

## Research Article

# Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib

Neil J Parrott,<sup>1,5</sup> Li J Yu,<sup>2</sup> Ryusuke Takano,<sup>3</sup> Mikiko Nakamura,<sup>4</sup> and Peter N. Morcos<sup>2</sup>

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**Abstract.** Alectinib, a lipophilic, basic, anaplastic lymphoma kinase (ALK) inhibitor with very low aqueous solubility, has received Food and Drug Administration-accelerated approval for the treatment of patients with ALK+ non-small-cell lung cancer. This paper describes the application of physiologically based absorption modeling during clinical development to predict and understand the impact of food and gastric pH changes on alectinib absorption. The GastroPlus™ software was used to develop an absorption model integrating *in vitro* and *in silico* data on drug substance properties. Oral pharmacokinetics was simulated by linking the absorption model to a disposition model fit to pharmacokinetic data obtained after an intravenous infusion. Simulations were compared to clinical data from a food effect study and a drug-drug interaction study with esomeprazole, a gastric acid-reducing agent. Prospective predictions of a positive food effect and negligible impact of gastric pH elevation were confirmed with clinical data, although the exact magnitude of the food effect could not be predicted with confidence. After optimization of the absorption model with clinical food effect data, a refined model was further applied to derive recommendations on the timing of dose administration with respect to a meal. The application of biopharmaceutical absorption modeling is an area with great potential to further streamline late stage drug development and with impact on regulatory questions.

**KEY WORDS:** biopharmaceutics; food effect; gastric acid-reducing agents; proton pump inhibitors.

## INTRODUCTION

Approximately 5% of non-small-cell lung cancer (NSCLC) cases have been shown to harbor anaplastic lymphoma kinase (ALK) fusion genes, which can contribute

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<sup>1</sup> Pharmaceutical Sciences, Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4070, Basel, Switzerland.

<sup>2</sup> Roche Innovation Center, New York City, New York, USA.

<sup>3</sup> Pharmaceutical Technology Division, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan.

<sup>4</sup> Translational Clinical Research Division, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan.

<sup>5</sup> To whom correspondence should be addressed. (e-mail: neil\_john.parrott@roche.com)

**ABBREVIATIONS:** NSCLC, Non-small-cell lung cancer; ALK, Anaplastic lymphoma kinase; SLS, Sodium lauryl sulfate; FeSSIF, Fed state simulated intestinal fluid; FaSSIF, Fasted state simulated intestinal fluid; PBPK, Physiologically based pharmacokinetics; PPIs, Proton pump inhibitors; C<sub>max</sub>, Maximal plasma concentration; AUC, Area under the curve.

to increased cell proliferation in tumors expressing these genes [1]. Alectinib (RO5424802, AF802) is a potent and highly selective ALK inhibitor which has demonstrated robust efficacy and good tolerability in patients with ALK+ NSCLC. Two pivotal phase I/II studies have established the clinical benefit of alectinib 600 mg dosed twice daily, supporting a Food and Drug Administration accelerated approval for Alecensa® for treatment of patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib.

Alectinib is a lipophilic basic compound which has a low systemic clearance by hepatic metabolism, a large volume of distribution, and a moderate bioavailability [2]. Alectinib permeability is moderate to good, but it has a very low aqueous solubility (Table 1), and so to maximize dissolution and thereby clinical bioavailability, alectinib is formulated as 150-mg strength hard capsules containing sodium lauryl sulfate (SLS) as an inactive functional excipient [3]. Given these properties, the absorption of alectinib is likely to be sensitive to several intrinsic and extrinsic factors, and this modeling was done to better understand these sensitivities in order to develop appropriate dosing recommendation for alectinib in the target population [3]. In addition, to support the new drug application (NDA), dedicated clinical pharmacology studies

Table I. Key Input Data Used in the Alectinib PBPK Model

Property	Value	Source
logD	1.96 at pH 3.575	Measured in Chugai
pKa	7.05 base	Measured in Chugai
Permeability	$2.5 \times 10^{-4}$ cm/s	Calculated with ADMET Predictor v7.1.0.12
Thermodynamic solubility of alectinib in aqueous NaCl/HCl buffer at 37°C	1 µg/mL at pH 1.2	Measured in Chugai
Thermodynamic solubility of alectinib-free base at a range of pH in titrisol buffer at 37°C	pH	Solubility (µg/mL)
	0.97	7.45
	2.33	4.49
	3.13	14.01
	4.10	0.869
	5.15	0.059
	5.95	0.013
	7.30	0.019
	7.90	0.015
	8.94	0.016
	9.63	0.015
	10.99	0.035
	11.65	0.168
Kinetic solubility of granules in clinical capsules measured at 37°C in 50 mL of biorelevant media after 4-h stirring with a paddle speed of 50 rpm [6]. Five milligram of RO5424802 was applied	FaSSiF pH 6.5 (3-mM bile salts; 23 µg/mL) FeSSiF pH 5 (15-mM bile salts; 77 µg/mL)	Measured in Chugai
Base solubility factor <sup>a</sup>	7124/544	Predicted with ADMET Predictor/measured in Chugai
API particle diameter	4 µm	Measured in Chugai
Blood/plasma ratio	2.6	Measured in Chugai
Free fraction in plasma	0.003	Measured in Chugai

<sup>a</sup> Ratio of the solubility of completely ionized drug to completely unionized drug

were undertaken to characterize the effect of food and the gastric acid-suppressing agent, esomeprazole, on the pharmacokinetics of alectinib.

Physiologically based pharmacokinetic models (PBPKs) are increasingly applied during pharmaceutical discovery and development because of their strength in data integration, delivery of mechanistic insights, and superior predictive power [4]. Physiologically based absorption models are especially useful when biopharmaceutical challenges are faced throughout the drug development life cycle since they enable the translation of drug product measurements and *in vitro* biopharmaceutical data into expected *in vivo* performance [5]. The capability of PBPK modeling to streamline late stage drug development, support drug registration and labeling, and avoid routine clinical studies has already been realized with drug-drug interaction studies [4]. The possibility to extend this to absorption modeling now exists. This paper exemplifies this by describing the construction of an absorption model for alectinib as part of an overall strategy including PBPK modeling of metabolism-based drug interaction potential (separately described). This paper focuses on application of the absorption model for prediction, interpretation, and extrapolation of the effect of food and for prediction and interpretation of the effect of gastric acid-reducing co-medications.

