

Effect of Hepatic Impairment on the Pharmacokinetics of Alectinib

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Abstract

Alectinib is approved and recommended as the preferred first-line treatment for patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer. The effect of hepatic impairment on the pharmacokinetics (PK) of alectinib was assessed with physiologically based PK modeling prospectively and in a clinical study. An open-label study (NCT02621047) investigated a single 300-mg dose of alectinib in moderate ($n = 8$) and severe ($n = 8$) hepatic impairment (Child-Pugh B/C), and healthy subjects ($n = 12$) matched for age, sex, and body weight. Physiologically based PK modeling was conducted prospectively to inform the clinical study design and support the use of a lower dose and extended PK sampling in the study. PK parameters were calculated for alectinib, its major similarly active metabolite, M4, and the combined exposure of alectinib and M4. Unbound concentrations were assessed at 6 and 12 hours postdose. Administration of alectinib to subjects with hepatic impairment increased the area under the plasma concentration–time curve from time 0 to infinity of the combined exposure of alectinib and M4 to 136% (90% confidence interval [CI], 94.7–196) and 176% (90%CI 98.4–315), for moderate and severe hepatic impairment, respectively, relative to matched healthy subjects. Unbound concentrations for alectinib and M4 did not appear substantially different between hepatic-impaired and healthy subjects. Moderate hepatic impairment had only a modest, not clinically significant effect on alectinib exposure, while the higher exposure observed in severe hepatic impairment supports a dose adjustment in this population.

Keywords

alectinib, hepatic impairment, PBPK, pharmacokinetics, physiologically based pharmacokinetic modeling

Alectinib (RO5424802; AF802) is a highly selective and potent anaplastic lymphoma kinase (ALK) inhibitor that has shown antitumor activity in preclinical models resistant to the previous standard of care, crizotinib, as well as in central nervous system tumor models.^{1,2} The clinical benefit of alectinib 600 mg twice daily (BID) was established in 2 pivotal phase 2 studies (NP28673 [NCT01801111] and NP28761 [NCT01871805]), which demonstrated robust efficacy in systemic disease as well as in the central nervous system, and good tolerability in patients with ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib therapy.^{3–5} More recently, the pivotal global, randomized, phase 3 ALEX study (BO28984, NCT02075840) in ALK-inhibitor naïve NSCLC confirmed the clinical benefit of alectinib in the first-line setting, with prolonged progression-free survival versus crizotinib.⁶ Based on the ALEX study results, the National Comprehensive Cancer Network guidelines were updated to include alectinib as the preferred first-line treatment option for patients with ALK-positive NSCLC.^{6,7} Alectinib 600 mg BID is approved for the treatment of patients with ALK-positive metastatic NSCLC in the United States and European Union.

Following single oral dose administration of alectinib 600 mg, plasma concentrations of alectinib increase, with a median time to maximal concentration (T_{max}) reached by approximately 4 to 6 hours under fed conditions, and thereafter decline with a single dose apparent half-life ($t_{1/2}$) of approximately 20 to 24 hours in healthy subjects and patients with cancer.^{8–10} Dose proportionality was observed across the 300- to 900-mg BID dose range.¹⁰ In vitro studies indicate that alectinib is metabolized in the liver to its major active metabolite, M4, with cytochrome P450 3A4 (CYP3A4)

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being the main isoenzyme involved.¹¹ A completed human mass balance study provides clinical evidence that the systemic elimination of alectinib is mainly via hepatic metabolism and subsequent excretion into the feces with negligible renal excretion.¹² Therefore, liver impairment has the potential to alter alectinib and/or M4 exposure. Population pharmacokinetic (PK) analyses of pivotal phase 1/2 studies previously demonstrated no clinically relevant effect of mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and aspartate transaminase greater than ULN or total bilirubin greater than 1.0-1.5 times ULN and any aspartate transaminase) on alectinib or M4 PK.¹³ The effects of moderate to severe hepatic impairment on alectinib, however, are unknown.

Physiologically based pharmacokinetic (PBPK) modeling is recognized as a useful mechanistic tool to understand patient specific factors that could contribute to observed PK variability.¹⁴ PBPK modeling integrates available nonclinical and clinical data during drug development and therefore offers the opportunity to leverage the cumulative molecule knowledge to inform clinical and regulatory decisions.¹⁵⁻¹⁷ PBPK modeling has been applied to provide mechanistic insights underlying absorption- or disposition-related variability or even to support dosing recommendations in settings of drug-drug interactions (DDIs) or in specific populations including pediatrics, geriatrics, and pregnancy.¹⁴ Use of PBPK to predict the effects of organ dysfunction has also been described¹⁸ and is currently an area of much investigation.^{19,20}

To inform the appropriate clinical use of alectinib in patients with underlying hepatic dysfunction, the effect of moderate and severe hepatic impairment on alectinib PK was investigated in a clinical study. A PBPK model for alectinib was utilized to prospectively predict the effect of moderate and severe hepatic impairment on the PK of alectinib to best inform the design of the dedicated clinical study.

