Nonlinear Mixed Effects Modeling of Disease Progression of Placebo Subjects from the Irbesartan Diabetic Nephropathy Trial

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Objectives: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease, and a large heterogeneity is present in the patient population and in the rates of disease progression. The objective of this study was to develop a model to characterize the estimated glomerular filtration rate (eGFR) decline profile in DN patients, as well as to identify and estimate the contribution of baseline risk factors to the variability in rate of eGFR decline.

Methods: Longitudinal eGFR data from the placebo arm of the IDNT trial (n=562) were used for analysis. Initial graphical analysis was performed to reveal the general profile of eGFR decline across the population strata. Base model building tested linear and asymptotic models, as well as combinations of between and within subject variability distribution models. The full model was constructed using univariate screening (p<0.05). The nonlinear mixed effect modeling approach was implemented using NONMEM and confidence intervals of parameter estimates were determined using bootstrapping.

Results: Repeated eGFR measurements of up to 48 months were adequately described by an exponential decline model, parameterized as the estimated baseline eGFR and rate constant of decline, with a lognormal distribution on the estimated baseline eGFR and Box-Cox transformation on the rate constant of decline. Within subject variability was described by an additive residual error model. Relative standard errors of the base model components were less than 20%. Covariates included on the rate constant of decline in the full model are baseline urinary albumin-to-creatinine ratio, eGFR, age, hemoglobin, serum calcium, serum sodium, serum phosphorus, total cholesterol, race, and the number of anti-hypertensive drugs taken during the study.

Conclusions: Longitudinal eGFR profiles in DN patients were best described by an exponential decline model with baseline risk factors on the rate constant. The results of this disease progression modeling are currently being utilized as part of a model-based tool to assist with designing trials in progressive chronic kidney diseases.