## MATERIALS AND METHODS

### Key Input Data for the Model

Hard capsules containing 161 mg alectinib hydrochloride (equivalent to 150 mg alectinib-free base) and including SLS as a functional excipient were used for the clinical studies included here. Key *in vitro* parameters for this formulation and the alectinib properties used as input parameters to the absorption model are provided in Table I. More details on these data are given below.

### Aqueous Buffer Solubility Measurements at Different PH

Solubility was measured at a range of pH from 1 to 12. One milligram of alectinib-free base was added to 500 µL of titrisol buffer, and the suspension was shaken for 24 h at 37°C. After filtering, the concentration of filtrate was determined by HPLC analysis. These values are reported in Table I together with the pH values measured at the end of the study.

### Solubility Measurements in Biorelevant Media

Kinetic solubility measured with alectinib capsules was generated in biorelevant media using a miniscale dissolution

test previously validated for lipophilic Biopharmaceutical Classification System class II drugs [6].

### Software

GastroPlus™ version 8.6 [7] was used to develop the physiologically based absorption model for alectinib. A general description of GastroPlus™ is available in the user's manual [7] and in several publications [5, 8–10], while details of the software particularly relevant for this work are described below. Additional information on model parameters and settings used for this work is provided in the Supplementary Material.

### The Influence of Gastrointestinal PH on Solubility

With a basic pKa value of 7 (Table I), alectinib solubility is highly dependent on pH. Two different approaches to model the pH dependency of solubility were used in this work. Initially, the Henderson–Hasselbalch equation [11] was used based on the measured pKa value, a single value of solubility, and a predicted solubility factor (Table I). The solubility factor, which is the ratio of the solubility of completely ionized drug to completely unionized drug, was estimated using the ADMET Predictor software [12]. Subsequently, detailed solubility *versus* pH measurements were made, and the pKa and solubility factor were fit to the data.

### Bile Salt Solubilization Model

This work applied the GastroPlus™ models for the fed and fasted states, which account for the solubility enhancement in the gastrointestinal lumen due to the different physiological concentrations of bile salts [13, 14]. According to Mithani [15], the relationship between the concentration of bile salt and the enhancement of solubility for a specific drug can be characterized by a solubilization ratio (SR), where

$$\text{Sol}_{\text{bile,pH}} = \text{Sol}_{\text{aqueous,pH}} + \text{SR} \times \text{MW} \times [\text{bile salts}].$$

In this equation,  $\text{Sol}_{\text{bile,pH}}$  is the solubility in bile salt-containing media at a given pH,  $\text{Sol}_{\text{aqueous,pH}}$  is the aqueous solubility at the same pH,  $[\text{bile salts}]$  is the bile salt concentration, and MW is the drug molecular weight.

In this work, we used solubility measured *in vitro* in biorelevant media with a known concentration of bile salts to derive the solubilization ratio [16]. Solubility measured in both fed state simulated intestinal fluid (FeSSIF) with a bile salt concentration of 15 mM and fasted state simulated intestinal fluid (FaSSIF) with a bile salt concentration of ~3 mM was used. GastroPlus then uses this solubilization ratio with regional profiles of the bile salt concentration in the intestinal tract to derive biorelevant regional solubility profiles [13].

### Modeling the Effect of Time of Dosing with Respect To Food

The default GastroPlus™ model for the fed state is designed to simulate the effect of food when a drug is dosed

close to simultaneously with food intake, as would be the case in a well-controlled food effect study. However, to provide practical guidance on drug intake with respect to meals in the clinical real-world setting, it can be important to know what effect a longer delay in dosing might have on exposure. To this end, the GastroPlus™ model was extended by integration of literature data on the time-dependent changes in gastrointestinal tract conditions after a meal [16, 17]. Three post-prandial states, corresponding to early, middle, and late stages after a meal, were defined (Table II). Assuming that the luminal solubility is proportional to the concentration of the bile salts as described above, the bile salt concentrations in Table II were used to adjust the luminal solubility used for the simulations of early, middle, and late dosing after a meal. Further details of this modeling are given in Supplementary Material 9.

### Effect of Gastric PH Elevation

Alectinib is a basic molecule with higher solubility at acidic pH. This raises the potential for interactions between alectinib and co-medications which alter gastric acid production [18]. To model the effect of gastric acid-suppressing proton pump inhibitors on gastrointestinal physiology, we searched the literature and found that fasting gastric pH increases to approximately 4.5 compared to the typical values measured in untreated individuals of 1 to 2 [19, 20]. Post-prandial gastric pH also increases into the range of 6 to 7 compared to the typical values measured in untreated individuals of around 4 to 5 [19]. Another effect of these drugs is to decrease the gastric-emptying rate [20]. The impact of administration of esomeprazole on alectinib absorption was modeled prospectively by increasing the gastric pH of the standard GastroPlus™ “human–physiological–fasted” model from 1.3 to 4.5. For the fed state, the “human–physiological–fed” model gastric pH was increased from 4.9 to 6.5. The effect of esomeprazole to decrease the fed state gastric-emptying rate was modeled by increasing the gastric-emptying time from the default value of 1 to 1.8 h [20].

