**METHODS CONT.**

Two alternative models for RIF induction with B) 2-fold increase in maximum fold induction (Indmax) for gut alone (induction of Elg or C) 2-fold increase in Indmax for gut and liver induction of Elg, Eln, and CL) were then assessed (Figure 3).

**RESULTS**

Fourteen clinical studies describing MDZ exposure (5 IV and 9 oral) before and after RIF administration were identified (Table 1).

The magnitude of DDI was larger and more variable (range 7.2-64.3) when MDZ is given orally compared to IV (range 1.5-2.2).

The extent of DDI with IV MDZ was accurately described by the model (FE range 0.7–1.4), however, the AUC ratios predicted for oral MDZ show under prediction (FE range 1.7–17.9; Figure 2).

Under prediction was reduced when either the Indmax for gut alone was increased (FE 0.9-8.4) or when Indmax for both gut and liver were increased (FE 0.6-4.7) with marginal changes in the accuracy of DDI predictions with IV MDZ (Figure 3).

**METHODS**

Literature searches in (PubMed, University of Washington Database) were used to identify relevant clinical DDI studies.

Simulated populations (Simcyp V10.1) were matched to reported populations in each clinical study (simulation trial design) and generated based on the co-variation (Figure 1) between demographics (e.g. age, sex) and physiological parameters (e.g. an individual's liver size or plasma albumin concentration). Default values for RIF and MDZ saved within the simulator’s databases were used (Base Model A; Figure 2).

**RESULTS CONT.**

Recovery of DDIs where SMV was given as the victim drug were most accurately described with the base model (FE 1.1, 1.5) vs. the model with increased Indmax for the gut (FE 1.4, 2.3) vs. increased Indmax for gut and liver (FE 2.5, 3.9; Figure 3).

**REFERENCES**

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