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

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Background:

ANF-Rho is a novel anti-neutropenic 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 1 study in 76 healthy subjects. Subjects received a single dose of ANF-RHO (range: 5-50 ug/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_{max} of ANF-RHO is 36 hr as compared to 16hr for Neulasta. A maximum mean ANC (8.6 x10^9/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 5 for Neulasta (66.98 cells/µL).

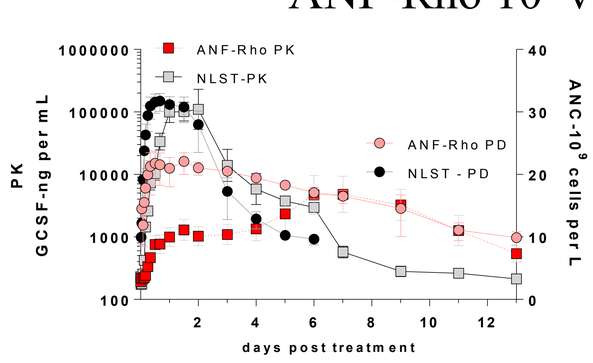
Cohort	Placebo	ANF-Rho 5 µg/kg	ANF-Rho 10 µg/kg	ANF-Rho 15 µg/kg	ANF-Rho 20LC µg/kg	ANF-Rho 20 HC µg/kg	ANF-Rho 30 µg/kg	ANF-Rho 50 µg/kg	Neulasta® 100 µg/kg	Total
No. of patients enrolled	13	3	8	8	8	8	8	8	12	76
No. of adverse events	E (N) %	E (N) %	E (N) %	E (N) %	E (N) %	E (N) %	E (N) %	E (N) %	E (N) %	E (N) %
ADVERSE EVENTS (total subjects)	20 (11) 85 %	10 (3) 100 %	15 (6) 75 %	44 (8) 100 %	13 (7) 88 %	27 (6) 75 %	31 (7) 88 %	50 (8) 100 %	75 (12) 100 %	285 (68) 89 %
Back pain	2 (2) 15 %	2 (2) 67 %	2 (2) 25 %	12 (7) 88 %	2 (1) 13 %	6 (4) 50 %	5 (4) 50 %	7 (7) 88 %	22 (12) 100 %	60 (41) 54 %
Headache	4 (4) 31 %		4 (4) 50 %	5 (4) 50 %	1 (1) 13 %	8 (4) 50 %	5 (3) 38 %	5 (4) 50 %	17 (9) 75 %	49 (33) 43 %
Injection site pain	1 (1) 8 %	2 (2) 67 %	1 (1) 13 %	4 (4) 50 %	7 (7) 88%	2 (2) 25 %	2 (2) 25 %	3 (3) 38 %	4 (4) 33 %	26 (26) 34 %
Pain in extremity	1 (1) 8 %	1 (1) 33 %	2 (2) 25 %	5 (3) 38 %		2 (1) 13 %	4 (4) 50 %	6 (3) 38 %	6 (6) 50 %	27 (21) 28 %
Arthralgia		3 (2) 67 %		5 (3) 38 %		1 (1) 13 %	5 (3) 38 %	9 (5) 63 %	2 (2) 17 %	25 (16) 21 %
Myalgia	3 (1) 8 %		2 (2) 25 %	5 (4) 50 %				4 (3) 38 %	6 (2) 17 %	20 (12) 16 %
Bone pain				2 (2) 25 %	1 (1) 13 %	1 (1) 13 %	3 (3) 38 %	2 (2) 25 %	2 (2) 17 %	11 (11) 14 %
Musculoskeletal pain	1 (1) 8%		1 (1) 13 %			1 (1) 13 %	2 (1) 13 %	2 (2) 25 %	4 (3) 25 %	11 (9) 12 %

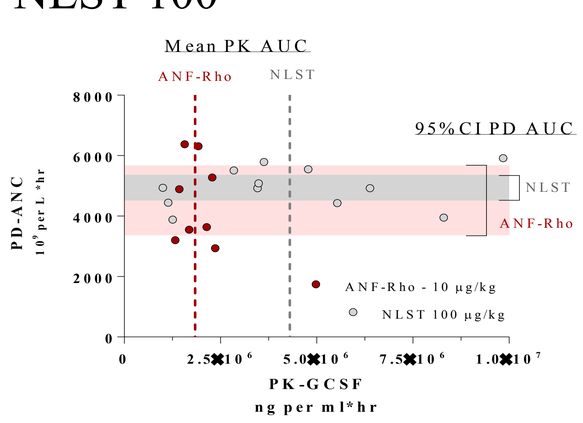
e: number of events — n: number of patients experiencing event — %: No of patients experiencing events/total enrolled patients

Pharmacokinetics & Pharmacodynamcis. 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. Asterisks indicated significant differences between indicated groups by ANOVA and Dunnet's multiple comparison tests ($p<0.05$). PK vs PD. Mean (±standard error) GCSF and ANC levels for 10µg per kg ANF-Rho and 100µg per kg NLST are expressed as a function of time post administration (1st panel, right). Mean PD-ANC-AUC are shown as a function of PK-AUC for each drug (2nd panel, right)

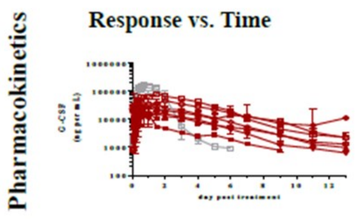
Pharmacokinetics vs Pharmacodynamics

ANF-Rho 10 vs. NLST 100

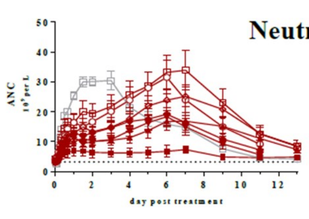




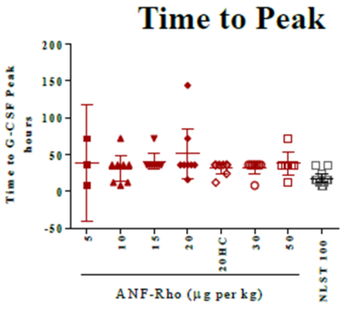
Pharmacokinetics



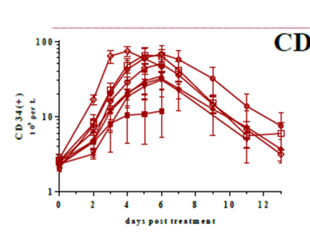
Pharmacodynamics



Time to Peak



CD34+



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.

For More Info Please Contact: www.prolongpharma.com

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