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Model Informed Drug Discovery (MIDD)
Webinar: 03.03.2021

Predicting the *in vivo* performance of BCS class II/IV drugs using a combined *in vitro - in silico* approach
Case study: Albendazole and Albendazole sulfoxide

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General objective

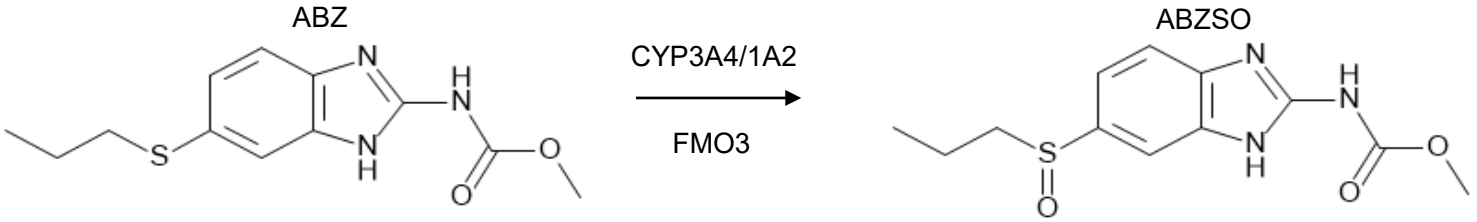
Use of *in vitro biorelevant experimentation in combination with in silico PBPK modeling* to accurately predict the plasma concentrations of Abendazole and its main metabolite Albendazole sulfoxide after the oral administration of a tablet formulation in the fasted state.

Albendazole – PBPK modeling considerations

Borderline BCS class II/IV drug[1]:

- Acid pKa 10.3, basic pKa 4.0 – ampholyte (weak base *in vivo*)
- LogP 3.56 – highly lipophilic
- Low intrinsic solubility: $S_o \cong$ 1.0 µg/mL
- Solubility decreasing with increasing pH of the GI tract (1.6 – 6.5)
  - supersaturation and precipitation upon gastric emptying

Extensive first pass metabolism (~100%) – by CYP3A4/1A2 and FMO3 to Albendazole Sulfoxide (ABZSO)



Limited information in clinical studies:

- Lack of intravenous data for both ABZ or ABZSO
- ABZ + ABZSO plasma concentrations only reported by one clinical study by Corti et al. 2009[2] (at 400 mg).
- ABZSO (Na-Bangchang et al. 2006[3], Mares et al. 2003[4] and Mirfazaelian et al. 2002[5]) at 400 + 800 mg – Model verification.

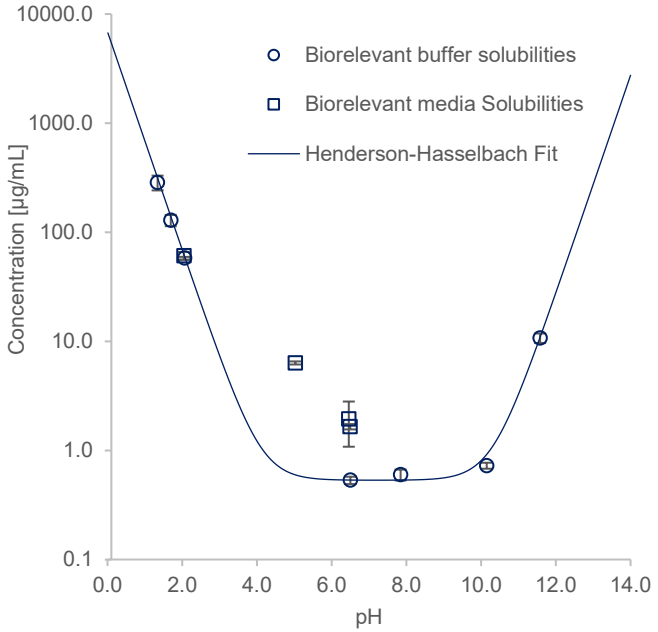
Absorption will then be governed by the physicochemical properties of the parent compound (ABZ) while the post-absorptive parameters will be those of the main metabolite (ABZSO).

1- Lindenberg et al. (2004), Eur. J. Pharm. Biopharm. Vol. 58 (2), 265-278. 2- Corti et al. (2009), Eur. J. Clin. Pharmacol., 65 (10), 999–1006. 3- Na-Bangchang et al. (2006), Tran. Royal. Soc.Trop. Med. Hyg., 100(4), 335-345.4- Mares et al. (2005), Basic Clin Pharmacol Toxicol, 97(2), 122-124 5- Mirfazaelian et al. (2002), Drug. Metab. Disp., 58(6), 403-408.

