

PRELIMINARY RESULTS FROM A LONG-TERM REPEAT DOSE TOXICITY AND TOXICOKINETIC STUDY OF ANF-RHO, A NOVEL ANTI-NEUTROPENIC FACTOR

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Background

ANF-Rho is a novel polyethylene glycol-modified granulocyte colony stimulating factor that has biophysical and biological properties that produce a prolonged pharmacokinetic and pharmacodynamic profile as compared to pegfilgrastim (Neulasta®). As such, it has potential applications in chemotherapy induced neutropenia and chronic idiopathic neutropenia. These disorders require prolonged administration of G-CSF agents to treat neutropenia. Therefore, long term toxicology, genotoxicity and Juvenile studies were conducted with ANF-Rho.

Aim

A 13-week study was conducted in Sprague Dawley rats and cynomolgus primates to assess various safety and pharmacokinetics of ANF-Rho as compared to Neulasta® (pegfilgrastim).

Methods

The study design used 288 rats, divided into 5 dosage groups: control, 100, 300, 1000 (high) and 1000 (positive) µg/kg. A total of 58 monkeys were also divided into 5 dosage groups: control, 75, 250, 750 (high dose) and 750 (positive) µg/kg of ANF-Rho. Doses were administered by weekly subcutaneous injections on Day 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85 and 92 at a dose volume of 5 mL/kg. Genotoxicity assessments were evaluated using *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay, rodent blood micronucleus assay and chromosomal aberration assay. Toxicology assessment included clinical observations, body weight change, food consumption, ophthalmic examination, function observational battery (motor activity, behavioral changes, coordination and sensory/motor reflex response), organ weight, bioanalytical and toxicokinetic analysis, immunogenicity, gross necropsy and histopathology.

Results

No observed clinical signs seemed to be related to ANF-Rho administration. There were no related effects in body weight changes or food consumption. Observed ophthalmic effects were considered procedural related due to low incidence. No biologically meaningful findings were noted during the function observational battery assessment. Preliminary analysis showed a dose related increase in spleen weight in rats and a dose dependent decrease in kidney weight in primates.

Genotoxicity studies found no signs of mutagenicity, clastogenicity or cytotoxicity.

Conclusion

The results from this preliminary toxicology studies are unremarkable and consistent with those of an earlier 28-day study. Results from the 28-day rat neutropenia dosage model found that the

blood pharmacodynamics parameters of ANF-Rho were significantly superior to PEG-filgrastim. Both PK and PD data demonstrate relatively predictable systemic exposures and activity following SC or IV dose levels in both rat and primate. It is anticipated that this long terms 13-week study will provide evidence of safety sufficient to support advancement of ANF-Rho into Phase II clinical studies in chemotherapy-induced neutropenia and chronic idiopathic neutropenia in Europe, USA and India.

Key words: neutropenia, ANF-Rho, toxicology

Category: 29. Infectious diseases, supportive care

Goal of abstract: to further provide evidence of superiority to Neulasta and safety data. To keep ANF rho in public space in EU

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