# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208434Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# OFFICE OF CLINICAL PHARMACOLOGY

## Clinical Pharmacology Review

| | |
|---|---|
| **NDA** | 208-434 |
| **Type/Category** | New Molecular Entity |
| **Brand Name** | Alecensa |
| **Generic name** | Alectinib (RO5424802) |
| **Indication** | Non-small cell lung cancer (NSCLC) |
| **Dosage Form** | 150 mg capsules with (b) (4)% w/w sodium lauryl sulfate (SLS) |
| **Route of Administration** | Oral |
| **Dosing Regimen and Strength** | 600 mg twice daily (BID) with food |
| **Applicant** | Roche |
| **OCP Division** | DCP V |
| **OND Division** | DOP 2 |
| **Submission Date** | July 6, 2015 |
| **PDUFA** | March 4, 2016 |
| **Primary Reviewers** | Stacy S. Shord, Pharm.D.<br>Jingyu (Jerry) Yu, Ph.D.<br>Ping Zhao, Ph.D. |
| **Secondary Reviewers** | Hong Zhao, Ph.D.<br>Yaning Wang, Ph.D.<br>Vikram Sinha, Ph.D. |

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# 1 EXECUTIVE SUMMARY

Alectinib is a kinase inhibitor that inhibits the anaplastic lymphoma kinase (ALK). The Applicant's proposed indication for alectinib is for the treatment of ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have progressed on or are intolerant to crizotinib at a dose of 600 mg twice daily (BID) with food. This review addresses three key questions.

1. *Do the exposure-response relationships support the proposed dosage regimen of 600 mg twice daily?* The exposure-activity relationship and safety profile observed in the dose finding portion of Study NP28761 supported the dose selection of 600 mg twice daily for the registration portion of Study NP28761 and Study NP28673. No exposure–response (E-R) relationship was identified for best overall response, grade 3 or higher adverse events or other adverse events at a dose of 600 mg BID. The dose of 600 mg BID appears well-tolerated based on safety profile and low dose modification rates in the clinical trials.
2. *What is an appropriate dose for patients taking a strong cytochrome P450 (CYP) 3A modulator?* Alectinib is metabolized by CYP3A4 to its major active metabolite M4; this pathway accounts for about 40% of alectinib's metabolism. No dose adjustment is needed for patients taking a CYP3A4 modulator, since no clinically meaningful change in the combined exposure of alectinib and M4 was observed following the coadministration of a single alectinib dose with multiple doses of rifampin or posaconazole.
3. *What is an appropriate dose for patients with hepatic impairment?* The registration trials included 59 patients with mild hepatic impairment. No dose adjustment is needed for patients with mild hepatic impairment based on the population pharmacokinetic (PK) analysis. A dedicated study in subjects with hepatic impairment is planned to determine an appropriate dosage regimen for patients with moderate to severe hepatic impairment.

## 1.1 RECOMMENDATIONS

This NDA is acceptable for approval from a clinical pharmacology perspective.

| Decision | Acceptable to OCP? | Comment |
|---|---|---|
| Overall | Yes | |
| Evidence of effectiveness† | Yes | |
| Proposed dose for general population | Yes | |
| Proposed dose adjustment for others | Yes | A postmarket study in subjects with moderate to severe hepatic impairment will be requested. |
| Pivotal bioequivalence | Not Applicable | |
| Labeling | Yes | |

†This decision is from a clinical pharmacology perspective only. The determination of the overall safety and effectiveness is made by the clinical review team.

## 1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

### 1.2.1 Post Market Requirements

| Drug Development Question | Rationale | PMR |
|---|---|---|
| What is an appropriate dose for patients with hepatic impairment? | The mass balance study indicates that 98% of a radiolabeled dose is eliminated in the feces, suggesting that hepatic elimination is the major elimination pathway. | Complete a pharmacokinetic (PK) trial to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment.<br>Trial Completion: July 2017<br>Final Report Submission: December 2017 |

### 1.2.2 Post Market Commitments

None.

### 1.2.3 Additional Comments

Conduct clinical pharmacokinetic trials to determine the effect of alectinib on the pharmacokinetics of a sensitive multidrug resistance protein 1 (MDR1) substrate and a sensitive breast cancer resistance protein substrate in accordance with the FDA draft Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” and submit the final study report to the IND.

**Signatures:**

| | |
|---|---|
| Stacy S. Shord, Pharm.D.<br>Reviewer<br>Division of Clinical Pharmacology V | Hong Zhao, Ph.D.<br>Team Leader<br>Division of Clinical Pharmacology V |
| Ping Zhao, Ph.D.<br>PBPK Scientific Lead<br>Division of Pharmacometrics | Vikram Sinha, Ph.D.<br>Division Director<br>Division of Pharmacometrics |
| Jingyu (Jerry) Yu, Ph.D.<br>Reviewer<br>Division of Pharmacometrics | Yaning Wang, Ph.D.<br>Acting Team Leader<br>Division of Pharmacometrics |
| | NAM Atiqur Rahman, Ph.D.<br>Division Director<br>Division of Clinical Pharmacology V |

CC**:** **DOP2:** RPM-G Davis; MO-E Larkin; MTL-G Blumenthal
**DCPV:** DDD – B Booth

## 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Alectinib is a kinase inhibitor that inhibits the ALK. The proposed indication is for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib at a dose of 600 mg BID administered with food.