### Modeling Strategy

The steps taken in model construction, verification, and application are illustrated in Fig. 1 and are briefly summarized here. Oral pharmacokinetics were simulated by linking the absorption model to a compartmental drug disposition model fit to clinical plasma concentration *versus* time data obtained after an intravenous dose [21]. The preliminary absorption model (model 1 in Fig. 1) was based on the measured biorelevant solubility and substance properties as given in Table I but without applying the GastroPlus bile salt models to adjust regional solubility. This preliminary oral absorption model was refined to produce model 2 by incorporating the effect of regional bile salt differences and by using data from a drug–drug interaction study between alectinib and posaconazole, a strong CYP3A inhibitor, to determine first-pass losses in the gut due to CYP3A metabolism [22]. The assumption of minor intestinal first-pass loss, which had been made in the preliminary model, was confirmed by these clinical data and will be reported separately. The effect of food on

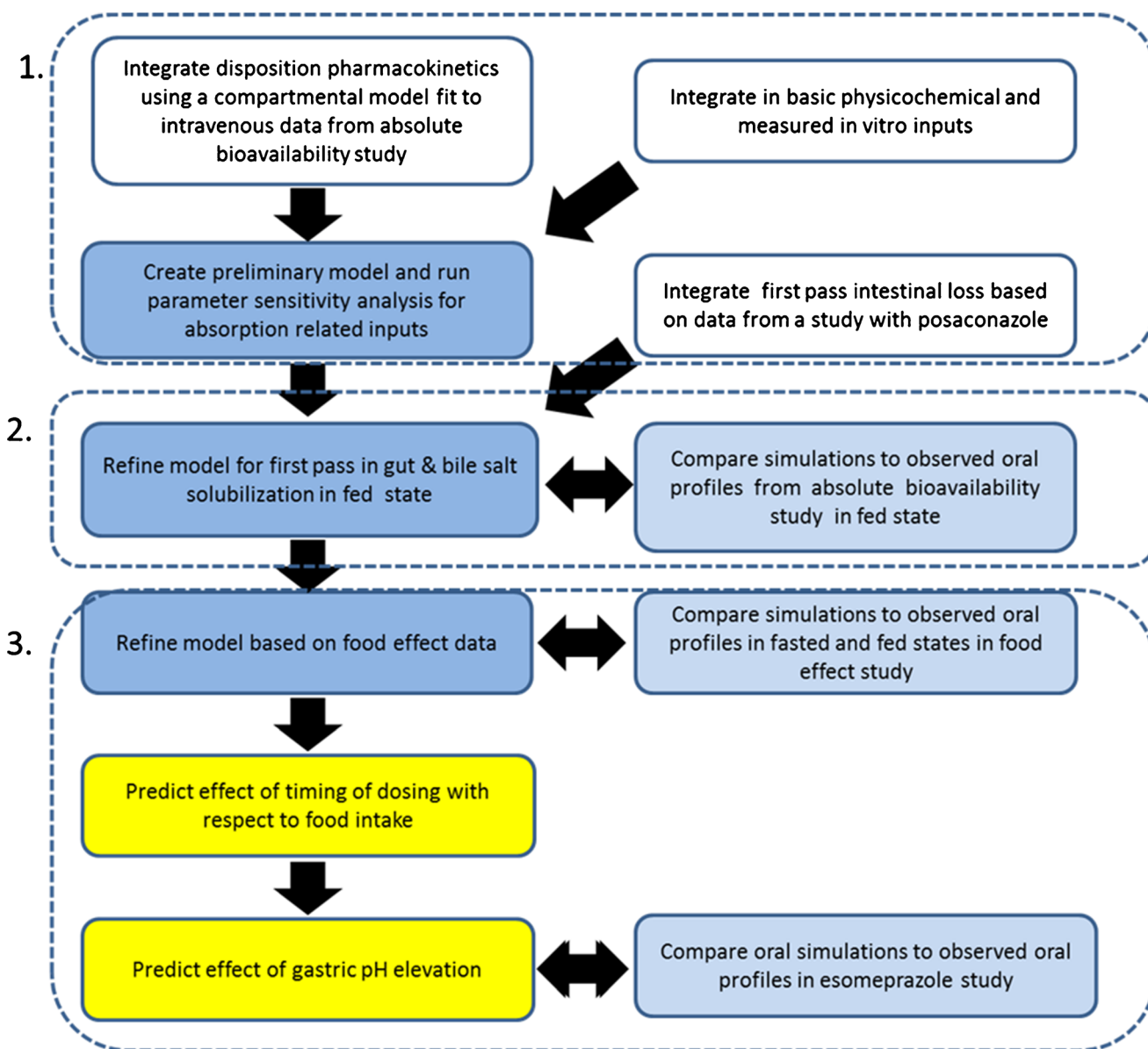
**Table II.** Definition of Post-Prandial Phases Based on Data from Jantratid *et al.*

	Time after meal start (min)	Bile salt concentration (mM)	Stomach transit time (h)	Lag time (h)
Early	0–70	10	1 <sup>a</sup>	3 <sup>b</sup>
Middle	70–160	7.5	0.7	1.9
Late	160–240	4.5	0.4	0.6
Fasted	600	3	0.25 <sup>a</sup>	0

Source: [16]

<sup>a</sup> GastroPlus defaults for the fed and fasted states

<sup>b</sup> A delay in the appearance of alectinib in the plasma was seen after dosing in the fed state and was captured with a lag time



**Fig. 1.** Steps taken in model construction, verification, and application. Three stages of model development are described. Stage 1 is a preliminary model used to assess the factors likely to be most influential on alectinib absorption. Stage 2 includes the additional measured input data and prediction of food effect. Stage 3 involves the refinement of the model based on clinical food effect data, further predictions of timing of dosing, and the effect of co-administration with esomeprazole

alectinib was then predicted with model 2. After comparison of model 2 simulations to clinical data from a food effect study [23], the solubility in the model was further refined so that simulations matched the clinical data producing model 3. This model was then used to extrapolate beyond the clinically tested situations to derive recommendations on the timing of alectinib administration with respect to meal intake. Finally, the model was applied to predict the effect of gastric pH elevation on alectinib pharmacokinetics, and the prediction was compared to clinical data from a drug interaction study with esomeprazole [23].

### Clinical Studies

The clinical studies used in this work are described in full elsewhere [21, 22, 23]. A high-level summary of these studies is given in Supplementary Material 1.

