Clinical Trial Design Based on Disease Progression and Pharmacological Effects in the Irbesartan Diabetic Nephropathy Trial (IDNT)

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Objectives: To characterize the type of drug action of amlodipine and irbesartan in diabetic nephropathy (DN) patients using a previously developed disease progression model\(^1\), and to utilize the model with the added treatment effects to conduct clinical trial simulations, to investigate study design options, and to perform a power analysis.

Methods: Immediate and delayed types of symptomatic and disease-modifying forms of drug actions were investigated to account for the time component of the drug effect in the two active treatment arms (amlodipine or irbesartan) of the IDNT. The updated model, that accounted for correlations between patient-specific characteristics in the trial, and incorporating previously identified statistically significant covariates for disease progression, was used for clinical trial simulation. Sample size power analysis for a hypothetical trial design was determined using Monte-Carlo mapped power method\(^2\), and the results were compared to a power calculation using a t-test.

Results: The model estimated an irbesartan effect of 17.4% less decline in glomerular filtration rate (eGFR) compared to placebo, whereas the effect of amlodipine was not statistically significant. Despite fitting repeated eGFR measurements for up to 48 months, statistical significance could not be differentiated between symptomatic and disease-modifying drug actions, and the final irbesartan model was determined to be immediate disease-modifying based on literature information\(^3\). Clinical trial sample size from the power analysis was greatly reduced (from 1800 to 1100 at 80% power) using the disease progression model-based method.

Conclusions: Longitudinal eGFR profiles in DN patients undergoing irbesartan treatment were best described by an immediate disease-modifying model. The results of this disease progression modeling can be utilized as part of a model-based tool to assist with designing trials in progressive chronic kidney diseases.

Reference:
1. Chan P et al, poster session presented at American Conference on Pharmacometrics; 2015 Oct 4-7; Crystal City, VA.