Population Pharmacokinetic Analysis for Naloxegol in Healthy Subjects and Patients with Opioid-Induced Constipation
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Purpose
To develop a population pharmacokinetic (PK) model to characterize the PK of naloxegol and investigate the effects of covariates on various PK parameters of naloxegol following oral administration of naloxegol to patients with opioid-induced constipation (OIC).

Methods
The population PK analysis dataset consisted of 11 Phase 1 studies in healthy subjects or patients, a 21-subject substudy from one Phase 2b study in patients with OIC and two Phase 3 studies in patients with OIC. The analysis was performed using NONMEM (Version VI or higher) and S-Plus /R statistical software. The performance of the model was evaluated using a battery of diagnostic plots and by posterior predictive check.

Results
A 2-compartment disposition population PK model adequately described the time course of plasma naloxegol concentration following oral administration in patients. Two sites of absorption were included in the model with one site being first order absorption and the second more complex absorption with a transit compartment. Of all the covariates examined during the covariate analysis, concomitant administration of p-glycoprotein (PGP) inducers (PGPD) or inhibitors (PGPH) and race-African-American was identified to have a statistically significant effect on naloxegol apparent clearance. The covariates age, gender, race-Asian, formulation, concomitant administration of PGPD or PGPH, baseline creatinine clearance (CrCL), and baseline opioid dose (BODD) had significant effects on V3/F. Concomitant administration of naloxegol with strong CYP3A4 inhibitors increased naloxegol systemic exposure (AUC and Cmax) by 8- to 9-fold. Population parameters estimates for apparent clearance (CL/F) and apparent volume of distribution of the peripheral compartment (V3/F) were 115 L/h and 160 L, respectively.

Conclusion
The Population PK model sufficiently described phase 1, 2 and 3 data. The model provided Naloxegol concentrations which were further used in modeling and simulation of exposure-response analysis.