Biorelevant *in vitro* model inputs

1. Thermodynamic solubility tests
   - In biorelevant buffers within the GI track pH range (for experimental pKa determination)
   - in biorelevant media (FaSSGF, FaSSIF and FeSSIF) for bile salt solubilization ratio determination

Media	Final pH[a]	Solubility [µg/mL]
Biorelevant buffer		
HCl/NaCl pH 1.2	1.34 ± 0.01	286.1 ± 44.2
HCl/NaCl pH 1.6	1.69 ± 0.01	128.9 ± 15.2
HCl/NaCl pH 2.0	2.07 ± 0.01	57.85 ± 1.64
Phosphate buffer pH 6.5	6.50 ± 0.01	0.53 ± 0.04
Phosphate buffer pH 8.0	7.85 ± 0.01	0.60 ± 0.07
Phosphate buffer pH 10.0	10.15 ± 0.04	0.73 ± 0.05
Phosphate buffer pH 12.0	11.58 ± 0.01	10.74 ± 1.07
Biorelevant media		
FaSSGF-V2 pH 2.00	2.04 ± 0.02	61.01 ± 5.12
FaSSIF-V1 pH 6.50	6.50 ± 0.05	2.21 ± 0.03
FaSSIF-V2 pH 6.50	6.46 ± 0.01	1.95 ± 0.86
FeSSIF-V1 pH 5.80	5.03 ± 0.01	6.35 ± 0.21
FaSSGF-V2:FaSSIF-V1[b]	5.89 ± 0.01	2.03 ± 0.56