## RESULTS

### Modeling of Alectinib Disposition

Alectinib disposition was modeled by fitting a three-compartment model to the arithmetic mean of plasma concentrations measured in six subjects dosed with an intravenous infusion. The fitted parameters and (CV%) were CL 0.45 L/h/kg (21%),  $V_c$  0.43 L/kg (33%), CL2 4.41 L/h/kg (3%), V2 3.32 L/kg (4%), CL3 0.426 L/h/kg (50%), and V3 3.02 L/kg (4%). Assuming that all clearance is hepatic and accounting for a blood/plasma ratio of 2.6 (Table I) and a hepatic blood flow of 90 L/h, the liver first-pass extraction was estimated to be 14%. Full details of the disposition model are provided in Supplementary Material 2.

### Preliminary Absorption Model and Model Parameter Sensitivity Analysis

Early in clinical development, a preliminary absorption model was constructed and simulations were performed to ascertain the factors most influential on alectinib absorption. These simulations used the logD, pKa, and permeability values listed in Table I with the GastroPlus™ human-physiological-fed model. As the input for solubility, the fed state solubility measured in biorelevant medium (77 µg/mL at pH 5) was used. Regional changes in solubility due to pH were calculated using the Hendersson-Hasselbalch relationship based on the measured pKa value and a solubility factor predicted with ADMET Predictor [12], and changes in solubility due to different regional bile salt concentrations were not considered. It was also assumed that first-pass metabolism was only occurring in the liver with negligible contribution from the intestine. With this model, the simulated oral bioavailability was 42%, which is in close agreement with the geometric mean of the absolute bioavailability of 37% estimated in the six subjects dosed at 600 mg [21]. A model parameter sensitivity analysis showed that, for this dose, solubility was the factor most influential on oral bioavailability since, and for changes which covered the estimated uncertainty in the key model inputs of permeability, solubility, precipitation time, and particle size, the effect on

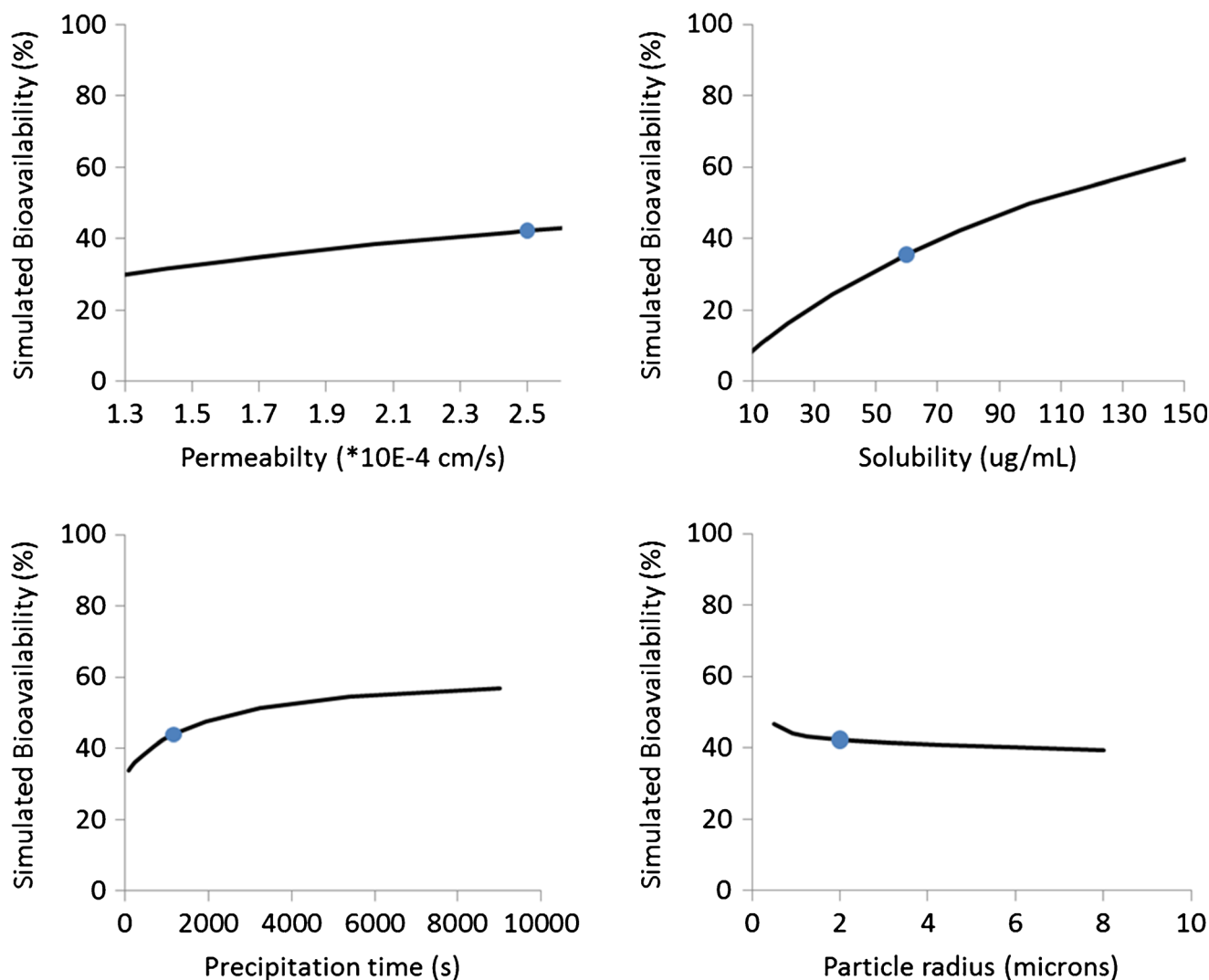
bioavailability was most pronounced for solubility (Fig. 2). More details of these initial simulations are provided in Supplementary Material 3 and 4.

