

Nintedanib physiologically based pharmacokinetic (PBPK) model to predict drug-drug interactions

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Nintedanib is an approved therapy for idiopathic pulmonary fibrosis with a narrow therapeutic index. To support development of new compounds for IPF, a PBPK model has been developed to assess the risk of DDI.

Introduction

- Nintedanib is a narrow therapy index drug and an essential medication to treat idiopathic pulmonary fibrosis (IPF).
- Nintedanib metabolised primarily by CES1 and to a minor extent by CYP3A4, and it is a substrate of the efflux transporter P-gp [1].
- When given with P-gp and/or CYP3A4 inhibitors (e.g. ketoconazole), it can elicit a drug-drug interaction (DDI) with an AUC ratio (with vs without perpetrator) of 1.59 [2].

Methods

- In this present work, a PBPK model for nintedanib was constructed in Simcyp (Version 23, Certara UK Ltd) by a middle-out approach using physicochemical properties, *in vitro* DMPK properties, and clinical PK data (hADME and DDI with itraconazole). P-gp Jmax and Km were measured in house and optimised using the 3-compartment model in Simcyp *In Vitro* Analysis tool (SIVA, Version 5, Certara UK Ltd).
- The model was verified with clinical data of nintedanib single ascending doses (50-200mg) and nintedanib (100mg) with itraconazole, a known P-gp and CYP3A4 inhibitor, mirroring the clinical trials.
- Model credibility was assessed by determining the geometric mean fold error (GMFE) for accuracy, absolute average fold error (AAFE) and percentage prediction error (PPE) for precision of Cmax and AUC.
- The nintedanib PBPK model was applied to predict the DDI with rifampicin (CYP3A4 and P-gp inducer) and AZD5055 (P-gp inhibitor), and the simulations were compared with clinical data of these interactions ([2,3]).

Limitations

- Nintedanib undergoes lysosomal trapping which likely alters tmax and distribution, presents non-specific binding and it is also metabolised by CES1 (major) which complicates nintedanib recovery in *in vitro* assays.

Conclusions

- A PBPK model of nintedanib was developed which captured the potential risk of DDI due to CYP3A4 metabolism and P-gp transport using a middle out approach.
- For IPF compounds in clinical development, predicting DDI risk with nintedanib, one of few approved IPF therapies, using this validated PBPK model will be impactful as it informs patient inclusion to clinical trials.