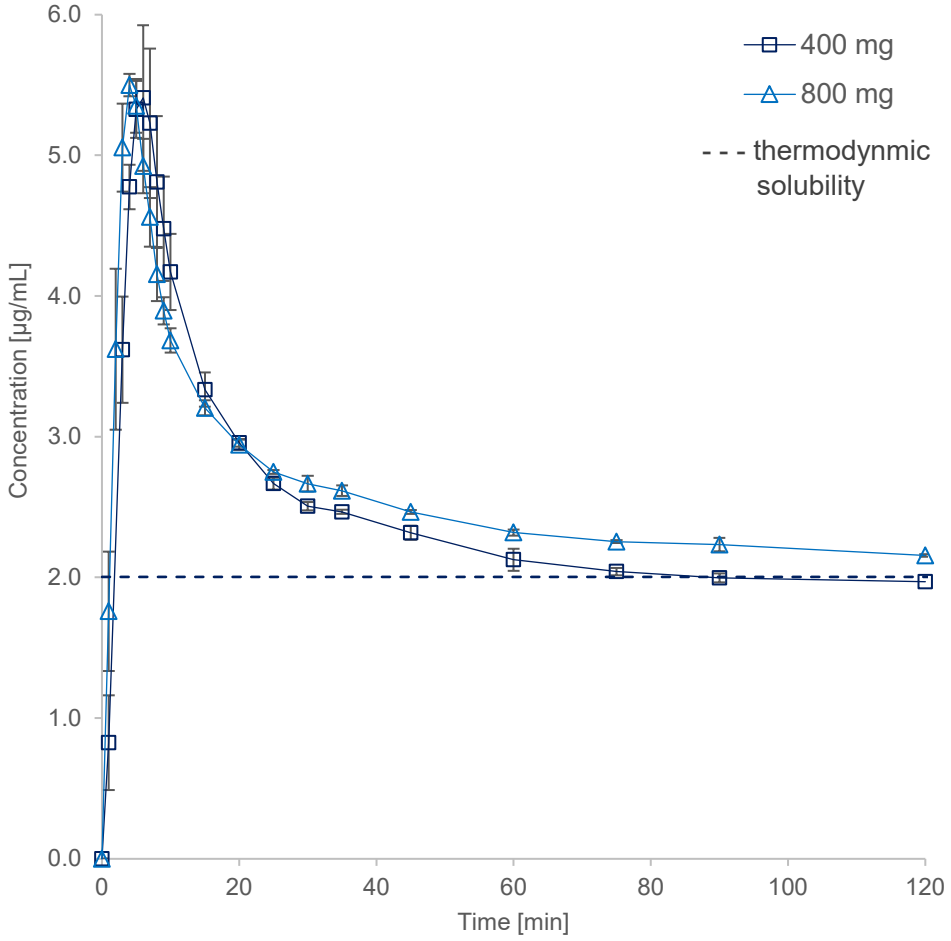


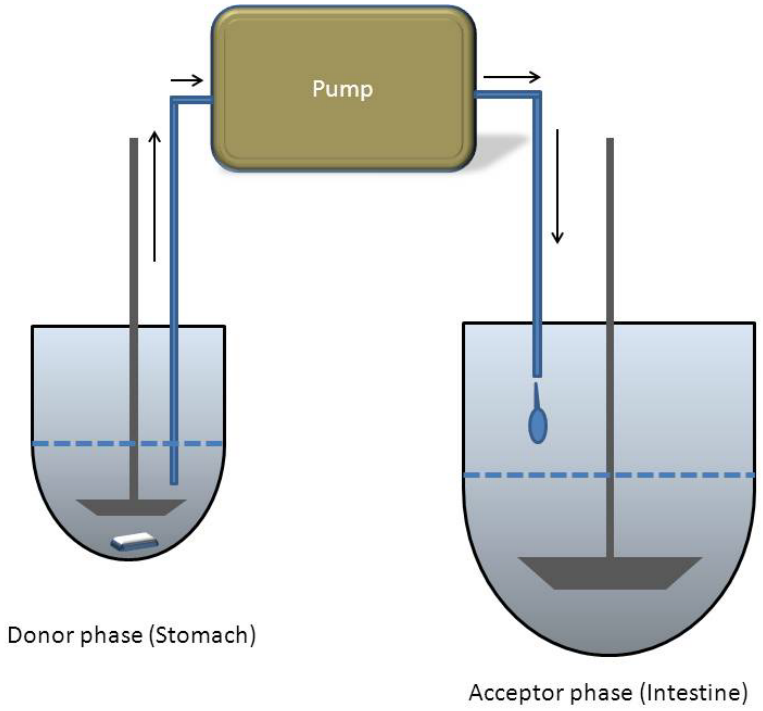
FaSSIF-V1 increasing bile salt concentrations[c]	BS [mM]	Lecithin [mM]	Final pH	Solubility [µg/mL]
BS x0.5	1.50	0.38	6.50 ± 0.01	1.62 ± 0.02
BS x1.0	3.00	0.75	6.50 ± 0.01	2.21 ± 0.03
BS x1.5	4.50	1.13	6.49 ± 0.01	3.65 ± 0.22
BS x2.0	6.00	1.50	6.48 ± 0.01	4.08 ± 0.11
BS x2.5	7.50	1.88	6.48 ± 0.01	4.73 ± 0.07
BS x3.0	9.00	2.25	6.47 ± 0.01	5.50 ± 0.22

Calculation of Bile Salt solubilitzation ratio

Transfer model tests - supersaturation and precipitation

2. Transfer model experiments (400 and 800 mg) to evaluate the supersaturation and precipitation behaviour (e.g. precipitation rate constant) of ABZ.