### Simulation of the Effect of Food on Absorption

Biorelevant solubility measurements showed that solubility in fluids simulating the fed state was approximately three times higher than in fluids simulating the fasted state (Table I). As described above, preliminary simulations for a 600-mg dose using the default GastroPlus™ human-physiological-fed model with the FeSSIF value as the solubility input were close to the observed data. However, this preliminary model did not consider the impact of the changing bile salt concentrations throughout the gastrointestinal tract, and as there are very low bile salt levels in the stomach and the large intestine, the physiological plausibility of this model was questionable. Indeed, simulations with the default GastroPlus™ human-physiological-fasted model with the FaSSIF solubility led to a simulated bioavailability that was higher than in the fed state and showed ~50% of the absorbed drug coming from the large intestine. This was considered implausible given the low aqueous solubility and emphasized the need to account for the different regional bile salt levels. As a further refinement to the model, a measured aqueous solubility *versus* pH profile became available (Table I) and showed significant differences to the profile used in the preliminary model, which had been calculated with the Henderson-Hasselbalch equation based on the measured pKa value. Fitting a pH solubility curve to the measured data resulted in a shift in the base pKa from 7.1 to 5.9 and a reduction in the solubility factor for the basic group from 7100 to 540 (see Supplementary Material 5).

The biorelevant solubility data for fasted and fed states were then used in GastroPlus™ to calculate the bile salt solubilization ratio. Measurements in media containing two different concentrations of bile salt were available, and so, two different values of the bile salt solubilization ratio could be calculated. Based on the FaSSIF measurement, the solubilization ratio was estimated as  $1.9 \times 10^7$ , while using the FeSSIF solubility, a 10-fold lower value of  $1.9 \times 10^6$  was obtained. The impact of this range of solubilization ratio on simulated absorption was explored and resulted in simulated bioavailability values ranging from 12 to 59%. Optimization of the solubilization ratio to match the mean bioavailability of 37% estimated in the six subjects dosed at 600 mg yielded a value of  $7.7 \times 10^6$ . Simulated profiles compared with observed plasma concentrations are provided in Supplementary Material 6.

Based on the optimized solubilization ratio, the food effect for alectinib was simulated using the default GastroPlus™ fed and fasted state models and indicated that a large food effect of almost ninefold. Although the possible values of the solubilization ratio for alectinib ranged quite widely, simulations of fasted and fed states covering this range all showed a large expected food effect of greater than sevenfold (see Supplementary Material 7 for more details). At this time, although no food effect study had been carried out, patient data from ongoing efficacy studies indicated that the true food effect might be less than was being predicted



**Fig. 2.** Parameter sensitivity analysis with the preliminary model showing simulated fed state bioavailability for changes in key model inputs. The *symbols* mark the baseline model values

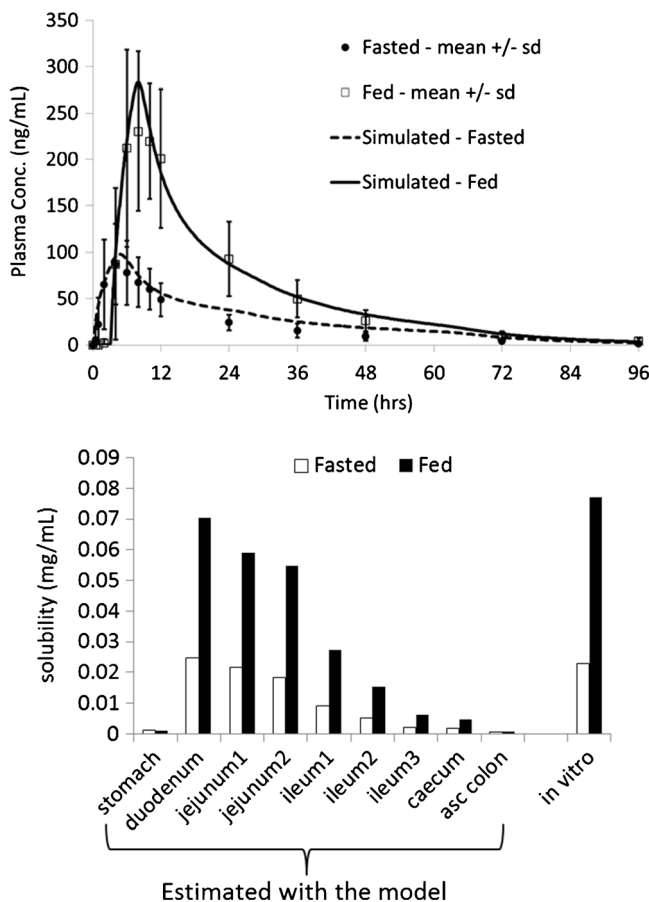
with this GastroPlus™ model. In addition, it was recognized that a weakness in the model was that the impact of the SLS excipient on luminal solubility was not being fully considered.

A clinical food effect study was conducted with a single 600-mg dose given to healthy volunteers and showed that a high-fat meal increased exposure to alectinib by approximately threefold relative to fasting conditions [23]. These new clinical data were then used as the basis for an optimization of the solubilization ratios for the fasted and fed states, assuming that the major effect of food was to enhance luminal solubility. The simulated and mean-observed plasma concentrations and the corresponding regional solubility profiles obtained with these optimized models are shown in Fig. 3. As can be seen, the optimized solubility values in the jejunum for the fed and fasted states were consistent with the measured solubility in FeSSIF and FaSSIF media, which simulate the upper gastrointestinal tract. Furthermore, the low-solubility values in the distal gut are consistent with the reduced bile salts in these regions, and the simulated fraction of the dose absorbed from the large intestine was low at 18% for the fed state and 7% for the fasted state. More details of the

optimized models for the food effect study are provided in Supplementary Material 8.

