted in rats and dogs. Drug was administered in 5% ethanol in 0.9% sodium chloride as a slow i.v. bolus dose to rats or a one-hour i.v. infusion to dogs once a day on days 1, 5 and 9. In range-finding studies, single doses of 0.75 mg/kg (4.5 mg/m<sup>2</sup>) were lethal to rats and two doses of 0.075 mg/kg/day (1.5 mg/m<sup>2</sup>/day) were lethal to dogs. Bone marrow toxicity appeared to be dose limiting in both rats and dogs. Intestinal toxicity was also present in dogs. *In vitro* bone marrow assays did not demonstrate significant species differences between human, dog and mouse CFU<sub>GM</sub> cell sensitivity to NSC-707389.

In the IND-directed, GLP toxicity studies, doses of 0.08 mg/m<sup>2</sup>/day produced no toxicity in either dogs or rats, while doses of 0.6 or 0.8 mg/m<sup>2</sup>/day produced reversible bone marrow toxicity in both species. Other toxicities were present in lymphoid tissue, testes and muscle. All observed toxicities (except testicular toxicity) were reversible in both dogs and rats.

The recommended starting dose for the Phase I clinical trial is 0.12 mg/m<sup>2</sup>/day. Based on the *in vivo* data in dogs, the highest non-severely toxic dose was 0.8 mg/m<sup>2</sup>/day and therefore 1/6 this dose would be 0.13 mg/m<sup>2</sup>/day. The MTD in rats was between 1.2 - 1.5 mg/m<sup>2</sup>/day and <1/10 of this dose would be 0.12 mg/m<sup>2</sup>/day. Therefore, a starting dose of 0.12 mg/m<sup>2</sup>/day is predicted to be safe in both species.