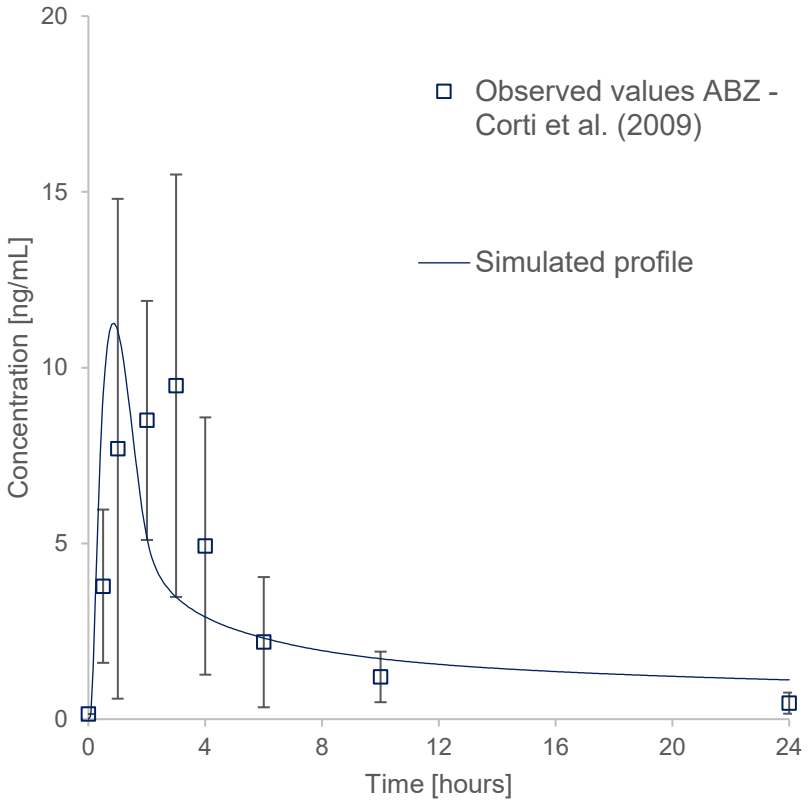




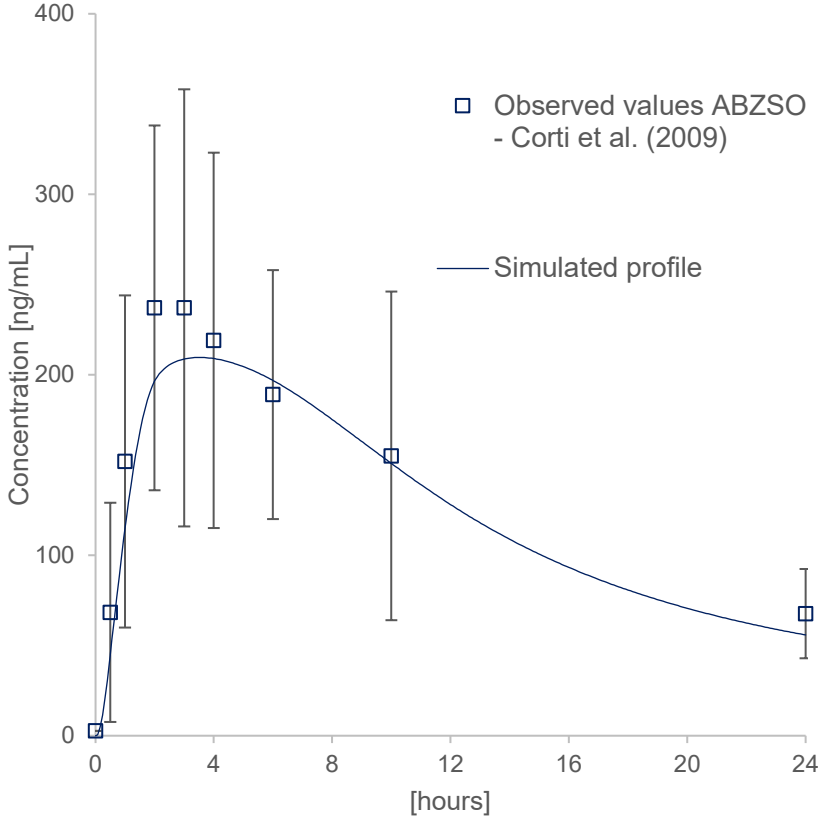
400 mg	
PRC [min-1] x 10^{-1}	1.08 ± 0.03
Precipitation time [sec]	**557 ± 13**
800 mg	
PRC [min-1] x 10^{-1}	1.38 ± 0.18
Precipitation time [sec]	**440 ± 60**

Suitability of PBPK model setup

Parent compound (Albendazole)



Metabolite (Albendazole Sulfoxide)

