PURPOSE
Identifying critical factors affecting bioavailability (F) and predicting the human oral bioavailability (Fhuman) before first-in-human trials are very important to prioritize and support drug discovery and development projects. At preclinical stage, animal in vivo pharmacokinetic studies and/or various in vitro measurements such as solubility and permeability (affording absorption into the gut-wall), metabolism (first pass-exclusion in gut-wall and liver) are conducted to understand/estimate the human oral bioavailability. Carefully collated dataset of 184 compounds by Musther et al. demonstrated no strong or predictive correlations between animal and human bioavailability for all species, individually and combined [1]. This comprehensive analysis showed that bioavailability estimated in animal studies are poorly reflecting that of humans. This raised a question if the mechanistic in vitro to in vivo extrapolation (IVIVE) commonly employed in the pharmacokinetics (PK) simulations can be used as an alternative to predict Fhuman.

OBJECTIVE(S)
Here, we present the preliminary results of a proof-of-concept study to assess the utility of mechanistic IVIVE to predict Fhuman for 25 compounds where we had access to in vitro data to parametrize the model.

RESULT(S)
Predicted Fhuman values using IVIVE (with verified/refined in vitro Cmax and CLint from the Simcyp library and literature in vitro CLint) compared with the observed Fhuman from are reported in Figure 1 A and B, respectively. Figure 2 A, B and C shows the rat, dog and monkey F versus Fhuman, for the same drugs where data were available in individual species. The IVIVE based predictions showed a good correlation with Fhuman close to line of identity with R² of more than 0.8 while animal predicted F showed relatively poorer correlation with human F. Figure 2D also demonstrates poor between-species (here rat and dog) correlation for animal F.

METHOD(S)
We have chosen 25 compounds out of the 184 compounds by Musther et al. that exist in the Simcyp compound library or a published PBPK model is available. Simcyp library compounds were chosen for this preliminary study as the required in vitro and physico data were readily available. Fraction absorbed into the gut-wall (Fg) was estimated using the method proposed by Matsumura et al. [2]. This method requires solubility of a given drug in FaSSiF (3mM bile salts and pH 6.5) for fasted oral dose and FaSSiF (15mM bile salts and pH 5) for fed state dosing and effective permeability (Peff). FaSSiF and FaSSiF solubility were predicted using the Glomme et al. [3] Qsar method as implemented within the Simcyp Simulator predicting partitioning of the drug in bile micelles (Kmicelle/water) using the molecule's lipophility (LogP). Permeability was either scaled from in vitro Peff to human Peff using the regression equations available in the Simcyp Simulator or estimated from polar surface area (PSA) and hydrogen bond donor (HBD) using Qsar method reported by Winiwarter et al. [4]. First-pass liver metabolism (Fm) was predicted using well-stirred liver model. The unbound human liver microsomal (HLM) CLHLM, values for a given drug were obtained from the Simcyp Simulator compound database or published PBPK models. Fraction of drug metabolised by CYP3A4 (fm3A4) with respect to the total unbound HLM CLHLM was obtained from the Simcyp database or from Yau et al [5]. Fraction of drug escaping first-pass gut-wall metabolism (Fg) was calculated using the ‘Qgut’ model [6] where the fm3A4 values used to determine the CYP3A4 contribution in the gut metabolism. Then Fhuman was calculated using Fhuman,pre = fP>Peff * Fg. Some of the CLHLM and fm3A4 values were informed or verified using clinical data which improves Fhuman,pre. To compare the predictions against the data solely measured in vitro, CLint, values measured in in-vitro assays were obtained from literature [5,7,8] and bottom-up IVIVE predictions were compared to observed Fhuman.

CONCLUSION(S)
The preliminary analysis of 25 drugs, which spans various BCS and BDDCs classes and diverse chemical nature (Log P range -1.6 to 4.8; MW 129 to 1202; PSA 37.6 to 279; HBD 0 to 5), showed mechanistic IVIVE predictions of human oral bioavailability are significantly better compared to the animal based predictions (Table 1). Using high quality in vitro data improves the IVIVE approach predictions, which in turn can reduce, refine and replace animal use in the research where there is known poor predictions in humans. We will further expand the compound database to investigate the approach for a wider dataset.

REFERENCE

The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not for profit organizations for research and teaching purposes.