Two open-label trials were conducted to evaluate the efficacy and safety of alectinib at a dose of 600 mg BID in patients with ALK-positive NSCLC. No E-R relationship was observed for best overall response, grade 3 or higher adverse events or other adverse events. The Applicant selected the proposed dose of 600 mg BID based on the exposure-activity relationship observed in the dose finding study and supported the dose with the safety and efficacy data from the registration trials.

Alectinib exposure increased in a dose proportional manner at doses of 460 mg to 900 mg under fed conditions after a single dose and at steady-state. The median maximal concentration ($T_{max}$) was observed at 4 hours. The absolute bioavailability is 37%. The administration of a single 600 mg dose with a FDA-specified high-fat, high-calorie meal resulted in a 3.1-fold increase in area under the curve ($AUC_{inf}$) of the combined exposure of alectinib and its major active M4 metabolite in healthy subjects. Alectinib demonstrated low solubility that decreased with increasing pH in vitro, but no clinically meaningful changes in the combined exposure were observed when a single 600 mg dose of alectinib was coadministered with multiple doses of esomeprazole.

Alectinib is metabolized by CYP3A4 to M4; this pathway accounts for about 40% of alectinib's metabolism based on the geometric mean metabolite to parent ratio estimated using the population PK model. No dose adjustment is recommended for patients taking strong CYP3A modulators with alectinib. Multiple dose of posaconazole increased the $AUC_{inf}$ of the combined exposure of alectinib and M4 by 1.4-fold when it was coadministered with a single 300 mg dose of alectinib. No statistically significant changes in the combined exposure were observed when multiple doses of rifampin were coadministered with a single 600 mg dose of alectinib. The geometric mean elimination half-life is 32 hours for alectinib and 31 hours for M4.

Alectinib and M4 inhibited CYP3A4 and induced CYP3A4 and CYP2B6 in vitro. No dose adjustment is recommended for concomitant CYP3A4 substrates, because no clinically meaningful changes in midazolam exposure were observed when alectinib at a dose of 600 mg twice daily was coadministered with a single midazolam dose. Alectinib inhibits CYP2C8 in vitro, but simulations suggest that no clinically meaningful changes in repaglinide exposure would occur when it is coadministered with multiple doses of alectinib. M4 is a multidrug resistance 1 (MDR1) substrate in vitro. Alectinib and M4 inhibited MDR1 and breast cancer resistance protein (BCRP) and alectinib inhibited bile salt export pump (BSEP) in vitro. Alectinib is not a substrate or inhibitor of OATP1B1 and OATP1B3.

Approximately 98% of the radiolabeled dose was excreted in feces following a single 600 mg oral dose of [$^{14}$C]-labeled alectinib. No dose adjustment is recommended for patients with mild hepatic impairment (as defined by National Cancer Institute criteria) or mild to moderate renal impairment (as defined by Cockcroft-Gault) based on population PK analysis. A postmarket study will be required to determine an appropriate dosage regimen for patients with moderate to severe hepatic impairment.

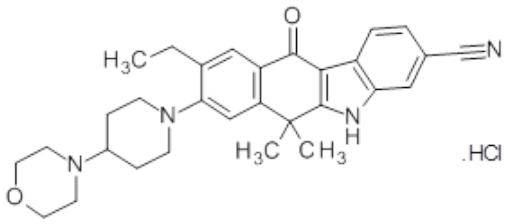
# 2 QUESTION BASED REVIEW

## 2.1 GENERAL ATTRIBUTES

### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they related to clinical pharmacology and biopharmaceutics review?

Alectinib is a kinase inhibitor with a molecular weight of 519 grams per mole (hydrochloride salt). The chemical structure is shown in **Figure 1**.

**Figure 1**. Chemical Structure of Alectinib Hydrochloride




Source: Figure2.3.S-1, Drug Substance.

The drug product is available as 150-mg capsules with (b)(4)% w/w sodium lauryl sulfate (SLS) to active pharmaceutical ingredient (API). The dose finding study in North American (NP28673) initially used 20-mg and 40-mg capsules with (b)(4)% w/w SLS. The 150-mg capsules were introduced into this dose finding study at a dose level of 600 mg and 900 mg. The remaining studies administered alectinib using the 150-mg capsules. The Applicant conducted an abbreviated PK comparison of the different capsule strengths as discussed in *Section 2.5*. No statically significant differences in exposure using the 150-mg and 20-mg and 40-mg capsules were observed.

Alectinib possesses low solubility that decreases with rising pH (**Table 1**). The solubility is substantially lower than the highest dose in 250 mL (2.4 mg/mL) of aqueous media over the pH range.