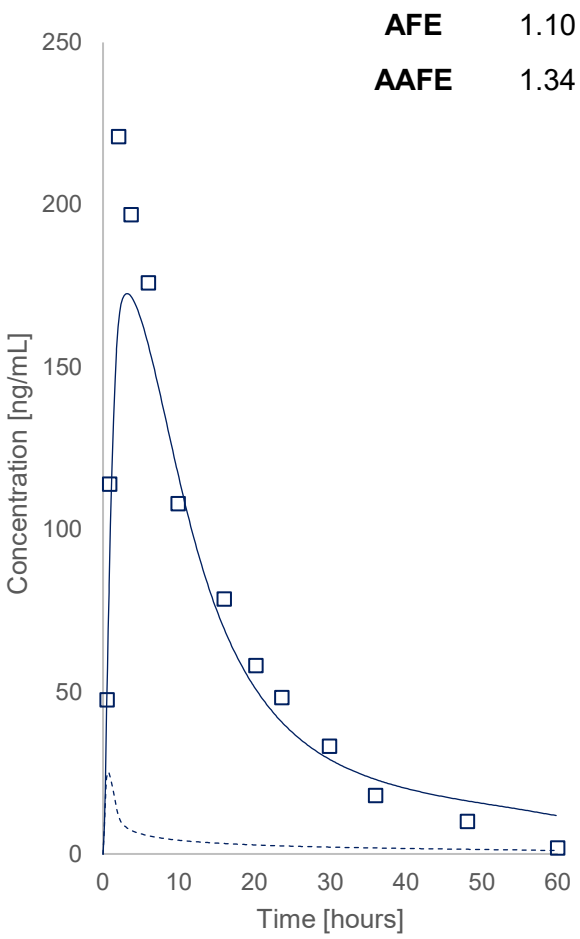


$$AAFE = 10^{\frac{1}{n}\sum \left|\log \frac{predicted}{observed}\right|}$$

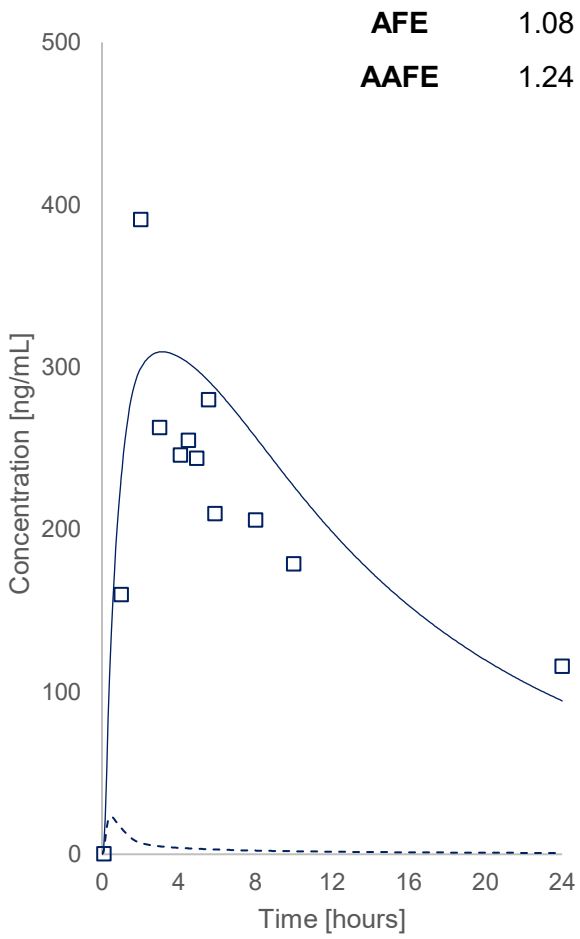
	AFE	*AAFE*
ABZ	**1.20**	**1.84**
ABZSO	**0.93**	**1.18**

Verification of PBPK model set up (400 and 800 mg)