Results

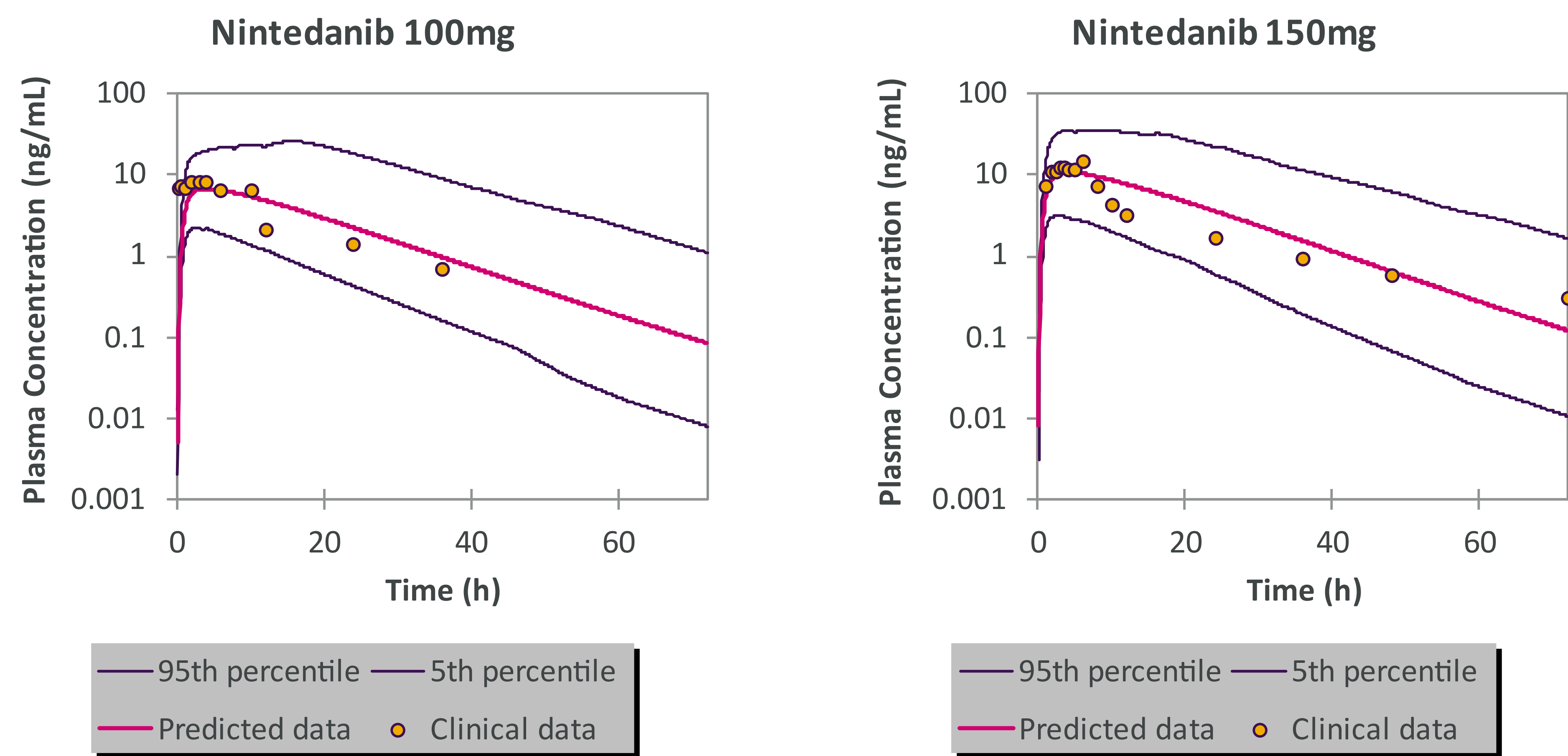


Figure 1. Model validation of nintedanib.
• Observed versus predicted plasma concentration profiles of nintedanib 100mg and 150mg single dose in healthy volunteers. Data is geometric mean of n=80 (10 trials of 8 subjects) for the 100mg dose and n=260 (10 trials of 26 subjects) for the 150mg dose.
• Additional validation was done with nintedanib 50mg and 200mg single dose, and nintedanib 50mg single dose with ketoconazole 400mg multiple dose.
• Geometric mean fold error (GMFE), absolute average fold error (AAFE) and percentage prediction error (PPE) for Cmax were 0.82-fold, 1.24-fold, and 10% and for AUC were 1.47, 1.49-fold, and 28%, respectively, based on 4 single dose nintedanib PK and 1 nintedanib-itraconazole DDI studies.

Table 1. Predicted vs. observed Cmax ratio and AUC ratio of the nintedanib model application

	Observed PK parameters		Predicted PK parameters		Predicted/Observed Ratio	
	Cmax ratio	AUC ratio	Cmax ratio	AUC ratio	Cmax ratio	AUC ratio
Nintedanib 100mg+ AZD5055 10mg ^[3]	1.01	0.94	1.00	1.00	1	1.07
Nintedanib 100mg + AZD5055 35mg ^[3]	1.11	1.03	1.01	1.01	0.91	0.99
Nintedanib 150mg+ Rifampicin 600mg ^[2]	0.58	0.49	0.56	0.48	0.96	0.98

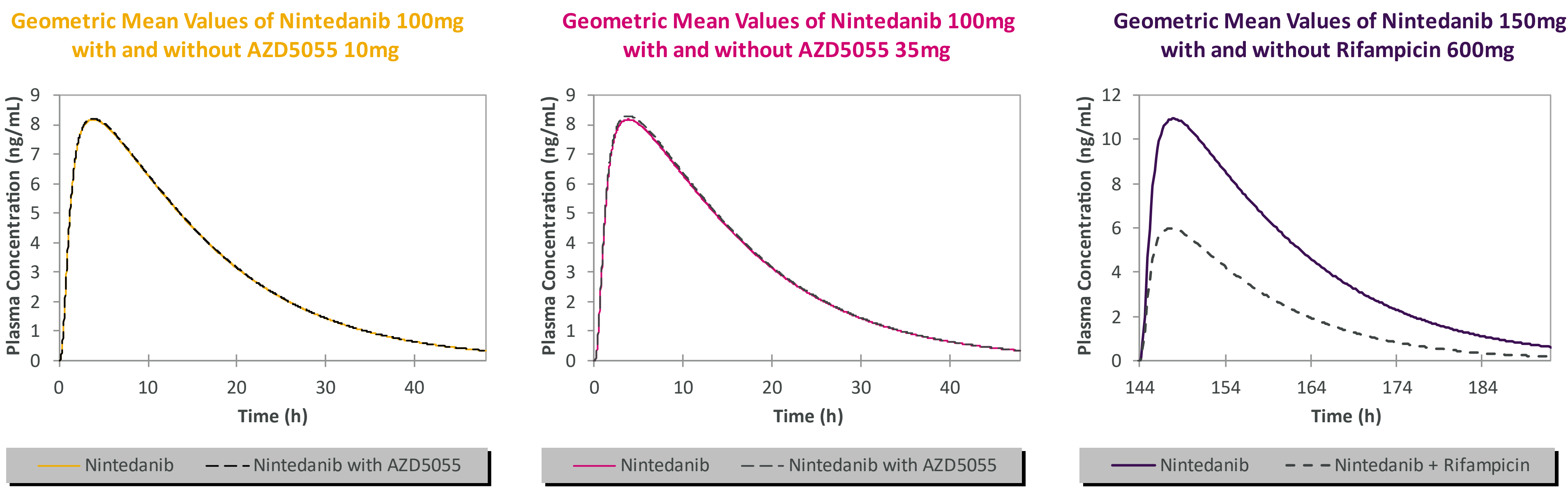


Figure 2. Model application of nintedanib.
• Nintedanib 100mg single dose plasma concentration with and without AZD5055 single 10mg (left) and 35 mg (center) and nintedanib 150mg single dose with and without rifampicin multiple dose 600mg (right) in healthy volunteers. Data is plasma concentration geometric mean of 10 trials of 18, 18 and 25 subjects per trial (from left to right).

References

- Wind et al. Clin Pharmacokinet. 2019 Sep;58(9):1131-1147. doi: 10.1007/s40262-019-00766-0.
- Luedtke et al. Eur J Drug Metab Pharmacokinet. 2018 Oct;43(5):533-541. doi: 10.1007/s13318-018-0467-9.
- Clinical trial code: NCT05644600.