#### **Prediction of the Effect of Time of Dosing Relative to Food Intake**

With the clinical food effect study, the effect of food on alectinib exposures was characterized under controlled conditions with doses administered within 30 min of a meal. A question remained as to the possible effect of the timing of alectinib dosing with respect to food intake. To address this question, the optimized absorption model was applied to investigate the possible effect of time of dosing relative to food intake. This was done by integrating literature data [16, 17] on the time-dependent changes in gastrointestinal tract conditions after a meal (Table II). Regional solubility profiles (Fig. 4) for the early, middle, and late post-prandial states were created by adjusting the solubility in each gastrointestinal region in proportion to the reported changes in bile salt concentrations. The resulting simulated plasma concentration profiles for a single 600-mg dose are shown in Fig. 4 overlaid with the mean-observed plasma concentrations for the fasted state and fed within 30 min. Associated PK parameters are

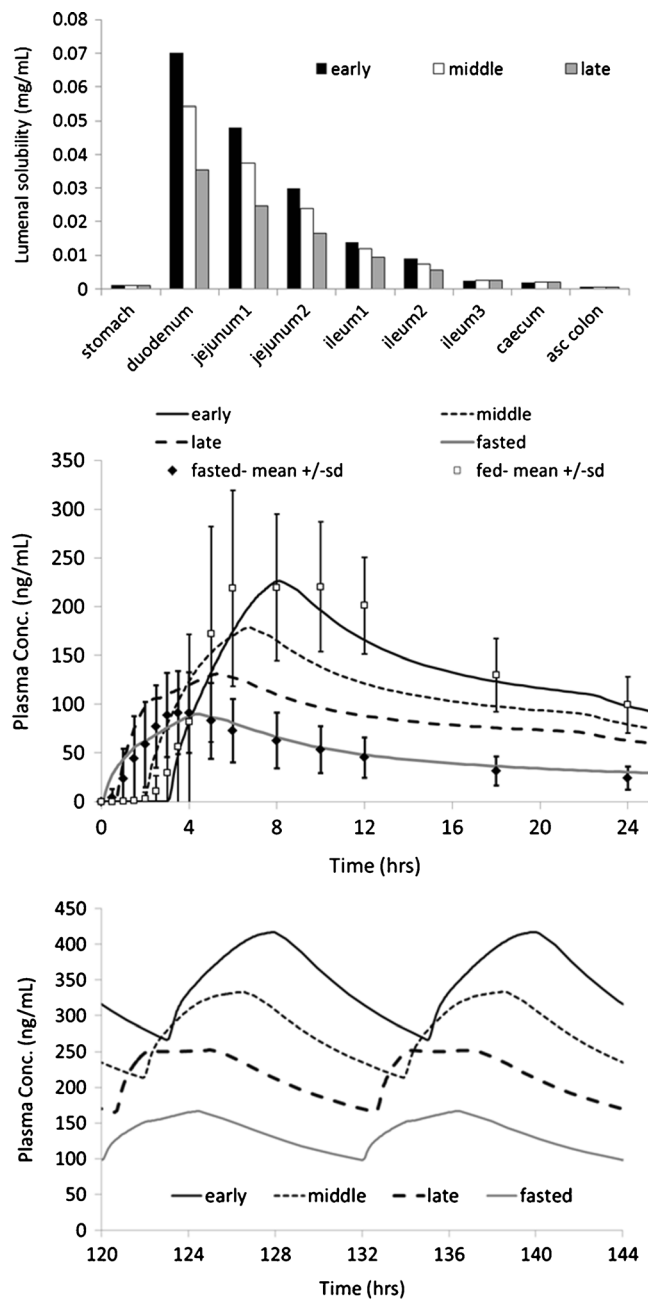


**Fig. 3.** *upper* Simulated and observed mean  $\pm$  SD of plasma concentrations for a 600 mg dosed to 18 subjects in fed and fasted states. Simulations used optimized solubilization ratio values of  $2.2 \times 10^7$  for the fasted state and  $5.8 \times 10^6$  for the fed state. *lower* Model estimated luminal solubility profiles compared to the *in vitro* measured solubility in FaSSiF and FeSSiF biorelevant media

given in Table III. The model predicts that if alectinib is dosed within 160 min of the start of a meal, the steady state  $C_{\max}$  and area under the curve (AUC) will be approximately 80% of the value of a dose given after 30 min. The simulations are consistent with observed patient PK data for alectinib, which showed that steady state  $C_{\max}$  and AUC did not differ more than 20% following administration within 30 min after a meal or with fasting 2 h before and 1 h after administration [24]. Furthermore, the prediction for the late fed state with dosing up to 240 min after food is that the AUC and  $C_{\max}$  are reduced to 70 and 60% of the 30-min values, respectively. Cumulatively, these simulations and clinical data support similar exposures with practical administration of alectinib in the clinical setting, where strict adherence to clinical trial-based dosing instructions may not be feasible.

### Simulation of the Effect of Esomeprazole

Model simulations of the effect of co-administration of alectinib with a proton pump inhibitor were made by increasing the gastric pH and adjusting gastric emptying as described in “MATERIALS AND METHODS” section. Simulations predicted no reduction of alectinib exposures with esomeprazole co-administration in either the fasted or



**Fig. 4.** Regional solubility profiles used to simulate exposures for alectinib dosed at different times after a meal (*upper*) and corresponding simulated single-dose profiles for 600 mg dosed at different times after a meal (*middle*). Clinical mean  $\pm$  standard deviation ( $N = 18$ ) observed data for fasted state dosing and dosing within 30 min of food are overlaid as symbols (*middle*). Simulated steady state profiles for 600 mg dosed bid at different times after a meal are also shown (*lower*)

fed states. This prediction was confirmed by clinical study results which showed no clinically relevant effect of esomeprazole co-administration on alectinib exposure [23]. The slight increase in exposures (approximately 20% increase in geometric mean ratios for both  $C_{\max}$  and AUC with esomeprazole co-administration) is well matched by simulations when the gastric-emptying time is increased to 1.8 h from the default fed state value of 1 h (Fig. 5). This is

**Table III.** Simulated Pharmacokinetic Parameters for Different Post-Prandial States

Food status	Time dosed after meal	Single 600-mg dose		600 mg two times per day	
		$C_{\max}$ (ng/mL)	AUC <sub>inf</sub> (ng h/mL)	$C_{\max}$ (ng/mL)	AUC <sub>24 h</sub> (ng h/mL)
Fed—early	0–70 min	230	5400	420	6700
Fed—middle	70–160 min	180	4600	330	5300
Fed—late	160–240 min	130	3800	250	3900
Fasted	>600 min	90	2100	160	3100