Methods

PBPK Modeling

The effect of moderate and severe hepatic impairment on the PK of alectinib and M4 was prospectively investigated using a previously developed PBPK model.²¹ Briefly, the base alectinib model was constructed using SimCYP[®] software with (1) absorption assuming a first-order rate constant and fraction absorbed as estimated previously,²² (2) volume of distribution predicted by mechanistic equations of the tissue partition coefficients,^{12,23,24} and (3) clearance (CL) based on plasma clearance determined following intravenous administration in humans.¹² The fraction metabolized through CYP3A4 enzyme (fm_{CYP3A4}) of alectinib was

estimated to be ~40% to 50% based on nonclinical hepatocyte data.¹¹ A combination of in vivo fm_{CYP3A4} of 40% and intestinal availability (F_G) of $\geq 90\%$ were directly estimated from clinical data from a DDI study with a potent CYP3A inhibitor using the PBPK model, and the corresponding intrinsic CL through CYP3A4 metabolism ($CL_{u,int,CYP3A4}$) and F_G were retained in the model.²¹ Subsequently, the model was verified with clinical DDI study results with CYP3A enzyme modulators, which were not included in the model development.²¹ This alectinib base model was then used to predict the effect of hepatic impairment on alectinib PK using default SimCYP[®] hepatic impairment models (Child-Pugh A-C).¹⁸ The alectinib CL of the hepatic-impaired population was scaled as follows:

$$\begin{aligned} CL_{u,int,CYP3A4} \text{ (L/min)} \\ &= CL_{u,int,CYP3A4} \text{ (\mu L/min/pmol)} \\ &\quad \times \text{Liver Weight (g)} \times \text{MPPGL (mg)} \\ &\quad \times \text{Abundance}_{CYP3A4,liver} \text{ (pmol/mg)} \end{aligned} \quad (1)$$

where $CL_{u,int,CYP3A4}$ was determined in the healthy subjects as described above. Liver weight and hepatic CYP3A4 enzyme abundance ($\text{Abundance}_{CYP3A4,liver}$) specific to each hepatic-impaired population and consistent microsomal protein per gram of liver (MPPGL) were according to Johnson et al.¹⁸ The hepatic CL through non-CYP3A pathways ($CL_{u,int,others}$) were scaled for the respective liver weight and microsomal protein per gram of liver. The sum of the $CL_{u,int}$ (equation 2) was applied to well-stirred liver model (equation 3) to obtain the hepatic blood CL ($CL_{H,B}$) of alectinib.

$$CL_{u,int} = CL_{u,int,CYP3A4} + CL_{u,int,others} \quad (2)$$

$$CL_{H,B} = \frac{CL_{u,int} \times f_{u_p}/BP \times Q_H}{CL_{u,int} \times f_{u_p}/BP + Q_H} \quad (3)$$

where unbound fraction in plasma (f_{u_p}) and blood to plasma partition coefficients (BP) were scaled based on the predicted serum albumin concentration and fraction of hematocrit for each hepatic impairment category.¹⁸ Although specific hepatic blood flow (Q_H) for the respective hepatic impairment category¹⁸ was applied, alectinib is a low-extraction drug; thus, the $CL_{H,B}$ can be approximated to be $CL_{u,int} \times f_{u_p}/BP$. Therefore, reduced abundance of CYP3A4 enzymes, liver size, and albumin concentration were assumed to be the major factors to alter alectinib CL with hepatic impairment.^{11,12,18} The alectinib hepatic impairment model accurately predicted the observed lack of relevant effect of mild hepatic impairment, which was

demonstrated by population PK analyses (data not shown). This model was considered suitable to predict effects of alectinib in moderate and severe hepatic impairment on alectinib PK.

A minimal PBPK model was developed for the major metabolite, M4, in which the apparent volume of distribution at steady state (V_{ss}) and CL (including 15% of hepatic metabolism through CYP3A4 enzyme) were empirically estimated from a clinical DDI study with a potent CYP3A inhibitor.²¹ The effect of hepatic impairment in the M4 model was incorporated primarily via reduced liver size; a reduction in CYP3A abundance, the known metabolic pathway for M4 elimination; and a reduction in albumin values.

Clinical Study

The clinical study was conducted at PRA Phase I Clinics in Prague, Czech Republic, and in Bratislava, Slovak Republic, in accordance with the Declaration of Helsinki and good clinical practice. The protocol was reviewed and approved by 2 ethics committees for the individual countries that participated in the trial: the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital with Multicenter Competence (Videňská 800 140 59 Prague 4, Czech Republic) and Etická komisia Bratislavského samosprávneho kraja (Sabinovská 16 820 05 Bratislava, Slovakia). All study participants provided written informed consent prior to any study-related procedures.

Eligibility

Eligible subjects were men or surgically sterile or postmenopausal (for the past year) women, aged 18 to 70 years, inclusive, with documented chronic stable moderate or severe hepatic impairment (Child-Pugh B/C) and healthy subjects matched for age (± 10 years; ≤ 70 years old), body weight ($\pm 10\%$; > 50 kg), and sex. Healthy subjects were recruited to match one or more of the subjects with hepatic impairment based on the criteria described above. Key exclusion criteria included use of any medication for healthy subjects and use of CYP3A or P-glycoprotein inhibitor for subjects with hepatic impairment within 2 weeks or any herbal supplements or metabolic inducers within 4 weeks or 5 half-lives before the first dose of study drug, whichever was longer, and while on treatment in the study; any clinically significant concomitant diseases or conditions (other than hepatic impairment in those subjects) that could interfere with the study objectives; and participation in an investigational drug study within 45 days (6 months for biologics) or 5 half-lives before alectinib dosing, whichever was longer. In subjects with hepatic impairment, additional key exclusion criteria included any major illness within 1 month or acute illness within 14 days prior to

dosing; history of liver transplantation, hepatocellular carcinoma, acute liver disease, severe ascites, current or recent history of severe hepatic encephalopathy, serum alanine aminotransferase or aspartate transaminase $> 5 \times$ ULN, or abnormal renal function at baseline.

Study Design and Treatment

This was a multicenter, open-label, parallel group study investigating the effect of moderate and severe hepatic impairment on the PK of alectinib and M4 following administration of a single oral dose of alectinib (ClinicalTrials.gov: NCT02621047).

