Random individual variability in PK parameters was described with an exponential distribution and variance-covariance matrix estimated from the adult data. Random residual variability was described as a combination additive and proportional error model, as estimated from the adult data.

An attempt was made to incorporate known physiologic relationships into the covariate-parameter models. For example, the change in physiologic parameters as a function of body size was both theoretically and empirically described by an allometric model (Equation 1-7).

For PED subjects less than 1 year of age, an age-dependent increase in the typical clearance (TFCL) was assumed, according to the time-dependent maturational relationship previously reported for morphine glucuronidation (Equation 1). In this model, \( \text{CL}_{\text{PED}} \) is a power parameter to be used to simulate or estimate age-dependent effects on clearance less than 1 year of age, and \( \text{AGE}_{\text{PED}} \) is 1 year.

RESULTS

Predicative performance of the adult model was good, as demonstrated by the predicative check results (Fig. 2). The performances of the trial design and parameter estimation conditions are displayed in Table 2. When the PED data simulated under the Nominal design were analyzed, parameter bias was acceptable for CL/F and V/F, but bias was quite large for other model parameters. Precision was poor across the list of estimated parameters (Table 2, left). When the model was anchored with HMI PK data from 12 adult subjects, estimation performance was dramatically improved (Table 2, right), and all fixed effect parameter estimates were within an acceptable range of bias and precision. Inclusion of the adult data did not bias the estimation of PED parameters and resulted in a good fit to the PED data (Fig 3).

Predictive Check

Five hundred Monte Carlo simulation replicates of the original data set were generated using the final adult population PK model. Distributions of a characteristic of the simulated data were compared with the distribution of the same characteristic in the observed HMP data set, using exploratory graphics (quantile-quantile plots and histograms). The characteristic of interest was the average concentration across all data points within each individual (\( C_{\text{avg}} \)).

NOMINAL TRIAL SIMULATION DESIGN

Trial design options were structured around a basic design, while variations due to the number of subjects, number of samples per subject, duration of therapy, and use of rescue doses were explored (Table 1). The most realistic (Nominal) design was characterized by a multiplicity, balanced design across five age groups: 1 < 1 month, 1-12 months, 1-12 years - 4 years, V = 1-12 - 16 years. This design was framed within the context of expected in-patient hospital stays for PED patients requiring opioid analgesics. The proposed study size was 60 PED subjects, with 12 individuals in each age group. For the four youngest age groups, doses were assigned according to expected changes in clearance across the age-weight range (Equation 1), with the goal of achieving exposures that were approximately equivalent to the exposure resulting from HMP doses of 12 mg/day in a 70 kg adult. Doses were administered every 6 hours as an IR oral solution. The oldest age group was dosed with a fixed 8 mg CR oral dose, once daily. Doses used in the trial simulations were based on a dosing rule defined in Equation 1. Rescue doses equal to half of the starting dose were allowed as an IR formulation every 2 hours, as needed.

The initial design, each subject could contribute up to 6 plasma samples for PK analysis over a three-day period. PK sampling times were defined by an initial random-block strategy, followed by trough samples, with the following time points (post first dose): 0.5-1.75, 3.5-7.5, 4.5-8.5, 9.5-12.5, 13.5-17.5, 24, 48, 72 hours. Subjects in the eldest age group were assigned a slightly different sampling scheme: 1.3-7, 4.25-7.5, 8.25-11.3, 23.23-29, 47.5-47.9, and 50-60 hours. Dose was randomly assigned to each subject with an equal probability of 24, 48, or 72 hours.

Each of the PED trial simulation replicates was analyzed in a separate estimation step, given the scaled adult model. Two estimation conditions were explored. The first condition incorporated only the data from the 60 PED subjects, while a second estimation condition augmented the PED data set with full-population PK data from 12 adult subjects.

Population parameter precision and bias were calculated based on the discrepancy between the resulting PK parameter estimates and the "true" simulation parameters. Bias was calculated as the Mean Percent Prediction Error (MPPE), and precision was calculated as the Mean Percent Absolute Error (MPAE).

EXPECTED HM PK IN PED PATIENTS

The population model with allometric scaling was used to project the plasma concentration-time profile for one-month-old children given a certain dosing regimen (0.09 mg q 6 h). As illustrated in Figure 4, the predicted range of concentrations is consistent with safe and effective exposure ranges in adults. If the assumption is made that clearance of HM is affected by maturation of UGT enzymes, higher exposures would be expected (Figure 4, right).

DISCUSSION & CONCLUSIONS

• Results for simulated trial design scenarios indicated acceptable estimation performance when the PED data set was augmented with minimal adult data. Bias was within +/-6% and precision was less than 20% for all fixed effect parameters.

• In particular, the parameters describing typical clearance and age-dependent maturation in children less than 1 year old, were very well estimated.

• Given these results, the proposed Nominal design is likely to provide sufficient information for the estimation of PK parameters in PED patients and it should lead to the definition of a robust dosing role.

• The trial simulation results also indicated that given the proposed doses, the PK profile and projected variability are consistent with safe and effective exposure ranges in adults.

REFERENCES