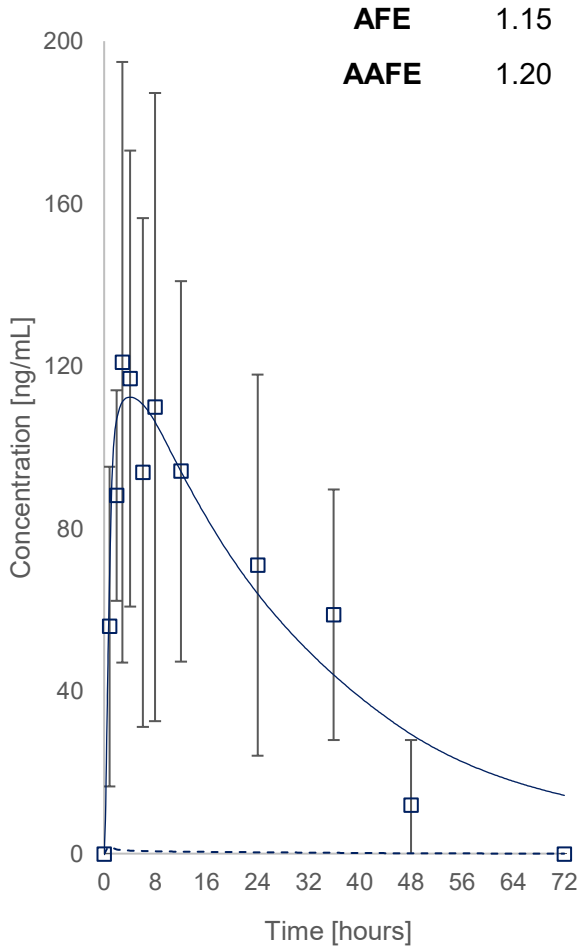
Na-Bangchang et al. (2006)[1] – 400 mg



Mirfazaelian et al. (2002)[2] – 400 mg



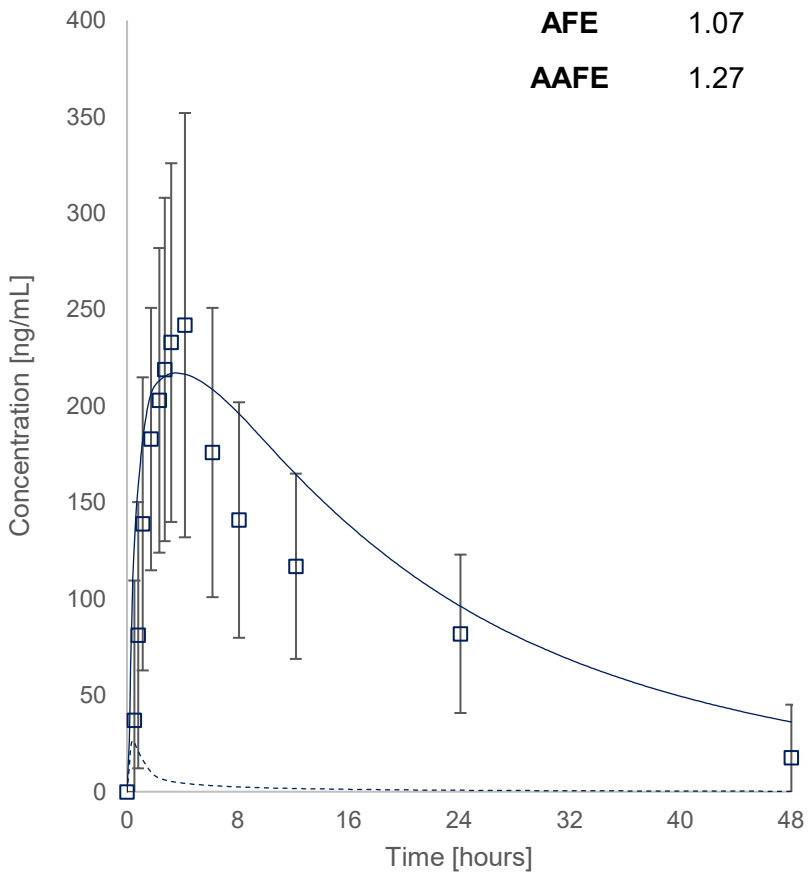
Awazdi et al. (2003)[3] – 400 mg



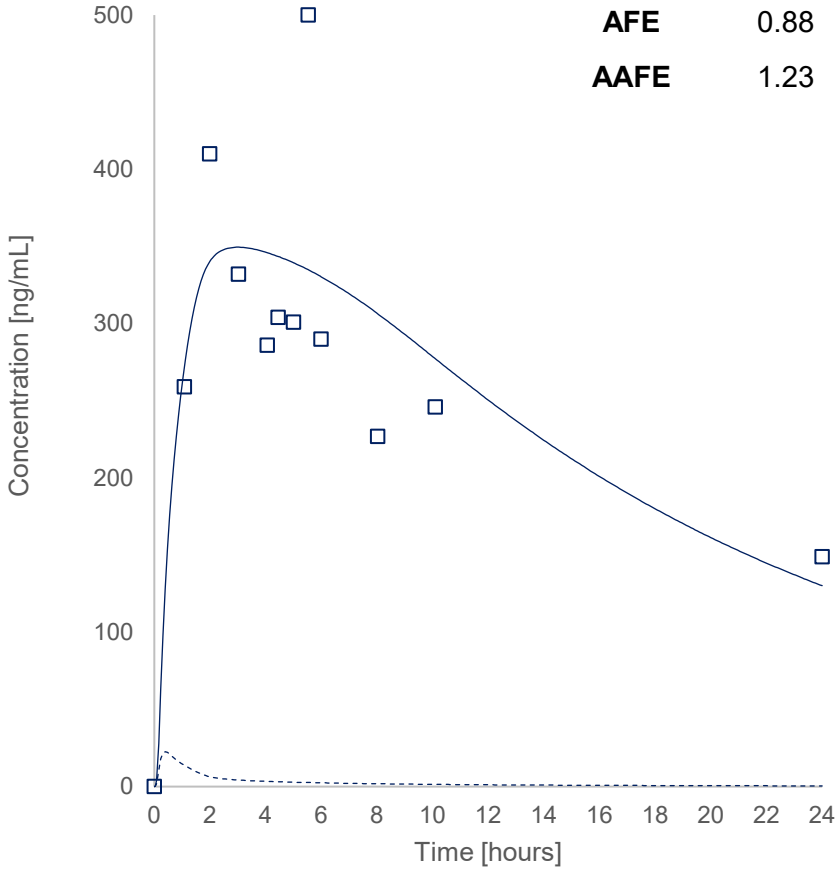
1- Na-Bangchang et al. (2006), Tran. Roy. Soc. of Trop. Med. Hyg., 100(4), 335-345. 2- Mirfazaelian et al. (2002), Drug. Metab. Disp., 58(6), 403-408. 3- Awadzi et al. (2003), Ann. Trop. Med. PH., 97(2), 165-178.

Verification of PBPK model set up (400 and 800 mg)

Mares et al. (2005)[1] – 800 mg



Mirfazaelian et al. (2002)[2] – 800 mg



1- Mares et al. (2005), Basic Clin Pharmacol Toxicol, 97(2), 122-124. 2- Mirfazaelian et al. (2002), Drug. Metab. Disp., 58(6), 403-408.

Summary and conclusions

- A combined *in vitro* – *in silico* approach was used to accurately predict ABZ and ABZSO plasma concentrations.

- Consideration of the supersaturation and precipitation behavior was important for accurately simulating plasma profiles and suggesting its importance *in vivo.*

- Critical assessment of the available literature data regarding input parameters (e.g.: *in vitro* HLM K_m and V_{max} scaling, enzyme expression factors, permeability values, etc.) was necessary for the development of a reliable model for ABZ.

- The validity of the *in silico* setup was verified using clinical data from different studies and at two different dose levels (400 and 800 mg) despite the lack of IV data and PK parameters for ABZSO.