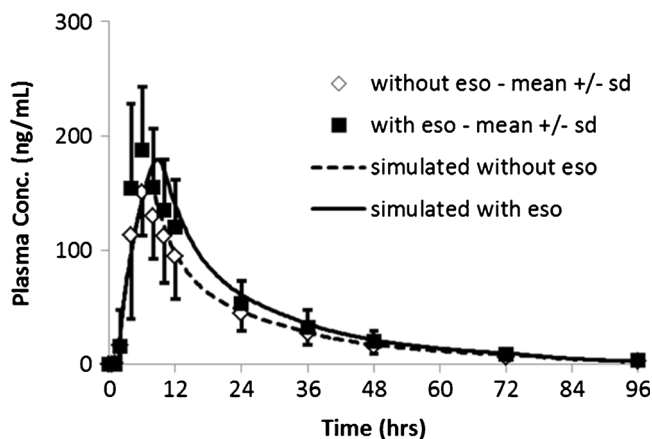
consistent with reports of (es)omeprazole effects on gastric emptying [20].

## DISCUSSION

The impact of PBPK drug development is well recognized with recent cross-industry white papers and conferences bringing together representatives from industry, regulatory bodies, and academia to share views and align on strategies [4, 25, 26]. Furthermore, the ability of PBPK modeling to support drug registration and labeling has been clearly demonstrated with many examples, where CYP450-based drug inhibition studies have been replaced with model simulations [27]. Nonetheless, it is clear that the current areas of regulatory application are restricted and represent only a fraction of the applications already established within companies for internal decision taking [4]. Therefore, there is great potential for a wider impact of PBPK on drug registration. Absorption modeling is one such area with great potential, and in this paper, we have highlighted this with the example of alectinib. In common with many drugs currently being developed, alectinib is lipophilic and exhibits poor aqueous solubility [28]. Very often for such molecules, there is increased absorption with food, and solubility measured in fluids simulating the fasted and fed states provides understanding of the mechanistic basis for this effect by showing enhanced solubility due to higher bile salt levels. Integrating these solubility values into a PBPK absorption model is the optimal way to translate quantitatively to the actual clinical effect, and numerous examples of successful PBPK model-

based forecasting of food effect have been published [9, 13, 29–31]. For alectinib, a positive food effect was to be expected, given the threefold higher solubility in fed state compared to fasted state media. However, a confident and precise prediction of the magnitude of the food effect in healthy volunteers based on the available data was challenging. Absorption of alectinib is solubility limited, and the enhancement of *in vivo* solubility by bile salts and other components in the luminal fluids is critical. The solubility enhancement could be measured in the biorelevant media, FaSSIF and FeSSIF, which are designed to simulate fasted and fed state conditions in the upper jejunum. However, in more distal regions of the gut, the bile salt levels are much reduced, and without accounting for the physiological changes in bile salt levels on solubility, the GastroPlus absorption model may tend to over-estimate absorption from the distal intestine. This was seen with the preliminary alectinib absorption model. Although the preliminary simulation for the fed state was in reasonable agreement with observed exposures, the simulated exposure for the fasted state was higher than in the fed state and showed a high proportion of absorption from the large intestine. The physiological changes in regional bile salt levels were then incorporated in the GastroPlus model, and the effect of bile salts on drug solubility was estimated via the bile salt solubilization ratio assuming a linear relationship between the solubility enhancement and the concentration of bile salts. According to this model, the solubility enhancement is dependent only on bile salt concentration and the solubilization ratio can be determined from the aqueous solubility at a given pH and the solubility in a medium of the same pH and containing a known concentration of bile salts. In practice, for alectinib, several intermediate steps were required for estimation of the solubilization ratio. Firstly, the aqueous solubility of alectinib-free base was measured across a range of pH. This identified a weakness in the preliminary absorption model, since when the initial pH *versus* solubility profile based on the pKa value was compared to the measured profile, it was found that the pKa value and solubility factor needed to be adjusted significantly. This is in line with previous reports that initial estimates of solubility profiles used in drug discovery based on limited data may be quite different to the more detailed measured profiles obtained later [32].

These aqueous solubility data were then used together with kinetic solubility of the clinical formulation measured in FaSSIF and FeSSIF media to estimate the effect of bile salts. Following this approach, it was found that the FaSSIF measurement gave an estimate of the solubilization ratio, which was an order of magnitude higher than the value obtained with FeSSIF. This difference would not be expected according to the assumptions of the bile salt model and



**Fig. 5.** Simulated and observed mean  $\pm$  SD ( $N=18$ ) plasma concentrations for alectinib dosed with and without co-administration of esomeprazole



suggested that caution was needed in the use of the model for prediction. Potential causes for the mismatch of simulated and observed food effects may include that the biorelevant media FaSSIF and FeSSIF are surrogates for the true intestinal fluids and continue to evolve [16, 31], and while bile salts are a major factor in the enhancement in solubility for lipophilic drugs, other factors such as phospholipid content, buffer capacity, osmolarity, and ionic strength all play a role and are not captured in the currently implemented solubilization ratio [33]. It also needs to be recognized that the extent and duration of the luminal solubility enhancement due to the functional excipient, SLS, included in the formulation is not accounted for in the GastroPlus model. A major effect of SLS in the formulation is believed to be to enhance the luminal solubility, which is supported by in-house dissolution tests (data not shown) and by published work of Vertzoni and others [34–36], who found that the addition of SLS increased solubility in physiologically relevant media for several basic and poorly soluble drugs.