**Table 1.** Alectinib demonstrates low and pH dependent solubility

| Aqueous Medium or Buffer | Solubility at 25°C, 1 h (mg/mL) | Solubility at 25°C, 24 h (mg/mL) |
|---|---|---|
| pH 1 Buffer | 0.0013 | 0.0011 |
| pH 2 Buffer | 0.0009 | 0.0007 |
| pH 3 Buffer | 0.0009 | 0.0008 |
| pH 4 Buffer | 0.0012 | 0.0009 |
| pH 5 Buffer | 0.0016 | 0.0008 |
| pH 6 Buffer | 0.0005 | <LOQ |
| pH 7 Buffer | <LOQ | <LOQ |
| pH 8 Buffer | <LOQ | <LOQ |
| pH 9 Buffer | <LOQ | <LOQ |
| Water | 0.0354 | 0.0221 |
| FaSSIF[a] | 0.0279 | 0.0014 |
| FeSSIF[a] | 0.1021 | 0.1111 |
| JP First Fluid[b] | 0.0010 | 0.0010 |
| JP Second Fluid[c] | <LOQ | <LOQ |

Note: LOQ=0.0004 mg/mL.

Abbreviations: FaSSIF=fasted state simulated intestinal fluid; FeSSIF=fed state simulated intestinal fluid; LOQ=limit of quantitation.

Source: Table S.1.3-2, General Properties.

### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action

Alectinib is a kinase inhibitor that inhibits human recombinant ALK with an $IC_{50}$ value of 1.9 nM (report no. 1054067). Its M4 metabolite also inhibits human recombinant ALK with an $IC_{50}$ value of 1.2 nM (report no. 1056380). Alectinib and M4 also inhibit RET and some mutant ALK enzymes with $IC_{50}$ values less than 5 nM. Inhibiting ALK subsequently inhibits downstream signaling pathways, such as STAT3 and PI3K/AKT, and ultimately inhibits proliferation and cell survival.

Proposed Indications

The proposed indication is for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib. The labeled indication will likely be limited to patients with metastatic disease who progressed on crizotinib, as relatively few patients with locally advanced disease or intolerant to crizotinib were enrolled into the registration trials.

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is 600 mg BID orally with food. Alectinib was administered within 30 minutes from the start of a meal in the registration trials. The meal content was not specified in the clinical trial protocols. The effect of food on alectinib exposure is discussed in *Section 2.5*.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology Studies

The clinical pharmacology program is comprised of 8 clinical studies as described in **Table 2**. This program is supported by additional studies conducted using human biomaterials and in animals and reports describing population PK analysis, E-R analyses for efficacy and safety and physiological based pharmacokinetic (PBPK) analyses for drug interactions and food effect.

**Table 2.** Description of Clinical Pharmacology Studies

| Study No. | Assessment | Dosage and Administration | N |
|---|---|---|---|
| ***Studies in healthy subjects*** | | | |
| NP29040 | Relative bioavailability and bioequivalence – capsules with different percentages of SLS | 600 mg single oral dose under fed and fasted conditions | 97 |
| NP28989 | Absolute bioavailability and mass balance | 600 mg single oral dose and 50 µg intravenous dose under fed conditions | 6 |
| NP28990 | Drug interaction – posaconazole | 40 mg or 300 mg single oral dose under fed conditions | 23 |
| NP29042 | Drug interaction – rifampicin | 600 mg single oral dose under fed conditions | 24 |
| NP28991 | Food and drug interaction – esomeprazole | 600 mg single oral dose under fed and fasted conditions | 42 |
| ***Studies in patients with cancer*** | | | |
| NP28761 | Dose escalation – North America | 240 mg, 300 mg, 460 mg, 600 mg, 760 mg, 900 mg twice daily under fed or fasted conditions | 47 |
| NP28673 | Dose escalation – global | 600 mg twice daily under fed conditions | 6 |
| NP28673 | Drug interaction – midazolam | 600 mg twice daily under fed conditions | 15 |

Clinical Studies

The proposed indication is based on the results of two open-label trials that evaluated the efficacy and safety of alectinib in 225 patients with ALK-positive NSCLC (NP28761 and NP28673). The patients were administered a dose of 600 mg BID with food. The objective response rate (ORR)

per independent central review was 38% (95% CI: 28%, 49%) for patients enrolled in Study NP28761 after a median follow-up of 4.8 months and 44% (95% CI: 36%, 83%) for patients enrolled in Study NP28673 after a median follow-up of 10.8 months. The median duration of response was 7.5 months (95% CI: 4.9, not evaluable (NE)) for Study NP28761 and was 12 months (95% CI: 9.6, NE) for Study NP28673.

An assessment of the ORR and duration of response for central nervous system (CNS) metastases was completed in 51 patients with measurable lesions in the CNS at baseline enrolled into these studies. The ORR in the central nervous system was 61% (95% CI: 46%, 74%) with a median duration of response of 9.1 months (95% CI: 5.8, NE).

