

Abstract Submission

29. Non-malignant hematopoietic disorders

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DEVELOPMENT OF A NOVEL ANTI-NEUTROPENIC FACTOR CLINICAL CANDIDATE FOR HEMATOPOIESIS DEFICIENCIES

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Background: A novel anti-Neutropenic factor (ANF) consisting of a pegylated granulocyte colony-stimulating factor with improved pharmacokinetic/pharmacodynamics (PK/PD) properties was developed through a combinatorial PEGylation approach to create a clinical candidate ideally suited for treating conditions of severe neutropenia.

Aims: Analyze ANF and marketed therapeutic(s) in parallel to identify unique properties of ANF thereby expediting selection of a superior clinical candidate for specific human clinical trials.

Methods: A series of *in vivo* and *in vitro* pre-clinical studies were conducted in comparison to marketed forms of filgrastim (F) or PEG-filgrastim (PF). Following pre-requisite and unremarkable GLP-toxicology studies, a phase 1 clinical study was conducted in healthy volunteers (signed, consenting) to assess safety and tolerability of ANF as well as the PK and PD. Subcutaneous, single dose treatment of ANF (or PF) with ascending dose were evaluated in a double-blind study that included PK, neutrophil and CD34+ analytical parameters to determine if pre-clinical ANF findings could also be observed within healthy human subjects. ANF was evaluated in a dose-escalation (5 – 50µg/Kg) study with each cohort including randomized treatment and controls. PF was administered at the single 6mg dosage (80 – 100µg/Kg), single-use syringe as a standard of care supplied by manufacturer.

Results: Rat neutropenia model dosage study results indicated the blood PD parameters of ANF were significantly superior to both F and marketed PF. Area under the curve (AUC) kinetic analysis showed the absolute neutrophil count (ANC) of ANF was equivalent at 4X lower dosage (25 vs. 100µg/Kg) and yielded significantly higher ANC than marketed PF when administered at equivalent 100µg/Kg dosage. A follow-on *in vitro* human neutrophil maturation study was conducted to evaluate CD34+ stem cell maturation effects of ANF compared to PF. Similar to rat study findings, ANF yielded a 4-6 fold increase in *de novo* neutrophil (CD66+) counts. Phase I clinical interim safety results were unremarkable, with no severe adverse events in any cohorts (ANF or PF). The ANF PK/PD parameters within the phase 1 study were similar to pre-clinical findings. PD results (ANC and CD34+) were markedly prolonged in the ANF treatment groups even at the lowest cohort. Mean ANC counts for all ANF cohorts showed an ANC C_{max} between 162 - 177hrs in contrast to PF that reached max concentrations at 52hrs. AUC analysis showed that ANF at 10µg/Kg was equivalent to PF at 100 µg/Kg (standard of care) demonstrating a >8-fold potency effect over PF in healthy volunteers. Peripheral blood CD34+ counts also yielded similar results; average ANF C_{max} was prolonged by 2 days over PF (7 vs. 5 days). PK results were prolonged with ANF in both the pre-clinical rat and phase-1 human study that correlated with the PD results.

Summary/Conclusion: Collectively these data showed that ANF, a novel anti-neutropenic factor, has unique, prolonged PK/PD attributes as compared to PF, and these qualities may provide an improved clinical benefit in further clinical studies. Phase 2 efficacy studies in severe neutropenia are planned to further understand the potential clinical applications and benefits of ANF.

Keywords: Growth factor, Hematopoiesis, Immunodeficiency, Neutropenia