Development of Time to Event Models for Exposure-Response Analysis of Peginterferon Beta-1a in Subjects with Relapsing Remitting Multiple Sclerosis

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Objectives: To compare semi-parametric models and parametric models for peginterferon beta-1a (PEG-IFN) exposure and time to relapse, and explore covariates that impacted time to relapse.

Methods: PK and relapse data were obtained from a double-blind placebo-controlled Phase 3 study in RRMS patients (n=1512), in which 125 mcg subcutaneous PEG-IFN every 2 (Q2W) or 4 (Q4W) weeks reduced ARR (primary endpoint) significantly [1]. Using post-hoc PK parameters derived from a population PK model developed using NONMEM [2], PEG-IFN exposure was represented by monthly cumulative AUC for each subject. The data was modelled using semi-parametric approach (cox proportional model) and parametric approach, including exponential, Weibull, Gaussian, logistic, loglogistic, lognormal models. The survival analysis was carried out in R [3].

Results: Based on Cox proportional hazard analysis, the AUC showed statistically significant impact on time to relapse (p<0.001), with increased exposure reducing hazard to relapse. Additionally, the following covariates were also significant (p<0.001): baseline relapse rate in the past 3 years, baseline Gadolinium enhanced lesion count, and baseline relapse rate in the past 1 year. With regards to parametric models, loglogistic model provided the best fit based on its log-likelihood values using placebo data. The covariates identified as significant in the parametric models were consistent with those identified in Cox proportional model, with baseline relapse rate in the past 3 years as the most significant covariate. The significant covariates were not sensitive to model selected.

Conclusions: Exposure-response models were developed for PEG-IFN. Greater exposure was associated with lower hazard to relapse. Other significant covariates included baseline relapse rate in the past 3 years, baseline Gadolinium enhanced lesion count, and baseline relapse rate in the past 1 year.

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