### 2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

For the registration trials (NP28761 and NP28673), the primary endpoint was ORR (i.e., defined as the proportion of patients who achieved a complete response (CR) or partial response (PR)) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The primary analysis was based on evaluation by independent central review. ORR is considered a surrogate endpoint that can support an accelerated approval in this disease setting. A key secondary endpoint was ORR in the CNS based on RECIST v1.1 and Response Assessment in Neuro-Oncology (RANO).

For the clinical pharmacology studies, PK parameters were estimated using non-compartmental analysis (NCA) and population analysis. The geometric mean ratio (GMR) and 90% confidence intervals (CI) were determined for comparative studies for alectinib, M4 and a combined molar aggregate.

### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Alectinib and its major active metabolite M4 were appropriately identified and measured in human plasma samples to assess their PK parameters and explore E-R relationships *(Section 2.6)*.

### 2.2.4 Exposure-response

#### 2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

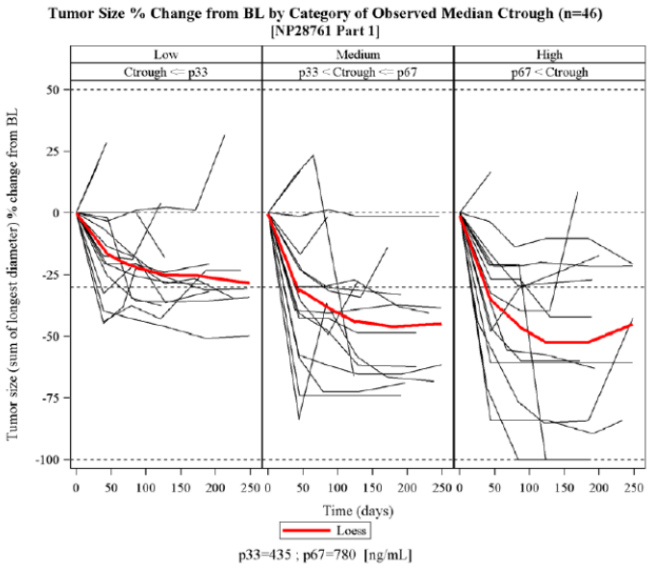
No E-R relationship was identified for the best overall response (BOR) in the registration trials. The proposed dosing regimen of 600 mg BID is based on the efficacy and safety data and the E-R relationships for safety and efficacy observed in the registration trials. Overall, the dosage regimen appears reasonable based on the available safety and efficacy data.

Dose Selection

The dose selection for the registration trials was based on safety and activity observed in dose finding portion of Study NP28761 (n=46). This trial evaluated single doses of 240 mg to 900 mg and multiple doses of 300 mg to 900 mg BID under fed conditions. The starting dose was based on the doses evaluated in the first-in-human study conducted in Japan (AF-001JP). The Applicant states that the change in tumor size from baseline, across the dose range of 300 mg BID to 900 mg BID, show that higher observed median steady-state trough concentrations

($C_{trough}$) are associated with greater reduction in tumor size and a plateau appears to be reached at the observed median steady-state $C_{trough}$ level corresponding to a dose of 600 mg BID (**Figure 2**). The Applicant states that the significant reduction in tumor size over time was observed in all exposure categories (i.e., low, medium and high) for patients treated at a dose of 600 mg BID.

**Figure 2**. Change in tumor size from baseline by category of observed median observed steady-state trough concentrations supports a dose of 600 mg twice daily




Source: Population Pharmacokinetic Report, Figure 23

ALK-positive Non-Small Cell Lung Cancer

Two open-label activity estimating trials were conducted in patients with ALK-positive NSCLC administered alectinib at a dose of 600 mg BID with food. The primary efficacy endpoint was ORR in both trials as described in *Section 2.2*. The schedule for efficacy and safety assessments and PK sampling differed for the two trials (**Table 4**). The median time to tumor response was not reported for either study. The population PK model suggests that alectinib and M4 reached steady-state concentrations by day 7 of cycle 1.

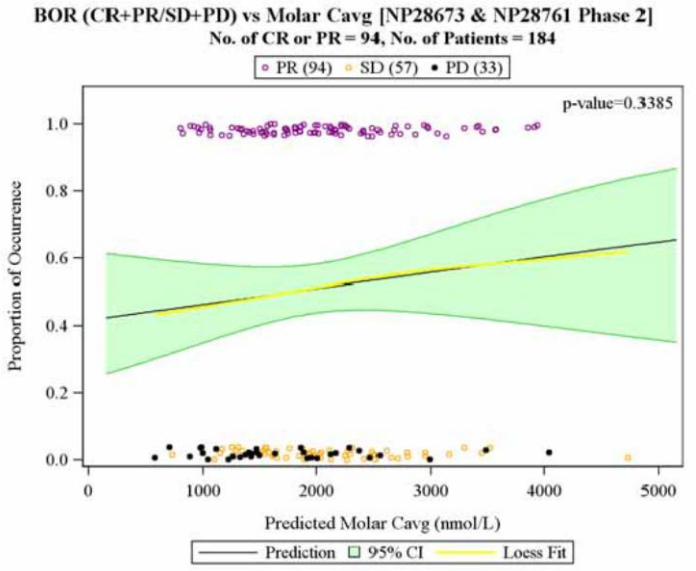
**Table 3.** Schedule of Efficacy, Safety and Pharmacokinetic Assessments in the Registration Trials