Following an overnight fast of at least 10 hours, subjects were administered a single oral 300-mg dose of alectinib 30 minutes after the start of a standard meal comprising approximately 514 total calories, with approximately 31% of calories from fat, 51% from carbohydrates, and 19% from protein; the meal was to be consumed in 30 minutes or less. A lower dose than the recommended 600 mg of alectinib was utilized based on predictions from PBPK modeling activities (see Results below).

Alectinib was administered as capsules with 240 mL of noncarbonated water, and no food was allowed for at least 4 hours after the alectinib dose. Regular meals were provided 4 and 10 hours after alectinib dosing. Subjects had the option to be confined in the study center starting on the day before dosing and discharged following completion of all scheduled assessments on the day of the last blood sample for PK assessment, or have daily outpatient visits starting 72 hours after dosing until day of discharge. Following discharge from the study center, subjects returned for a follow-up assessment 7 to 10 days after last study drug administration.

Pharmacokinetic and Safety Assessments

PK samples were collected for determination of total alectinib and M4 plasma concentrations at predose and 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose. Extended PK sampling was supported by the PBPK modeling predictions, suggesting increased exposure secondary to reduced clearance of alectinib with hepatic impairment (see Results below). Total alectinib and M4 concentrations were determined by liquid chromatography–tandem mass spectrometry as previously described.²⁵ The lower limit of quantification was 1.50 ng/mL for both analytes, with a calibration range of 1.50 ng/mL to 1500 ng/mL.

Additional samples were collected for determination of unbound alectinib and M4 plasma concentrations at 6 (anticipated peak concentration) and 12 (anticipated trough concentration when given BID)

hours postdose. For each subject and time point, 3 plasma aliquots were dialyzed. The corresponding 3 final plasma and 3 final buffer probes were submitted for liquid chromatography–tandem mass spectrometry analysis. Study samples were spiked with alectinib, M4, or both compounds if the concentrations of alectinib and M4 were predicted to be too low to allow their free fraction determinations directly. Exclusion of single data points from triplicate determinations was conducted if up to 1% fraction unbound ($fu\%$) outlier could be removed from the average value calculation if the coefficient of variability was $>45.0\%$. If 1 outlier was to be excluded, the coefficient of variability of the 2 remaining values was $\leq 20.0\%$. The geometric mean value of the triplicate determinations was reported as the $fu\%$ at each time point per subject.

Alectinib and M4 PK parameters were determined by standard noncompartmental methods using Phoenix WinNonlin Version 6.2 (Pharsight Corporation, Cary, North Carolina), including maximum observed plasma concentration (C_{max}); area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$); T_{max} ; $t_{1/2}$; apparent oral clearance for alectinib (CL/F); apparent volume of distribution for alectinib; and molecular weight-adjusted M4 metabolite/parent (M/P) C_{max} and $AUC_{0-\infty}$ ratio. The $fu\%$ was determined as unbound concentration/total concentration $\times 100$ at respective time points. Results showed similar $fu\%$ at 6 and 12 hours postdose (data not shown), and therefore the mean $fu\%$ across the 2 time points was determined for each subject, compared across hepatic function groups, and used to calculate unbound alectinib and M4 PK parameters by multiplying $fu\% \times$ total PK parameter.

Safety evaluations included collection of adverse event (AE) data, vital signs, clinical laboratory assessments, and electrocardiograms.

Sample Size and Statistical Analysis

No formal sample size calculations were performed. For each level of hepatic impairment, 8 subjects were planned for recruitment, chosen based on practical considerations and recommendations in guidance documents.^{26,27} Nonetheless, assuming a between-subject coefficient of variability of $\sim 39\%$ as reported previously,⁹ 8 subjects in each group would enable 80% power to detect a 1.84-fold increase (which was at least predicted from the prospective PBPK modeling; see Results below) with a 2-sided significance level of 0.05 using a 2-sided t-test in alectinib AUC.

Individual subject ratios (moderate hepatic impairment/matched healthy subjects or severe hepatic impairment/matched healthy subject) of the values for C_{max} and $AUC_{0-\infty}$ of alectinib and M4 were summarized. Analysis of variance was applied

to the log-transformed C_{max} and $AUC_{0-\infty}$; results were back transformed to provide geometric mean ratios (GMRs) and confidence intervals (CIs). Models were fit separately for each hepatic impairment group and the corresponding matched healthy controls and included a fixed effect for group as well as a random effect reflecting the matching of healthy controls to hepatic-impaired patients.

Given that both alectinib and M4 are pharmacologically active, with similar activity and potency against *ALK*,²⁸ statistical analyses for C_{max} and $AUC_{0-\infty}$ were performed on the molecularly weight adjusted combined exposure of alectinib and M4. Analyses were conducted on total and unbound PK parameters for the respective analytes.

Results

PBPK Modeling

The prospective PBPK modeling predicted a 2.25-fold and 2.34-fold increase in alectinib $AUC_{0-\infty}$ in subjects with moderate and severe hepatic impairment, respectively, relative to matched healthy subjects. These predictions were used to support the selection of the reduced alectinib 300-mg dose and the use of extended PK sampling in the clinical study. The prospective PBPK modeling predicted an 11% increase and 12% decrease in M4 $AUC_{0-\infty}$ in subjects with moderate and severe hepatic impairment, respectively, relative to matched healthy subjects.

Clinical Study

Subjects. A total of 28 subjects, 8 subjects with moderate and severe hepatic impairment each and 12 healthy subjects, participated in the study. Baseline demographics were generally similar between hepatic impairment and all healthy subjects (Table 1). All subjects in the hepatic impairment groups completed the study per protocol, while 1 healthy subject was prematurely withdrawn due to an unrelated serious AE (see Safety Results below).

Total Pharmacokinetics. Figure 1 illustrates plots of mean total alectinib, M4, and combined exposure of alectinib and M4 plasma concentrations over time for subjects with moderate and severe hepatic impairment and matched healthy subjects. Table 2 and Table 3 provide a summary of total PK parameters and the statistical analysis of the effect of hepatic impairment, respectively.

