PK analyses were performed using NONMEM®, version 5.1.1 using the first-order conditional estimation method (FOCE) with interaction. For each analysis, the minimum value of the objective function (OFV) was reported.

The SD and MD data were always fit separately to avoid any biases that may have resulted from trying to fit a model to all data combined. The following evidence supported this approach:

- substantial differences for several of the model-estimated parameters (with the exception of CL and Vc);
- reverse superpositioning demonstrated that the MD model consistently underpredicted concentrations with dose groups 25 and 50 mg compared with the SD data.

RESULTS

The SD and MD data were not pooled and fit with a single model. The reduced Phase 1 data collected on Day 9 or 10 (203 samples, 174 subjects) resulted in substantial differences for several of the model-estimated parameters with the exception of CL and Vc.

Based upon these differences, SD and MD data always separately in the Phase 1 population.

The Phase 1 population for all studies combined was:

- median weight = 76 kg (ranged from 50 to 112 kg)
- median height = 171 cm (ranged from 150 to 202 cm)
- median age = 35 years (ranged from 18 to 49 years)