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Toxicology studies and results for determining safety of a novel anti-neutropenic factor–ANF-Rho™

ANF-Rho is a novel polyethylene glycol-modified granulocyte colony stimulating factor that has biophysical and biological properties that produce a distinct pharmacokinetic and pharmacodynamic profile as compared to pegfilgrastim (Neulasta®). ANF-Rho was evaluated in a series of studies to assess the pharmacokinetics, pharmacodynamics and toxicity in the rat and primate as compared to Neulasta®. Rats were made neutropenic by injection of cyclophosphamide to determine pharmacokinetic and pharmacodynamics effects of ANF-Rho. Both single and repeat dose toxicity studies administered for up to 5 once weekly doses. Endpoints for toxicological studies included clinical observations, body weights, food consumption, ophthalmic exams, neurotoxicity, clinical pathology, immunogenicity, necropsy and histopathology. Pharmacokinetics were determined following subcutaneous (SC) or intravenous (IV) administration of either 50, 75 or 100 µg/kg in Sprague Dawley rats and 10 or 100 µg/kg in cynomolgous primates. Neulasta was dosed at 100 µg/kg. Analysis of variance (ANOVA) with a Dunnet's post-hoc test was performed to demonstrate significant differences ($p<0.05$) between treatment groups. The half-life of ANF-Rho SC in the rat ranged from 17.99 to 18.05 hours for the 3 doses as compared to 5.63 for the Neulasta group. Pharmacodynamic analysis of the area under the curve (AUC) kinetic analysis showed the absolute neutrophil count (ANC) of ANF-Rho was equivalent at 4X lower dosage (25 vs. 100 ug/kg) and yielded significantly higher ANC than Neulasta when administered at equivalent 100 µg/kg dosage. ANF-Rho yielded a 4-6 fold increased in de novo neutrophil (CD34+) counts. No observed toxicologically or significant findings for any endpoint in rats receiving a single dose of 100, 1000, 3000, 10000 or 25000 µg/kg of ANF-Rho in the rat for maximum tolerated dose (MTD) study. No clearly adverse effects were seen following treatment with ANF-Rho in rats over a 28 days treatment period with a calculated NOAEL of 1000 µg/kg. Primates were dosed with 250 or 750 µg/kg. The NOAEL was to be determined to be greater than 750 µg/kg. Rat neutropenia dosage model results found that the blood pharmacodynamics parameters of ANF-Rho were significantly superior to Neulasta. Both PK and PD data demonstrate relatively predictable systemic exposures and activity following SC or IV dose levels in both rat and primate. The toxicology studies were unremarkable and sufficient to support advancement of ANF-Rho into Phase I clinical studies.

Biography

Hemant Misra received his PhD from Lucknow University in Medicinal and Pharmaceutical Chemistry and has published over 65 articles and a patent. He is VP Clinical Development for Prolong Pharmaceuticals. He has over 30 years of biopharmaceutical development, global clinical study management and corporate development experience. He has managed drug development, CGMP manufacturing, CTM, quality systems and multiple global clinical trials.

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