Following administration of the single oral 300-mg dose of alectinib, alectinib was absorbed with the median T_{max} reached by approximately 6 hours across groups (Figure 1, Table 2). Relative to matched healthy subjects, administration of alectinib to subjects

Table 1. Summary of Baseline Demographics

Category/Statistic		Moderate (N = 8)	Severe (N = 8)	Healthy (N = 12)
Sex, n (%)	Male	5 (62.5)	4 (50.0)	7 (58.3)
	Female	3 (37.5)	4 (50.0)	5 (41.7)
Race, n (%)	White	8 (100.0)	8 (100.0)	12 (100.0)
Ethnicity, n (%)	Not Hispanic or Latino	8 (100.0)	8 (100.0)	12 (100.0)
Age (y)	Mean (range)	54.6 (35-62)	53.1 (44-61)	52.2 (39-65)
Weight (kg)	Mean (range)	82.6 (61.0-105)	87.1 (54.0-115)	82.0 (58.8-115)
Height (cm)	Mean (range)	171 (158-184)	169 (157-186)	170 (149-183)
BMI (kg/m ²)	Mean (range)	28.6 (21.8-34.7)	30.1 (18.3-34.7)	28.1 (21.0-34.3)

BMI indicates body mass index.

with moderate or severe hepatic impairment resulted in no appreciable difference in C_{max} , while alectinib $AUC_{0-\infty}$ was increased to 160% and 220% for moderate and severe hepatic impairment, respectively (Table 3). Consistent with the observed effect on $AUC_{0-\infty}$, alectinib apparent CL/F was reduced in hepatic impairment subjects compared with matched healthy subjects (Table 2). Alectinib arithmetic mean elimination $t_{1/2}$ was prolonged in subjects with moderate hepatic impairment (26.9 hours) and severe hepatic impairment (40.4 hours) relative to matched healthy subjects (20.5 and 23.2 hours for those matched to subjects with moderate and severe hepatic impairment, respectively).

Administration of alectinib resulted in the appearance of M4 with its median T_{max} reached by 8 hours across groups. M4 exposure was lower in moderate and severe hepatic impairment relative to matched healthy subjects. In subjects with moderate hepatic impairment, M4 C_{max} and $AUC_{0-\infty}$ were reduced to 64.6% and 80.6%, respectively, relative to matched healthy subjects (Table 3). In subjects with severe hepatic impairment, M4 C_{max} and $AUC_{0-\infty}$ were reduced to 60.8% and 65.6%, respectively, relative to matched healthy subjects (Table 3). The molecular weight–adjusted M/P ratios were reduced in subjects with hepatic impairment relative to matched healthy subjects, reflecting the observed changes in the individual analytes. The geometric mean M/P ratio for $AUC_{0-\infty}$ was 0.231 and 0.415 for subjects with moderate hepatic impairment and matched healthy subjects, respectively, and 0.128 and 0.428 for subjects with severe hepatic impairment and matched healthy subjects, respectively.

Administration of alectinib to moderate and severe hepatic impairment subjects resulted in no appreciable difference in C_{max} of the combined exposure of alectinib and M4 while resulting in higher $AUC_{0-\infty}$ of the combined exposure of alectinib and M4. The $AUC_{0-\infty}$ GMRs were 136% (90%CI, 94.7–196) and 176% (90%CI, 98.4–315) for subjects with moderate and severe hepatic impairment, respectively, relative to matched healthy subjects (Table 3).

Unbound PK. Both alectinib and M4 display high binding to plasma proteins *in vitro*²⁸; therefore, clinical samples were collected to investigate the effect of hepatic impairment on fu% for both analytes. Figure 2 illustrates box plots of individual mean fu% for alectinib and M4, respectively, by hepatic function.

Distributions of individual mean fu% show moderate to high variability between subjects with a large overlap in fraction unbound for alectinib and M4 between both moderate and severe hepatic impairment and respective matched healthy subjects (Figure 2). The alectinib median value of individual mean fu% in moderate and severe hepatic impairment was 0.229% and 0.179%, respectively, compared with 0.206% and 0.140% in respective matched healthy subjects. For M4, the median value of individual mean fu% in moderate and severe hepatic impairment was 0.922% and 0.351%, respectively, compared with 0.632% and 0.603% in respective matched healthy subjects. A post hoc exploratory paired t-test between subjects with hepatic impairment and respective matched healthy subjects revealed no statistical differences ($P \geq .2$) in fu%, suggesting no substantial differences in fraction unbound for alectinib and M4 across populations. The individual mean fu% was used to calculate unbound PK parameters.

Table 4 provides the statistical analysis of the effect of hepatic impairment on unbound PK parameters. Statistical analyses showed that, relative to matched healthy subjects, alectinib unbound C_{max} was modestly higher in subjects with hepatic impairment with no clear relationship with degree of hepatic impairment, while alectinib unbound $AUC_{0-\infty}$ was increased to 186% and 285% for moderate and severe hepatic impairment, respectively, relative to matched healthy subjects (Table 4). Consistent with the observed effect on $AUC_{0-\infty}$, alectinib apparent unbound CL/F was reduced following administration in hepatic impairment subjects relative to matched healthy subjects. The arithmetic mean unbound alectinib CL/F was 530 L/hour and 436 L/hour for moderate and severe hepatic impairment, respectively, compared with