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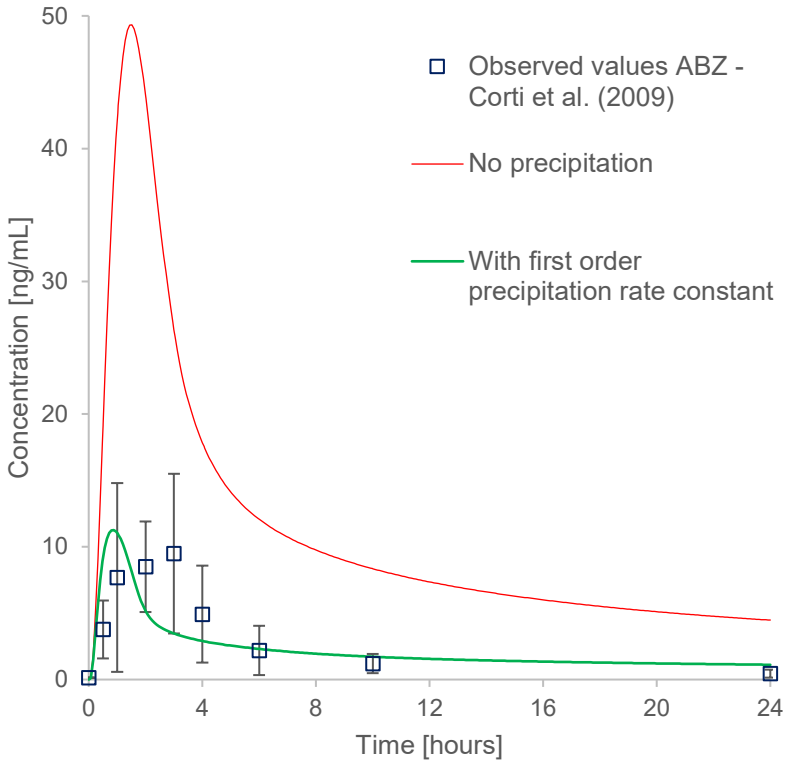
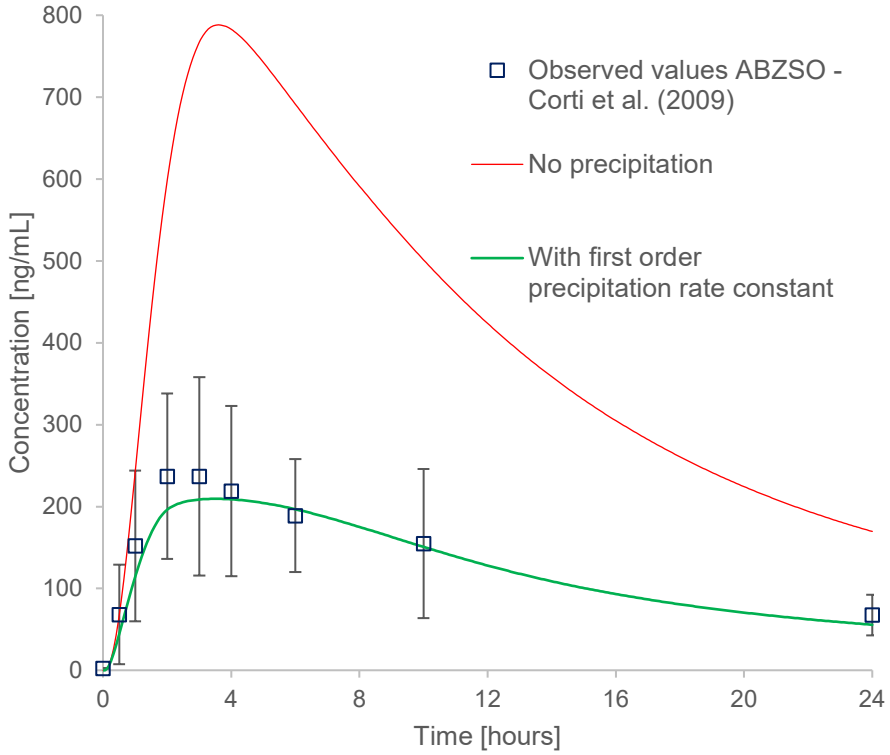
Thank you very much for your attention!

Questions?