| Study | Efficacy | Safety | Pharmacokinetic |
|---|---|---|---|
| NP28673 | Screening, every 8 weeks during first year; every 12 weeks during second year; every 16 weeks until progression. | Baseline, Cycle 1 Days 1, 8, 15 and 21; Cycles 2 to 5 Day 1; and every 4-week cycle thereafter. | Cycle 1 Days 1 and 21: pre-dose and up to 8 hours after morning dose; Cycle 1 Day 15: pre-dose and 4 hours after morning dose; Cycles 2 to 5 Day 1: pre-dose. |
| NP28761 | Screening, every 6 weeks until disease progression. | Baseline and on Cycle 1 Days 1, 8, and 15; Cycle 2 to 5 Day 1; and every 3-week cycle thereafter. | Cycles 1 to 5 Day 1: pre-dose and 4 hours after morning dose |

Source: Population Pharmacokinetic Report

No E-R relationship was observed between the BOR and the combined average steady-state concentration of alectinib and M4 (**Figure 3**). Multivariate logistic regression analyses showed that only baseline tumor size was a statistically significant predictor of BOR; larger baseline tumor size was associated with a decreased probability of a complete or partial response.

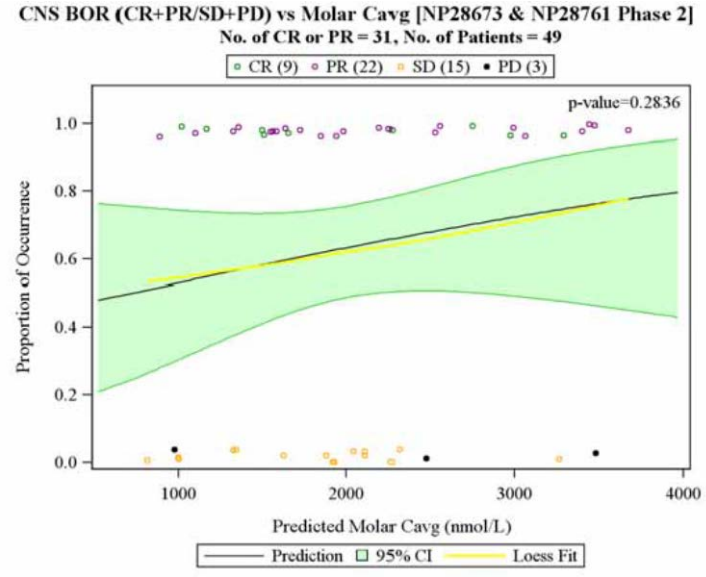
**Figure 3**. No exposure-response relationship observed between best overall response and the combined average concentration of alectinib and M4




Data source: Population Pharmacokinetic Report, Figure 25

No E-R relationship was identified between BOR in the CNS and the combined average steady-state concentration of alectinib and M4 (**Figure 4**) (n=49). This analysis included only patients with measurable disease in the CNS. None of the prognostic factors evaluated using multivariate logistic regression analyses were significant in predicting the probability of having a BOR in the CNS.

**Figure 4**. No exposure-response relationship observed for best overall response in the central nervous system and the combined average concentration of alectinib and M4




Source: Population Pharmacokinetic Report, Figure 28

**2.2.4.2** *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

No E-R relationship was observed for the mean probability of serious adverse events, grade 3 or higher adverse events or the common adverse events of any grade. The proposed labeling recommends a dose of 600 mg BID based on the efficacy and safety data and E-R relationships for safety and efficacy observed in the registration trials. Overall, the dosage regimen appears reasonable based on the available data.

Dose Selection

The Applicant supported their dose selection for the registration trials based on safety and activity observed in a dose escalation portion of Study NP28761. Two dose limiting toxicities were observed in the dose escalation portion following a dose of 900 mg BID administered with food (grade 3 headache and grade 3 neutrophil count decreased). These events occurred before study day 10 and lasted 5 to 9 days. The Applicant stated that both dose limiting toxicities resolved without sequela after a dose reduction to 600 mg. Based on these observations, the Applicant identified a dose of 600 mg BID as the recommended phase II dose. The dose selection was supported by tolerability of a dose of 600 mg BID in the limited dose finding portion of Study NP28673 (n=6).