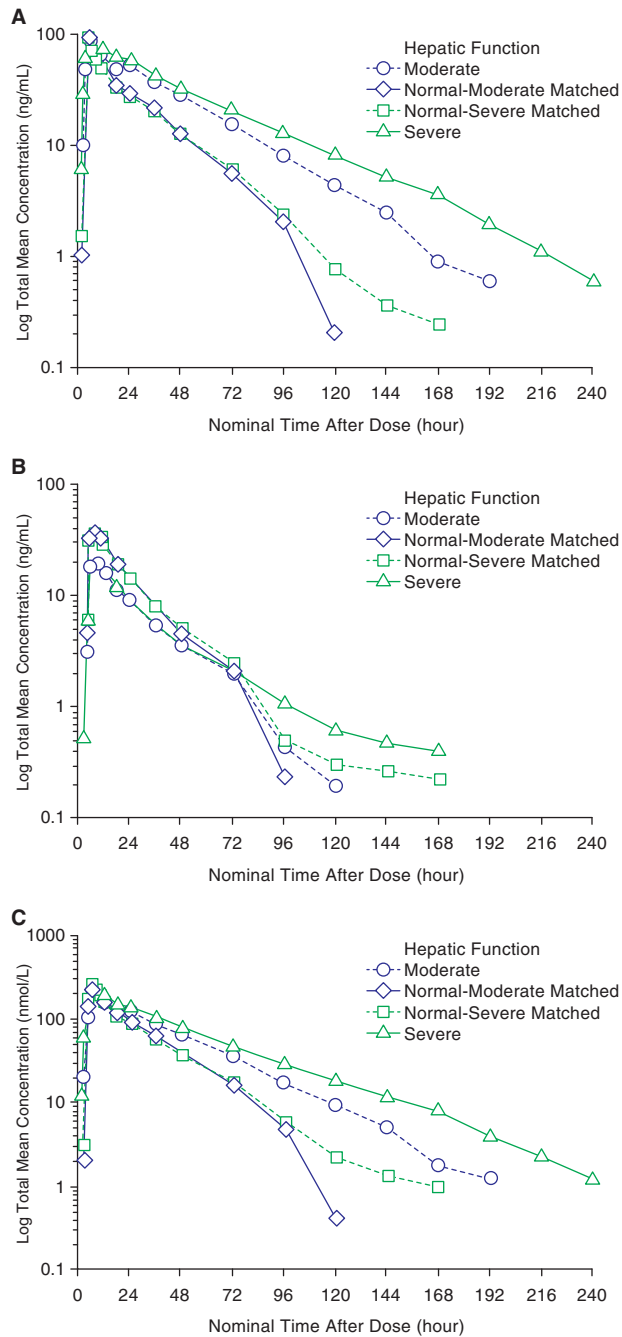


Figure 1. Mean plasma concentration vs time profiles of total alectinib, M4, and alectinib+M4 in subjects with moderate and severe hepatic impairment and respective matched healthy subjects (log-linear scale).

874 L/hour and 1430 L/hour for respective matched healthy subjects.

Statistical analyses showed that following alectinib administration there was no clear change in M4 unbound C_{max} or unbound $AUC_{0-\infty}$ in moderate hepatic impairment relative to matched healthy subjects. In subjects with moderate hepatic impairment, M4 unbound C_{max} and unbound $AUC_{0-\infty}$ were 85.1% and

104%, respectively, relative to matched healthy subjects (Table 4). In subjects with severe hepatic impairment, M4 unbound C_{max} and unbound $AUC_{0-\infty}$ were reduced to 59.0% and 63.7%, respectively, relative to matched healthy subjects (Table 4).

Administration of alectinib to subjects with moderate and severe hepatic impairment resulted in no appreciable difference in unbound C_{max} of the combined exposure of alectinib and M4 while resulting in modestly higher unbound $AUC_{0-\infty}$ of the combined exposure of alectinib and M4 (Table 4). The unbound $AUC_{0-\infty}$ GMRs were 134% (90%CI, 99.6-181) and 157% (90%CI, 91.8-268) for subjects with moderate and severe hepatic impairment, respectively, relative to matched healthy subjects (Table 4).

Safety. Alectinib administered as a single oral dose of 300 mg was well tolerated in healthy subjects and subjects with moderate or severe hepatic impairment. Only 2 AEs were reported in 2 healthy subjects: 1 healthy subject with concurrent arterial hypertension reported a serious AE of unstable angina pectoris, while another subject experienced a mild arthralgia. Both AEs were considered unrelated to the study drug by investigator. No AEs were reported in any subject with moderate or severe hepatic impairment.

No clinically significant changes in vital signs, laboratory values, or electrocardiogram measurements were observed during the study.

Discussion

In vitro metabolism studies and clinical mass balance results indicate that the elimination of alectinib is mainly through metabolism in the liver by CYP3A4 to its major similarly active metabolite, M4.^{11,12} The effect of moderate or severe hepatic impairment on the PK of alectinib was assessed in a clinical study in subjects with underlying hepatic impairment and compared with a population of healthy subjects with normal liver function, matched by age, body weight, and sex.

The clinical study was designed based on the knowledge of alectinib and M4 PK and recommendations in guidance documents.^{26,27} A single-dose study design was selected, as previous investigations have shown similar M4/alectinib exposure ratios following single and multiple dosing, suggesting no change in alectinib metabolism over time.^{10,13} Additionally, this design would support operational feasibility, as only single alectinib doses could be administered to healthy subjects or otherwise healthy subjects with hepatic impairment (ie, non-cancer patients) based on nonclinical safety data for alectinib.²⁹ The Child-Pugh classification was used for assessment of hepatic impairment,

Table 2. Summary of Alectinib and M4 Total Pharmacokinetic Parameters Following a Single 300-mg Dose of Alectinib Administered to Subjects With Moderate and Severe Hepatic Impairment and Respective Matched Healthy Subjects