Once clinical food effect data became available, it was established that exposures were threefold higher for a 600-mg dose given after a high-fat meal compared to fasted conditions. It was not possible to optimize a single bile salt solubilization ratio so that model simulations matched both fasted and fed state data. However, good simulations were achieved through optimization of separate solubilization ratios for the fed and fasted states and the regional solubility profiles obtained were plausible with fasted and fed state solubilities in the upper gastrointestinal tract close to the *in vitro* FaSSIF and FeSSIF measurements. Again, the need for two different solubilization ratios indicates that the bile salt models are not adequate for a fully mechanistic description of the behavior. This may be partly because the effect of SLS in the alectinib formulation was not considered and more work is needed to develop a model accounting for the combined effect of the surfactant in the formulation and the intrinsic physiological food-related factors. Another reason may be that a pH dependency of the solubilization ratio was not accounted for. To our knowledge, the accuracy of predicted solubility *versus* pH profiles in biorelevant media has been little studied. The relationship for estimation of the solubilization ratio currently employed in GastroPlus is based on original experimental work done with uncharged molecules by Mithani [15]. The work of Mithani was later confirmed for wider set of neutral compounds and extended to mixed bile salt/lecithin micelles by Glomme [37]. Glomme also found that the bile salt/water solubility ratio for acids and bases showed a sigmoidal relationship with pH in contrast to the linear relationship expected for neutral drugs. Therefore, it would be recommended to enhance the current implementation of the solubilization ratio to better describe the behavior of ionizable molecules, where pH changes might lead to different solubility ratios along the GI tract. Our inability to derive a single solubilization ratio for alectinib using FaSSIF and FeSSIF may be related to this, and further experimental assessment and development of models for the combined effects of pH and bile salts on luminal solubility would be valuable.

A brief comment is also needed on the lag time which needed to be introduced to fit a feature of the observed concentration *versus* time profiles for the fed state, which is not captured by the first-order gastric-emptying rate which is implemented in GastroPlus. A delay of at least 2 h was seen before measurable plasma concentrations were seen (see plot

in Supplementary Material 8). In our experience, such lag times are often seen for poorly soluble drugs dosed with a high-fat meal [38] and may be due to the dosage form floating on the top of the gastric contents.

Based upon the obtained regional solubility profiles, we took the food effect predictions further by integrating data on the changes in luminal bile salt concentrations at different times after a meal to predict the impact of a delay in alectinib administration. This is of importance since, based on guidance from the European Medicines Agency, when there is a marked food effect, additional food-interaction studies investigating the effect of a meal taken at different times before and after the drug might be needed to support dosing recommendations [39]. The predictions for alectinib gave reassurance that a delay in taking alectinib of several hours would have limited impact on the enhancing effect of food. These predictions are supported by results from a clinical study, which compared steady state alectinib exposure in ALK-positive NSCLC patients dosed within 30 min of a meal to exposures of patients dosed after fasting for 2 h and without food for 1 h after alectinib intake [24]. The predictions are further supported by comparison to observed data for quazepam, a drug with very similar properties to alectinib, which was studied in healthy volunteers dosed either after overnight fasting, 30 min after a standard meal, or 180 min after eating the same meal [40]. For dosing 180 min after the start of a meal, the quazepam  $C_{\max}$  was 83% of the value following dosing at 30 min, which is very similar to our prediction of the reduction to 80% for alectinib dosing at 240 min. Our modeling of the effect of dosing time with respect to food was included in the NDA submission to the Food and Drug Administration, and the reviewers concluded that alectinib can be administered without specifying a dosing time relative to meal administration [41]. We believe that providing a well-described and well-optimized absorption model illustrating the likely effect of delayed dosing helped the reviewers to reach their decision, and the fact that the modeling work was mentioned by the reviewers is an encouraging sign that solid absorption modeling based on the right *in vitro* data could alleviate the need for “tick box” clinical studies in the future.

Alectinib is a basic molecule with a pH-dependent solubility, and it is well known that the absorption of such drugs may be altered when co-administered with a gastric acid-reducing agent [18]. In fact, many orally administered anticancer therapies are weak bases, and as cancer patients frequently take acid-reducing agents to alleviate symptoms of gastroesophageal reflux disease, there is concern that decreased exposures due to this drug-drug interaction could result in failure of therapy [42]. Currently, clinical assessment of the potential for pH-dependent drug-drug interactions is generally requested by health authorities, although it has been suggested that PBPK modeling could be used to predict the extent of such DDIs and to provide insights into study designs and risk mitigation strategies [18]. There are currently few published examples of avoidance of clinical studies in this area, although some successes have been communicated [43]. The potential is well illustrated with alectinib, where an accurate prospective simulation of the 1.2-fold increase in  $C_{\max}$  and AUC on co-administration with esomeprazole was demonstrated. The model predicted that gastric pH changes would not affect alectinib exposure because alectinib dissolution in the stomach is dependent on the aqueous solubility,

which remains <10 µg/mL at all pH values (Table I). Thus, even at the lowest pH, the stomach solubility of 10 µg/mL is very much lower than the solubility needed for complete dissolution of the dose in a glass of water, which would be 2.4 mg/mL (600 mg/250 mL). Thus, even though the solubility decreases as gastric pH increases to a pH of 6, this has negligible effect on the absorption of alectinib. Again, this absorption modeling was included in the NDA submission to the Food and Drug Administration. Reviewers concluded that no dose modification is recommended for patients taking alectinib with an acid-reducing agent [41].

## CONCLUSION

This paper has described the construction of a physiologically based absorption model for alectinib integrating *in vitro*, non-clinical and clinical data into a single mechanistic model. Simulations with this model have supported the development of alectinib by assisting in the design and interpretation of clinical pharmacology studies to investigate the impact of food and co-administered gastric acid-reducing agents on alectinib absorption. Although the exact magnitude of the food effect could not be predicted with confidence, the predicted positive food effect and negligible impact of gastric pH elevation were confirmed by clinical studies. After optimization of the absorption model based on the clinical food effect data, the refined model was further applied to derive recommendations on the time of dosing with respect to a meal. Overall, this paper has illustrated the application of biopharmaceutical absorption modeling, an area with great potential to further streamline late stage drug development and impact on regulatory questions. With continued research and validation of PBPK absorption models, we can envisage a time when it will be possible to replace routine clinical studies for food effect and absorption-related drug interactions with solid PBPK modeling founded on good non-clinical and clinical PK data. This absorption-related work was part of a broader PBPK modeling strategy including impactful predictions of metabolism-related drug-drug interactions which will be reported separately.

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