**METHODS**

**Study Data**

- Approximately 100 Phase 1 subjects provided nearly 2500 concentrations and nearly 700 Phase 2 subjects provided over 4000 concentrations.
- Number of samples/subject: 7 to 33 in Phase 1 studies, 4 to 7 in Phase 2 studies.
- In Phase 2 studies, subjects were recruited without regard to 20% genotypes.
- Of those classified: Poor Metabolizers (PM) (8%), Intermediate Metabolizers (IM) (32%), Extensive Metabolizers (EM) (55%), Ultra-Extensive Metabolizers (UIM) (5%).
- Genotype data was unavailable for 100 Phase 2 subjects (~12% of all subjects).

**Modeling Methods**

- NONMEM (V5.2) was used to develop a structural model describing and quantifying the mean pharmacokinetic (PK) characteristics, as well as interindividual variability and residual variability in PK.
- Individual variability in parameters was modeled using an exponential error model.
- Residual variability was modeled as a constant coefficient of variation.
- The first-order conditional estimation (FOCE) with interaction method was used at all stages of the model development process.
- Assessment of goodness of fit for the core and mixture models was based on:
  - Estimation outcome (convergence) and convergence step outcome.
  - Agreement in scatterplots of population predictions versus observed concentrations.
  - Agreement in scatterplots of individual predictions versus observed concentrations.
  - Lack of trends in scatterplots of weighted residuals versus population and individual predicted observations.
- A core base structural model was fitted using data only from subjects with known genotype.
- Mixture modeling
  - Four population models were defined: Specled genotypes were assigned to Population 1, and their genotypes were not estimated.
  - The other 4 populations were used to assign the subjects with unknown genotypes to 1 of the 4 genotype classification groups (that is, PM, IM, EM, UIM).
  - It was assumed that genotype data was missing completely at random (independently of any observed or unobserved variables).
- Details on parameterization and coding can be seen in Figure 1.

**RESULTS**

- A 2-compartment model with first-order absorption was found to best fit the classified data. Goodness-of-fit plots for the model without genotype are shown in Figure 2.
- Elimination rate was dependent on genotype.
- Parameter estimates for Core Base Model fitted to the subjects with known genotype are listed in Table 1 and goodness-of-fit plots are shown in Figure 3.
- Parameter estimates for the ‘Base Mixture Model’ fitted to all data are listed in Table 1 and goodness-of-fit plots for genotype-unknown subjects are shown in Figure 4.
- Parameter estimates for “Core Base Model” and “Base Mixture Model” were similar, indicating that the unknown genotypes were classified appropriately.
- The proportion of unknowns belonging to each genotype was not estimated with good precision. However, this was not required to adequately predict the concentration profiles for most subjects.

**CONCLUSIONS**

- Genotypic metabolizer status is an important determinant of individual subject plasma concentrations for Drug X.
- Using the subjects with known genotypes to anchor the PK parameter estimates provides a means of classifying subjects with unknown genotypes and of estimating their PK parameters.
- As indicated by the similar parameter estimates and the concomitance of observed and predicted concentrations, the classification of the unknown subjects was relatively unbiased and reasonable estimates of the concentrations for these subjects were obtained.
- Parameters associated with the proportion of subjects in each subpopulation in each subpopulation could not be precisely estimated. This may be a reflection of a small number of unknown subjects (~100) and the rarerness of some of the genotypes.
- Mixture models have been used previously to explain interindividual heterogeneity as arising from the mixing of unknown subpopulations. This case study illustrates the novel and successful use of a mixture model to obtain predicted drug concentrations for a subset of subjects with a missing key categorical covariate.