	Healthy Subjects—Matched for Moderate	Moderate Hepatic Impairment	Healthy Subjects—Matched for Severe	Severe Hepatic Impairment
Alectinib				
Parameter ^a (units)				
C _{max} (ng/mL)	94.3 (46.7)	111 (27.8)	103 (58)	93.5 (35)
AUC _(0-∞) (ng • h/mL)	1950 (740)	3280 (1470)	1990 (939)	4260 (1890)
T _{max} (h), median (range)	6.0 (4.0-6.1)	6.0 (3.8-23.8)	5.0 (3.9-6.1)	7.0 (2.0-11.9)
t _{1/2} (h)	20.5 (4.84)	26.9 (7.41)	23.2 (7.59)	40.4 (10.4)
Vz/F (L)	5500 (3300)	4350 (2380)	7430 (7760)	5330 (3690)
CL/F (L/h)	175 (67.5)	120 (83.7)	203 (144)	88.2 (53.3)
M4				
Parameter ^a (units)				
C _{max} (ng/mL)	37.1 (23.1)	21.9 (10.7)	36.5 (22.6)	23.2 (15.0)
AUC _(0-∞) (ng • h/mL)	837 (443)	588 (87.4)	888 (580)	670 (500)
T _{max} (h), median (range)	7.9 (5.9-10.0)	8.1 (6.1-35.8)	8.1 (5.9-11.6)	8.0 (6.0-11.9)
t _{1/2} (h)	19.6 (3.55)	26.6 (10.8)	21.0 (7.6)	35.3 (18.8)
Vz/F (L)	—	—	—	—
CL/F (L/h)	—	—	—	—

AUC_{0-∞} indicates area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL/F, oral clearance for alectinib; C_{max}, maximum observed plasma concentration; SD, standard deviation; t_{1/2}, half-life; T_{max}, time to maximal concentrations; Vz/F, volume of distribution for alectinib.

^aData are presented as arithmetic mean (SD) except where indicated.

Table 3. Statistical Analysis of the Effect of Moderate and Severe Hepatic Impairment on the Total Pharmacokinetic Parameters of Alectinib, M4, and Alectinib+M4

Moderate Hepatic Impairment/Matched Healthy Subjects			
Analyte	Parameter (Units)	GMR, %	90%CI
Alectinib	C _{max} (ng/mL)	128	86.5-188
	AUC _{0-∞} (ng • h/mL)	160	105-243
M4	C _{max} (ng/mL)	64.6	36.2-115
	AUC _{0-∞} (ng • h/mL)	80.6	50.2-130
Alectinib+M4	C _{max} (nmol/mL)	116	78.6-172
	AUC _{0-∞} (nmol • h/mL)	136	94.7-196
Severe Hepatic Impairment/Matched Healthy Subjects			
Analyte	Parameter (Units)	GMR, %	90%CI
Alectinib	C _{max} (ng/mL)	100	55.1-183
	AUC _{0-∞} (ng • h/mL)	220	131-369
M4	C _{max} (ng/mL)	60.8	26.6-139
	AUC _{0-∞} (ng • h/mL)	65.6	26.9-160
Alectinib+M4	C _{max} (nmol/mL)	98.1	51.7-186
	AUC _{0-∞} (nmol • h/mL)	176	98.4-315

AUC_{0-∞} indicates area under the alectinib plasma concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio.

as it is a widely recognized grading system. PBPK modeling was undertaken to predict the effects of hepatic impairment by accounting for known alectinib disposition pathways and clinical PK properties and the physiologic alterations due to hepatic impairment. PBPK was used to support the dose selection and design of the clinical study.

Following administration of a single 300-mg alectinib dose to healthy subjects in this study, alec-

tinib geometric mean PK parameters (AUC_{0-∞} and C_{max}) were as expected and approximately half of the geometric mean values achieved in previous studies in which healthy subjects received single 600-mg alectinib doses with a similar meal type.^{8,9} Following administration to hepatically impaired subjects, alectinib AUC_{0-∞} GMRs were 160% and 220% for moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared with matched healthy subjects. Increases in exposure of ≥2.4-fold with hepatic impairment have been seen for other kinase inhibitors that are eliminated through hepatic metabolism.^{30,31} The observed magnitude of alectinib exposure increase in this study is close to that predicted by the PBPK modeling, which supported the selection of the lower alectinib 300-mg dose in the study. Hepatic impairment may affect the exposure of hepatically metabolized agents through various mechanisms, including alterations in liver blood flow, binding to plasma proteins, and reduced hepatic intrinsic clearance due to lower expression of CYP enzymes, among other factors.³² Previous investigations have supported that alectinib is subject to low hepatic extraction.¹² For such drugs, hepatic clearance is primarily determined by the intrinsic metabolizing capacity of the liver and by the free drug fraction. Therefore, the observed higher alectinib exposures in the subjects with hepatic impairment is likely attributed to reduced hepatic intrinsic clearance, as no major changes were seen in fu% (as observed in the clinical study results). Indeed, published reports indicate that the expression of CYPs, including CYP3A4, decrease with increasing hepatic impairment severity, and other PK studies have shown a decrease