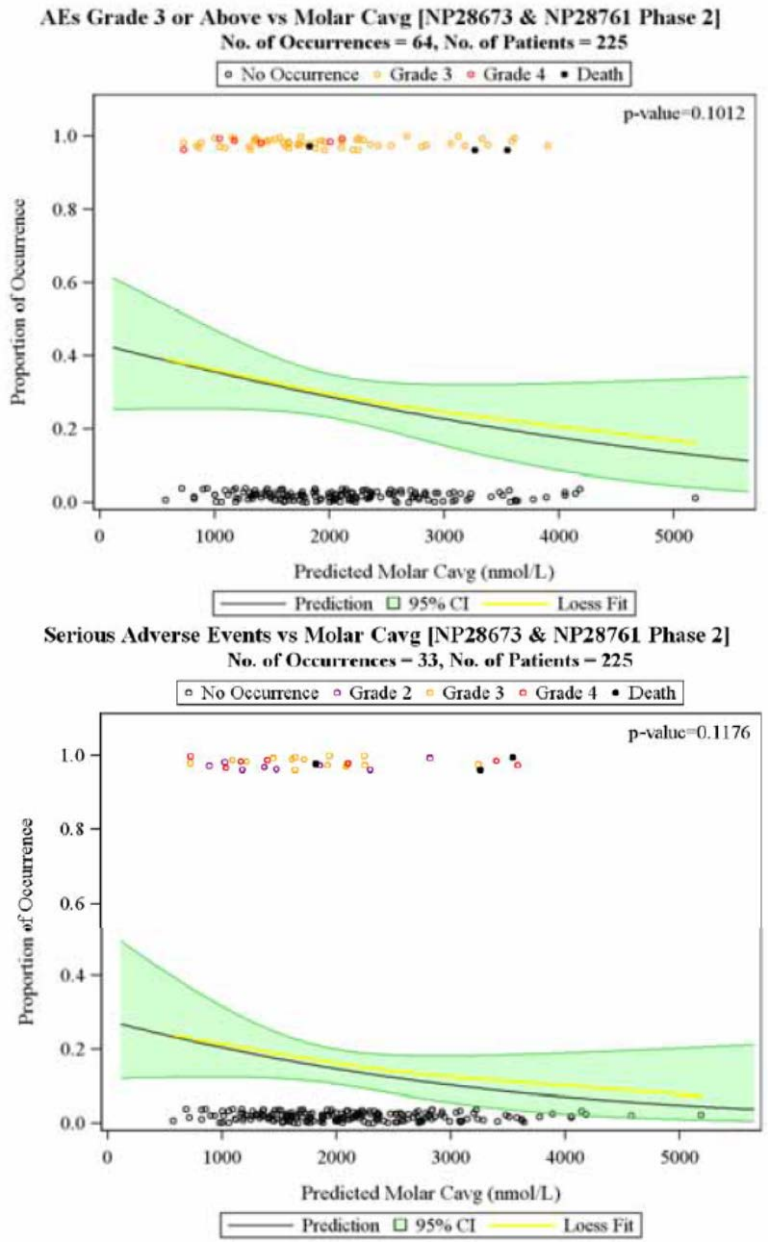
Overall, the median treatment duration was relatively long, with median treatment duration of 17.3 months (2 months, 26 months) in the dose finding portion of Study NP28761. The median treatment duration does not appear dependent on dose.

ALK-positive Non-Small Cell Lung Cancer

Data from 225 patients enrolled into Studies NP28673 and NP28761 were pooled to conduct an exposure-safety analysis to examine the probability of grade 3 or higher adverse events or serious adverse events as a function of the combined average steady-state concentration. This pooled

analysis showed that there was no significant relationship between the combined concentration of alectinib and M4 and the probability of grade 3 or higher adverse events or serious adverse events (**Figure** 5).

**Figure 5.** No exposure-response relationship for grade 3 or higher adverse events (top) or serious adverse events (bottom) and the combined average concentration of alectinib and M4




Source: Population Pharmacokinetic Report, Figures 32 and 33

Additional exposure-safety relationships were explored for patients with serious adverse events or grade 3 or higher adverse events not including gastrointestinal disorders (e.g., constipation, diarrhea, nausea and vomiting), AST elevation, ALT elevation, bilirubin elevation, abnormal kidney function, and muscular adverse events or creatine kinase elevation for patients treated at a dose of 600 mg BID. These adverse events were defined using MedDRA terminology and graded using Common Terminology Criteria for Adverse Events (CTCAE). No significant relationship between the combined average steady-state concentration of alectinib and M4 and these adverse events (grade 0 vs. grade 1 or higher) were identified.

Additional analyses were also performed for the following adverse events: gastrointestinal disorders (defined by MedDRA), constipation, diarrhea, nausea, and vomiting. An apparent inverse relationship between exposure and these adverse events (grade 0 vs. grade 1 or higher) was observed. About 55% of patients experienced their first gastrointestinal disorder within 14 days after starting alectinib. The Applicant states that the apparent inverse relationship was driven by patients with these early events.

Dose Modifications

Relatively low rate of dose discontinuations, reductions, or interruptions secondary to adverse events were reported (**Table 4**). The adverse events associated with dose reductions or interruptions were elevated creatine kinase levels, elevated liver laboratory tests, gastrointestinal disorders, asthenia and pyrexia. The protocols permitted dose modifications of one (450 mg BID) or two (300 mg BID) dose levels. The proposed labeling recommends permanent discontinuation if a dose of 300 mg BID is not tolerated.

