Quantitative Characterization of the Effects of Acute Radiation (AR) and Treatment with Filgrastim (Neupogen) on Absolute Neutrophil Counts (ANC) and Overall Survival (OS) in Non-Human Primates (NHP)

John Harrold¹, Per Olsson Gisleskog², Isabelle Delor², Philippe Jacqmin², Juan Jose Perez-Ruixo³, Sameer Doshi¹, Bing-Bing Yang¹, Andrew Chow¹, Murad Melhem¹*

¹Amgen Inc.; ²SGS Exprimo NV; ³Janssen

Objectives: Develop a population model quantifying the myelosuppressive effect of AR exposure on ANC time-course in NHPs, and establishing the relationship between ANC time-course and OS in NHPs following AR exposure, in the presence or absence of treatment with filgrastim a recombinant granulocyte colony-stimulating factor.

Methods: Modeling was performed using data in adult rhesus macaques (weight 4-6.5kg) that were exposed to 750cGy of whole body irradiation [1]. NHPs were either given placebo or subcutaneous 10μg/kg of filgrastim daily beginning one day after irradiation. ANC levels were measured at baseline and every 1-2days for 60days after irradiation. The time to death or last observation was collected for OS analysis. Population pharmacodynamic modeling of ANC response and OS following irradiation with or without filgrastim treatment was performed.

Results: The granulopoiesis model consisted of three components: 1) a catenary model of synthesis, proliferation and maturation of neutrophils from stem cells; 2) K-PD model of radiation injury (duration 10days) [2]; and 3) a pharmacodynamics-mediated drug disposition model of filgrastim. Receptor occupancy was used to drive efficacy of both stem cell production (STIM=4.5) and maturation (STIM=2.2). OS was described using a survival model with time varying hazard, relating log hazard to a Box-Cox transformation of ANC, delayed through an effect compartment. The ANC timecourse (neutropenia depth and duration) was found to explain 76% (95% CI:41-97%) of the survival benefit from filgrastim treatment (OS=79.2%) over placebo (OS=40.9%)

Conclusions: The granulopoiesis model adequately captured the ANC time-course after irradiation with and without filgrastim treatment. The OS model confirmed that NHP OS depends on the duration and depth of neutropenia and that ANC is a valid surrogate to predict OS in NHPs receiving irradiation.

References: