A Phase I study of a novel anti-neutrophilic agent, ANF-RHO™: Safety, Pharmacokinetics and Pharmacodynamics

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Background:
ANF-Rho is a novel anti-neutrophilic agent that exhibited greater activity than Neulasta (pegfilgrastim) in preclinical studies. A Phase I study was conducted to determine its safety profile, pharmacokinetics, pharmacodynamics and the potential to limit dose-dependent side effects such as bone pain.

Methods:
A double-blind, randomized Phase I study in 76 healthy subjects. Subjects received a single dose of ANF-RHO (range: 5-50 µg/kg), placebo, or Neulasta (6 mg). Outcome measures included safety/tolerability, pharmacokinetic and pharmacodynamic effects of peripheral absolute neutrophil count (ANC) and CD34+ progenitor cells.

Results:
ANF-RHO was well to moderately-well tolerated up to a dose level of 50 µg/kg and appeared to be better tolerated than Neulasta. Mean bone pain scores were lower in the 5 to 30 µg/kg ANF-RHO groups compared to the Neulasta. There were no clinically significant findings for ANF-RHO with respect to clinical and physical assessments. The \( t_{1/2} \) ranged between 38.5 and 51 hours (hr) for ANF-RHO and 28hr for Neulasta. The \( t_{\text{max}} \) of ANF-RHO is 36 hr as compared to 16hr for Neulasta. A maximum mean ANC (8.6 x 10^9/L) (5 µg/kg) to 45x10^9/L (50 µg/kg) was reached between Day 6 and Day 10 as compared to Day 4 for Neulasta (21.5x10^9/L). A maximum number of CD34+ cells (10.74 (5 µg/kg) to 71.4 (50 µg/kg) cells/µL) was reached on Day 7 as compared to Day 6 for Neulasta (66.98 cells/µL).

Pharmacokinetics & Pharmacodynamics. Blood plasma samples were collected at indicated time points and drug levels were determined by G-CSF ELISA (top) and absolute neutrophil counts and CD34+ cells were determined by flow cytometry (bottom). Mean (± standard error) drug and ANC values for each cohort were expressed as a function of time post administration (left). Time to peak and area under the curve was calculated for both drug and ANC (right) and data are expressed as mean and 95% confidence intervals. Astersisks indicated significant differences between indicated groups by ANOVA and Dunnet’s multiple comparison tests (p<0.05).

Pharmacokinetics vs Pharmacodynamics

ANF-Rho 10 vs. NLST 100

Summary:
In healthy volunteers, ANF-RHO was administered without significant adverse effects. ANF-RHO was better (5 to 30 µg/kg) or equally well (50 µg/kg) tolerated and had lower mean bone pain scores as compared to Neulasta. ANF-RHO achieved CD34+ and ANC numbers at significantly lower doses and had a significantly longer circulating half-life than Neulasta. These results suggest that ANF-RHO can be provided less frequently at a lower dose and with fewer side effects. Phase 2 trials are planned in febrile neutropenia.

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The Conflict of Interest disclosure forms for above authors have been satisfied