Supersaturation and precipitation kinetics in PBPK model setup



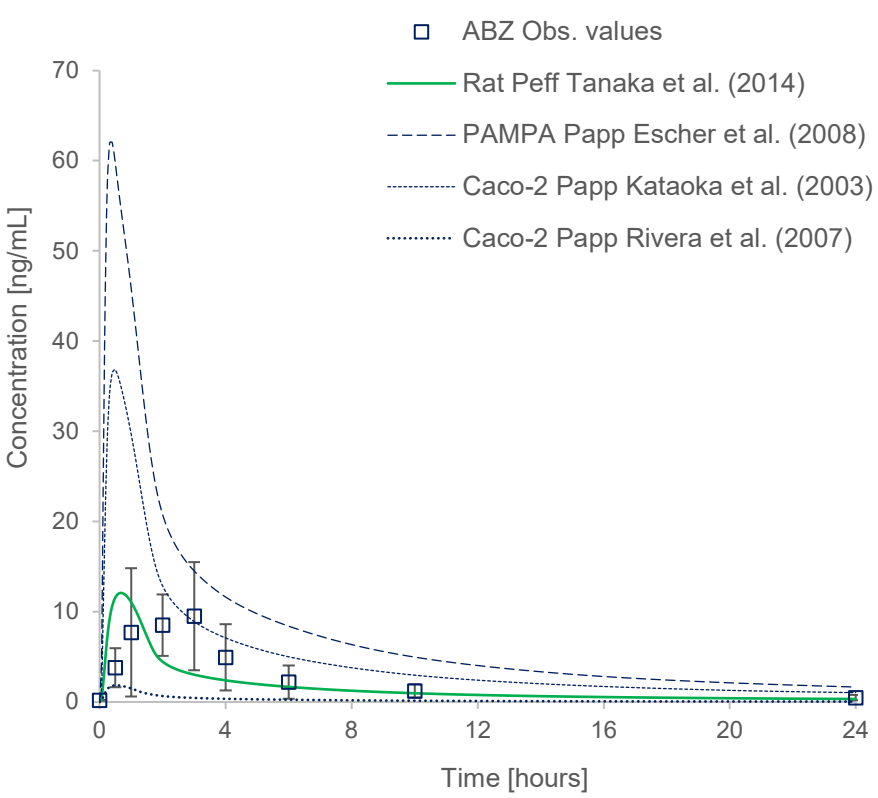


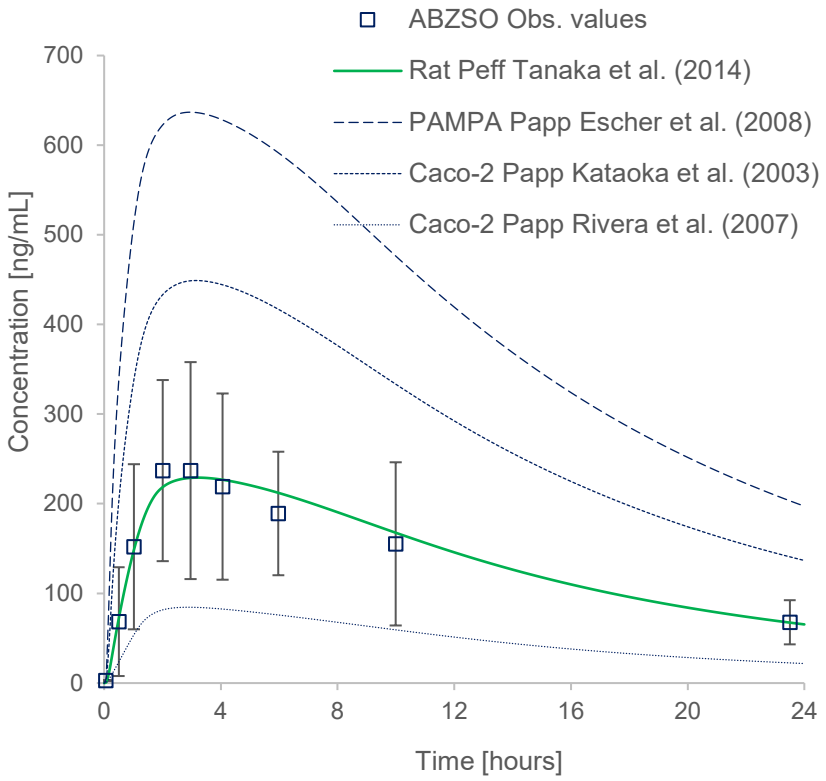
- Crucial to account for precipitation in the model to accurately predict plasma concentrations by using the input in vitro data from transfer experiments.

AFE/AAFE	ABZ	ABZSO
Including precipitation	1.20 / 1.84	0.93 / 1.18
Nelgecting precipitation	4.32 / 4.32	3.99 / 3.99

Corti et al. (2009), Eur. J. Clin. Pharmacol., 65 (10), 999–1006.

Relevance of using a representative permeability value





AFE/AAFE	ABZ	ABZSO
Rat Peff[1] - 0.4 x 10^{-4} cm/s	1.20 / 1.84	0.93 / 1.18
PAMPA Papp[2] - 7.60 x 10^{-4} cm/s	5.49 / 5.49	2.51 / 2.51
Caco-2 Papp Kataoka[3] - 79.71 x 10^{-6} cm/s	3.30 / 3.30	2.30 / 2.30
Caco-2 Papp Rivera[4] - 0.65 x 10^{-6} cm/s	0.19 / 5.52	0.37 / 2.69

1-Tanaka et al. (2014), J. Pharm. Sci., 17(1), 106-130. 2- Escher et al. (2007), Environ. Toxicol. Chem., 27(4), 909-918. 3- Kataoka et al. (2003), 20(10) 1674-1680. 4. Rivera et al. (2007), Int. J. Pharm,, 343 (1-2), 159-165.