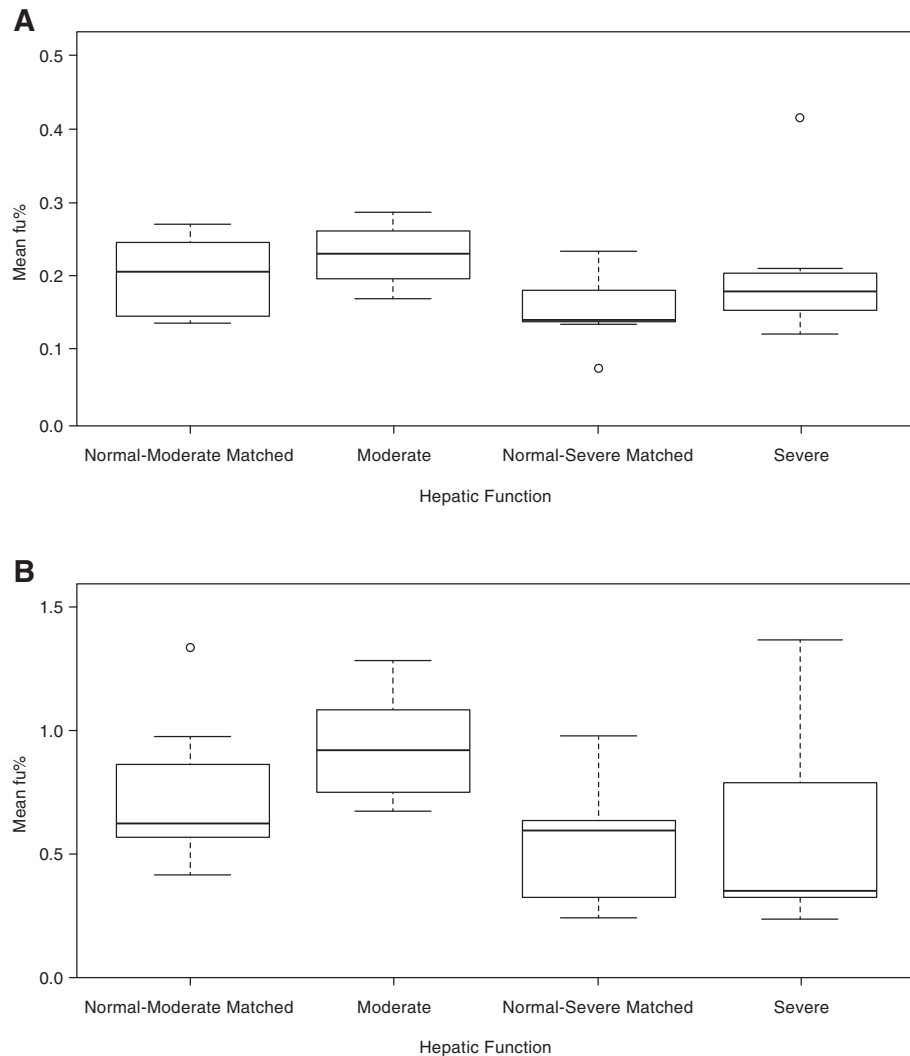


Figure 2. Box plots of the distribution of individual mean percent fraction unbound ($f_u\%$) in subjects with moderate and severe hepatic impairment and respective matched healthy subjects.

in the clearance of drugs metabolized by CYP3A in liver dysfunction.^{32–40} Consistently, coadministration of a potent CYP3A inhibitor increased the exposure of alectinib by 75%, supporting this hypothesis.⁹ The *in vivo* $f_{m_{CYP3A4}}$ and F_G of alectinib derived from the established PBPK model were estimated to be 40% and $\geq 90\%$, respectively. The prospective simulations for alectinib in hepatic impairment assumed scaling of the intrinsic CL of alectinib using the reported physiologic and anatomic data of the hepatic impairment population according to Johnson et al.¹⁸ These scaled intrinsic CL values suggest that contribution of CYP3A metabolism to the total CL of alectinib decreases from 40% in the patients with normal hepatic function to 21% and 14% in the moderate and severe hepatic impairment population, respectively, due to the reduced CYP3A enzyme expression. Any discrepancy between the prospective PBPK model predictions and observed

effects could be associated with assumed changes in free fraction in the PBPK model, which were not clearly observed in this study (see below); potential alterations (other than CYP3A4) in alectinib elimination pathways not accounted for in the modeling exercise; and/or potential disease-mediated alterations in drug absorption.³² While hepatic impairment-related effects on absorption have been postulated for another agent, bosutinib,⁴¹ the lack of relevant effect on alectinib C_{max} in the study suggests that disease-mediated effects on alectinib absorption are unlikely under fed conditions. The PBPK modeling exercise was nonetheless still useful in successfully informing the clinical study design by predicting an effect on alectinib PK and supporting the use of the lower alectinib 300-mg dose along with the extended PK sampling in the clinical study.

Alectinib C_{max} showed no relevant difference in subjects with hepatic impairment compared with matched

Table 4. Statistical Analysis of the Effect of Moderate and Severe Hepatic Impairment on the Unbound Pharmacokinetic Parameters of Alectinib, M4, and Alectinib+M4

Moderate Hepatic Impairment/Matched Healthy Subjects			
Analyte	Parameter (Units)	GMR, %	90%CI
Alectinib	C_{max} (ng/mL)	148	106-208
	$AUC_{0-\infty}$ (ng · h/mL)	186	122-281
M4	C_{max} (ng/mL)	85.1	55.5-130
	$AUC_{0-\infty}$ (ng · h/mL)	104	76.8-141
Alectinib+M4	C_{max} (nmol/mL)	115	85.2-154
	$AUC_{0-\infty}$ (nmol · h/mL)	134	99.6-181
Severe Hepatic Impairment/Matched Healthy Subjects			
Analyte	Parameter (Units)	GMR, %	90%CI
Alectinib	C_{max} (ng/mL)	130	75.4-225
	$AUC_{0-\infty}$ (ng · h/mL)	285	175-466
M4	C_{max} (ng/mL)	59.0	34.2-102
	$AUC_{0-\infty}$ (ng · h/mL)	63.7	34.0-119
Alectinib+M4	C_{max} (nmol/mL)	96.6	55.6-168
	$AUC_{0-\infty}$ (nmol · h/mL)	157	91.8-268

$AUC_{0-\infty}$ indicates area under the alectinib plasma concentration–time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; GMR, geometric mean ratio.