**Table 4**. Summary of Dose Modifications for Adverse Events in the Registration Trials

| | NP28761 (n=87) | NP28673 (n=138) |
|---|---|---|
| Discontinuations, n (%) | 2 (2%) | 11 (8%) |
| Reductions<br>Median Time to Reduction | 14%<br>22 days | 9%<br>70 days |
| Interruptions<br>Median Time to Interruption<br>Median Duration of Interruption | 29%<br>24 days<br>7 days | 20%<br>57 days<br>8 days |

Source: Summary of Clinical Safety

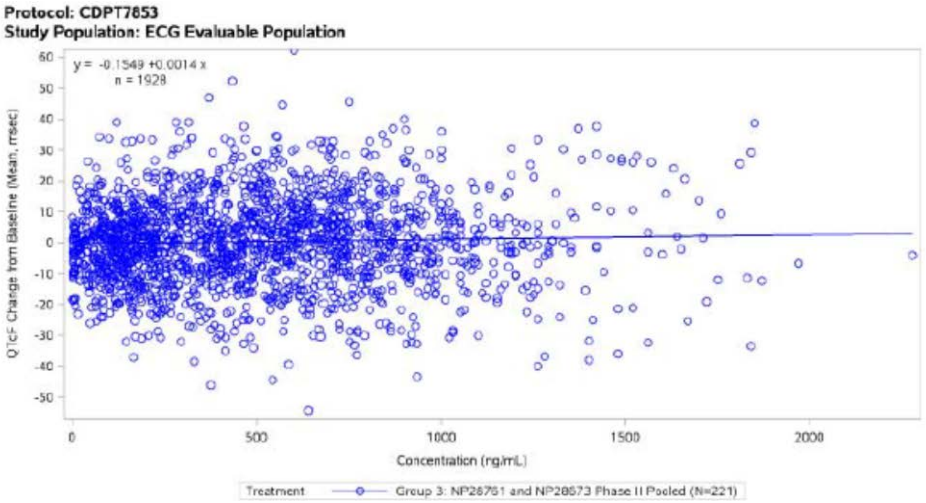
### 2.2.4.3 *Does this drug prolong the QT or QTc interval?*

No large mean change (i.e., > 20 msec) in the QTc interval was detected and no concentration-ΔQTcF relationship was observed in patients administered a dose of 600 mg BID with food. The ECG data was pooled from the activity estimating portion of the registration trials (NP28761 and NP28673). A thorough QT study was not conducted as multiple doses of alectinib cannot be safely given to healthy subjects and the exposure of alectinib and it major active metabolite M4 following a single dose in healthy subjects would not reflect the combined exposure of alectinib and M4 in cancer patients at steady-state. Alectinib and M4 exposure both accumulate ~6-fold after twice daily dosing (steady-state ~7 days).

Pooled QT/QTc Analysis

Using pooled data from activity estimating portion of Study NP28761 (n=81) and Study NP28673 (n=136) in which time matched PK and central ECG data were collected, alectinib did not prolong the QT/QTc interval (report no. 1060441). The upper one-sided 95% confidence interval for the maximum mean ΔQTcF was < 10 msec at each time point in which PK and ECG data were available. **Table 3** lists the schedule for the PK assessments in each trial. No relationship between time-matched alectinib concentrations and ΔQTcF was identified (**Figure 6**).

**Figure 6.** No concentration-ΔQTcF relationship for alectinib in cancer patients




Source: ECG Report, Figure 4

Two patients experienced ΔQTcF > 500 msec or QTcF > 60 msec following the administration of alectinib at a dose of 600 mg in the registration trials (**Table 5**). No patients experienced ventricular arrhythmia (Torsade's de pointes) and no deaths associated with QT interval prolongation were reported during alectinib clinical development.

**Table 5**. Summary of Maximum ΔQTcF and QTcF Values in Registration Trials

| | NP28761 | NP28673 |
|---|---|---|
| Maximum QTcF Change from Baseline (ms) | n=83 | n=137 |
| ≤ 30 msec | 77 (94%) | 113 (83%) |
| 31 to ≤ 60 msec | 4 (4.9%) | 24 (18%) |
| > 60 msec | 1 (1.2%) | 0 |
| Maximum Post-baseline QTcF Value (ms) | n=82 | n=137 |
| ≤ 450 msec | 79 (95%) | 120 (88%) |
| 451 to ≤ 480 msec | 4 (4.8%) | 14 (10%) |
| 481 to ≤ 500 msec | 0 | 2 (1.5%) |
| > 500 msec | 0 | 1 (0.7%) |

Source: ECG Report, Table 4

**2.2.4.4** *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?*

Yes, the dose and dosing regimen selected by the Applicant is based on the dose level evaluated

in the activity estimating portion of the registration trials and supported by the known exposure-safety and exposure-efficacy relationships. There is no unresolved dosing or administration issue (b) (4)

### 2.2.5 What are the PK characteristics of the drug and its major metabolite?

#### 2.2.5.1 *What are the single dose and multiple dose PK parameters?*

Alectinib demonstrates linear PK across the dose range of 460 mg to 900 mg after a single dose and at steady-state under fed conditions. Its exposure accumulates about 6-fold with multiple doses; the accumulation was anticipated as alectinib has an elimination half-life of 32 hours and it is given twice daily. The absolute bioavailability at the recommended dose of 600 mg is 37% consistent with limited solubility. Alectinib's PK profile is adequately described by first-order absorption and first-order elimination via population PK analysis. The geometric mean (coefficient of variation %) maximal concentration at steady-state for alectinib was 665 ng/mL (44%; 1.3 μM based on molecular weight of 483 grams per mole) and for M4 was 246 ng/mL (45%; 0.5 μM based on molecular weight of 456 grams per mole).

