### ABSTRACT

ANG1005 is an antimicrotubule agent that contains the proprietary sequence of amino acids responsible for receptor-mediated pinocytic transport across the blood brain barrier (BBB). This study was designed to evaluate the safety and pharmacokinetics of ANG1005 in nonclinical rodent studies and to evaluate the dose that would be tolerated in the clinical setting. ANG1005 was administered to both sexes (10M/10F per group) at different dose levels across the BBB. The highest single IV dose was 400 mg/m² and the maximum tolerated single IV dose was 75 mg/m². The results demonstrated that ANG1005 is well tolerated and has an excellent pharmacokinetic profile across the BBB. The NOAEL in this study was 25 mg/m², and the maximum tolerated dose was 400 mg/m².

### METHODS

In vivo xenograft studies were conducted in mice and rats. Toxicology studies of ANG1005 were conducted in Sprague-Dawley rats and Beagle dogs (90-day studies). Safety Pharmacology: ANG1005 was administered in single IV doses to rats (10M/10F per group) at various dose levels. Effects on one blood cell (and related parameters) and plasma cautions were observed at dose levels 250 mg/m². Chromatographic findings in organs were observed at the plasma of 193 mg/m² and for the testes at 50 mg/m². ANG1005 administered in single IV dose of 400 mg/m² (375 mg/m²) to rats and 50 mg/m² to mice resulted in a peak serum concentration (Cmax) of 37.7 ± 10.4 µg/mL and 32 µg/mL, respectively. The general pharmacology studies included standard endpoints such as toxicity, clinical observations, transcytosis (TK), clinical pathology, body weight and food consumption parameters, splenic and hepatic (repeated-dose), clinical pathology, necropsy, organ weights, macroscopic, and microscopic (repeated-dose) observations.

### RESULTS

The general pharmacology studies included standard endpoints such as toxicity, clinical observations, transcytosis (TK), clinical pathology, body weight and food consumption parameters, splenic and hepatic (repeated-dose), clinical pathology, necropsy, organ weights, macroscopic, and microscopic (repeated-dose) observations. The NOAEL in this study was 25 mg/m² and the maximum tolerated single IV dose was 75 mg/m². The results demonstrated that ANG1005 is well tolerated and has an excellent pharmacokinetic profile across the BBB. The NOAEL in this study was 25 mg/m², and the maximum tolerated single IV dose was 400 mg/m². The general pharmacology studies included standard endpoints such as toxicity, clinical observations, transcytosis (TK), clinical pathology, body weight and food consumption parameters, splenic and hepatic (repeated-dose), clinical pathology, necropsy, organ weights, macroscopic, and microscopic (repeated-dose) observations.

### CONCLUSIONS

The preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized. Preclinical pharmacology, pharmacokinetics, and toxicokinetics of ANG1005 have been well characterized.