Non-Homogeneous Poisson Process (NHPP) Analysis of Time to First Flare for Canakinumab (CAN) Dose Justification in SJIA

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**Objectives:** To provide dose justification argument for sBLA submission by: 1) exploring the relationship between SJIA flare reduction and CAN exposure with consideration of patient baseline characteristics; 2) predicting the effects of CAN dosing regimens at 1 to 6 mg/kg every 4 weeks on SJIA flare rates compared with placebo.

**Methods:** While traditional Cox regression model assumes proportional hazard, a model-based NHPP analysis was performed that naturally linked the time-changing plasma concentration of CAN to the time-changing flare hazard. The model considered treatments and multiple covariates, including baseline steroid dose, heterogeneity of the population with respect to disease severity, and declining CAN concentrations over time due to washout in patients on PBO who received CAN previously. The model was also used to explore the dose-response relationship between flare hazard and CAN dose based on 1000 simulated trials, each with 700 patients randomized to 1 of 7 treatment arms: PBO and 1 to 6mg/kg (all administered every 4 weeks) of CAN.

**Results:** Based on the simulations, CAN at 4mg/kg every 4 weeks reduces the probability of flare (90% CI) over PBO by 39% (28%, 49%) over 12 months, consistent with the clinical data observed. The predicted changes in flare probability are +13%, +6%, +2%, -2%, and -3% for the 1 to 6 mg/kg every 4 weeks doses respectively, compared to 4 mg/kg. These results support 4 mg/kg every 4 weeks as the appropriate dose for preventing SJIA flare events. Doses greater than 4mg/kg provide only marginal gain in flare reduction, while doses less than 4mg/kg relatively increase the risk of experiencing a flare.

**Conclusions:** A NHPP-based modeling approach was adopted and able to re-produce the observed Kaplan-Meier curves with fidelity. Inferences from the NHPP model include: 1) CAN can fully suppress flare hazard with high statistical significance; 2) CAN suppresses flare hazard in a concentration dependent manner; 3) a CAN dose-flare rate relationship sufficiently justifies the recommended CAN dose in SJIA.