healthy subjects with normal hepatic function. Hepatic impairment is reported to alter the architecture of the liver with development of portal-systemic shunting resulting in reduced presystemic elimination of drugs.³² The lack of relevant effect on alectinib C_{max} suggests minimal effect of hepatic impairment on presystemic elimination of alectinib in line with its low hepatic extraction.¹² Similarly, only a minor effect was seen on alectinib C_{max} following coadministration of a potent CYP3A inhibitor.⁹

Administration of a single 300-mg alectinib dose to healthy subjects similarly resulted in M4 geometric mean PK parameters ($AUC_{0-\infty}$ and C_{max}) within the range expected based on previous studies.^{8,9} In subjects with hepatic impairment, the exposure of M4 was reduced when compared with matched subjects with normal hepatic function. The minimal PBPK model for M4 did not appear to predict well the magnitude of observed effect in M4 PK. This could potentially be due to the limited knowledge in the complete M4 elimination pathways.^{11,12} In vitro studies support that M4 is further metabolized by CYP3A;¹¹ however, the observed effects in this study, likely reflecting a reduction in the formation of M4 from alectinib in subjects with hepatic impairment, suggest a lower fraction metabolized of M4 by CYP3A than for alectinib. Notably, similar observations of a reduction of M4 exposure were seen following coadministration of a potent CYP3A inhibitor.⁹ Mean M4 elimination $t_{1/2}$ appeared to modestly prolong with hepatic impairment, which may be contributed to by variability at

low concentrations in the terminal phase, or longer $t_{1/2}$ of the parent and/or potential reduced elimination via CYP3A, which also metabolizes M4. The reported M/P ratios across the groups in this study reflect the reduced metabolism of alectinib to M4.

As both alectinib and M4 inhibit ALK with similar potency in vitro²⁸ the effect of hepatic impairment on the combined exposure of alectinib and M4, adjusted for molecular weight, was determined in this study. This approach has been explored for other alectinib clinical pharmacology investigations^{8,9,13} and for other small-molecule kinase inhibitors with active metabolites.⁴² The AUC of the combined exposure of alectinib and M4 was increased in hepatic impairment compared with matched subjects with normal hepatic function. $AUC_{0-\infty}$ GMRs were 136% and 176% for moderate and severe hepatic impairment, respectively, compared with matched subjects with normal hepatic function.

Both alectinib and M4 show high protein binding in vitro ($\geq 99\%$)²⁸ and therefore, consistent with recommendations in guidance documents,^{26,27} the $fu\%$ was estimated for both analytes. Alectinib and M4 $fu\%$ values did not appear substantially different between hepatic impairment and respective matched healthy subjects. Observations of no substantial differences in $fu\%$ between subjects with hepatic impairment and healthy subjects have been reported for liraglutide, another agent with high protein binding.⁴³ Conversely, the default SimCYP[®] PBPK model assumes some alterations in the free fraction with hepatic impairment due to expected changes in albumin values in patients with hepatic impairment. The reason for this potential difference is not clear, but the extremely high protein binding for both alectinib and M4 may be associated with challenges in measuring the small free fraction of both analytes with high precision across populations in the clinical study.⁴⁴ Of note, up to 2-fold variability in assay results is not unexpected and has been previously reported for other highly protein-bound molecules (Roche, data on file).⁴³ The clinical study results support no substantial differences between populations and the overall estimated $fu\%$ were within the range attained from in vitro experiments.²⁸ The effect of hepatic impairment on unbound PK parameters generally followed a similar direction as total PK parameters. For the combined exposure of alectinib and M4, unbound $AUC_{0-\infty}$ GMRs were 134% and 157% for subjects with moderate and severe hepatic impairment, respectively, relative to matched healthy subjects.

The clinical relevance of the observed exposure changes with hepatic impairment were considered in the context of known exposure–response relationships for alectinib efficacy and safety. Completed population-based exposure–response analyses have demonstrated

no significant relationships between the combined exposure of alectinib and M4 and safety events following administration of alectinib 600 mg BID in global pivotal studies.¹³ Those analyses support that the modest increases seen in the combined exposure of alectinib and M4 in moderate hepatic impairment are not clinically meaningful and support no dose adjustment in moderate hepatic impairment. The greater increases seen in the combined exposure of alectinib and M4 in the potentially vulnerable severe hepatic impairment population, however, support dose adjustments in patients with underlying severe hepatic impairment. With the available 150 mg capsule strength for alectinib, a dose adjustment to alectinib 450 mg BID, representing 75% of the recommended 600 mg BID dose, would provide alectinib exposure similar to the exposure seen in the subjects with moderate hepatic impairment where no dose adjustments are warranted (severe hepatic impairment alectinib+M4 $AUC_{0-\infty}$ GMR: $176\% \times 75\% = 132\%$) and closer to the reported exposures achieved in the matched healthy subjects with normal hepatic function. Further dose reductions would result in lower alectinib exposures compared with matched healthy subjects.

Conclusions

The effect of underlying hepatic impairment on the PK of alectinib and its major active metabolite were investigated in a clinical study with support of PBPK modeling and simulation. Results from the clinical study, regardless of whether protein binding is taken into account, support the optimal use of alectinib in this specific population where there was a lack of information. The observed study results support that dose adjustments are not needed for patients with moderate hepatic impairment, while a starting dose adjustment is supported in patients with severe hepatic impairment. The PBPK modeling exercise enabled an informed clinical study design and provided mechanistic insight of the observed effects through integration of the known nonclinical and clinical data for alectinib and physiologic alterations with underlying hepatic impairment.

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Data Accessibility Statement

The data used in this manuscript are not accessible.

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Declaration of Conflicting Interests

P.N.M., Y.C., C.S.-P., E.G., M.A., M.D., F.V., B.B., N. P., and L. Y. are employees of, and own stock/stock options in, Roche.

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