Dose Escalation Study

The dose escalation portion of Study NP28761 was completed in 48 patients with ALK-positive NSCLC who received alectinib as a single dose followed by twice daily dosing starting three days after the single dose. Serial PK samples were collected up to 72 hours after the single dose and up to 10 hours after multiple doses. **Table 6** lists the PK parameters for each dosing cohort following a single dose and multiple doses.

**Table 6**. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of Alectinib following a Single Dose (cycle 1 day -3) and Steady-State Dose (cycle 2 day 1)

| Cycle 1 Day -3 | Capsule | Fed or Fasted | $AUC_{inf}$ (ng*h/mL) | $C_{max}$ (ng/mL) |
|---|---|---|---|---|
| 240 mg (n=3) | 20 or 40 mg | Fasted | 1310 (31) | 73 (16) |
| 300 mg (n=3) | 20 or 40 mg | Fasted | 967 (46) | 45 (20) |
| 240 mg (n=1) | 20 or 40 mg | Fed | 858 | 88 |
| 460 mg (n=7) | 20 or 40 mg | Fed | 2630 (86) | 125 (62) |
| 600 mg (n=6) | 20 or 40 mg | Fed | 3160 (34) | 146 (49) |
| 760 mg (n=7) | 20 or 40 mg | Fed | 3690 (59) | 243 (40) |
| 900 mg (n=7) | 20 or 40 mg | Fed | 3110 (76) | 155 (72) |
| 600 mg (n=7) | 150 mg | Fed | 2790 (70) | 181 (26) |
| 900 mg (n=7) | 150 mg | Fed | 6120 (86) | 267 (56) |
| Cycle 2 Day 1 | Capsule | Fed or Fasted | $AUC_{0-10h}$ (ng*h/mL) | $C_{max}$ (ng/mL) |
| 300 mg (n=6) | 20 or 40 mg | Fed | 1720 (32) | 247 (35) |
| 460 mg (n=7) | 20 or 40 mg | Fed | 4200 (44) | 597 (30) |
| 600 mg (n=5) | 20 or 40 mg | Fed | 5880 (20) | 747 (25) |
| 760 mg (n=5) | 20 or 40 mg | Fed | 5720 (16) | 728 (13) |
| 900 mg (n=7) | 20 or 40 mg | Fed | 8880 (52) | 1060 (41) |
| 600 mg (n=6) | 150 mg | Fed | 4620 (62) | 607 (49) |
| 900 mg (n=4) | 150 mg | Fed | 9180 (32) | 1160 (30) |

Source: Clinical Study Report, NP28761, Tables 36 and 37
Fasted: 10 hours before and 2 hours after the dose; Fed: within 30 minutes from the start of a meal

**2.2.5.2** *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

A cross study comparison suggests that alectinib exposure is similar in cancer patients and healthy subjects. The population PK model only included concentration-time data collected from patients with ALK-positive NSCLC.

A Cross Study Comparison

A cross study comparison of alectinib and M4 exposure suggests that alectinib geometric mean exposure is similar in healthy subjects compared to cancer patients following the administration of a single 600 mg dose with food (**Table 7**); the difference between the geometric mean alectinib values was less than 32% when comparing the value obtained in NP28671 to that obtained in NP29042 or NP28991 - esomeprazole. Alectinib and M4 exposure appear substantially higher for one study (NP28991 – food effect) conducted in healthy subjects compared to other studies conducted in the patient population. The higher exposures likely reflect the meal content. Alectinib was administered with an FDA specified high-fat, high-calorie meal in this study cohort, whereas the other studies did not specify the meal content. A high-fat, high-calorie meal increased alectinib exposure by about 3-fold as discussed in *Section 2.5*.

**Table 7**. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of Alectinib following a Single 600 mg Dose under Fed Conditions in Healthy Subjects and Cancer Patients

| Study | Alectinib | | M4 | |
|---|---|---|---|---|
| | $AUC_{inf}$ (ng*h/mL) | $C_{max}$ (ng/mL) | $AUC_{inf}$ (ng*h/mL) | $C_{max}$ (ng/mL) |
| Cancer Patients | | | | |
| NP28761 (n=6) | 2790 (70) | 181 (26) | 1250 (45) | 50 (26) |
| NP28673 (n=28) | NA | 204 (34) | NA | 57 (47) |
| Healthy Subjects | | | | |
| NP29042 - rifampin (n=24) | 3690 (39) | 199 (37) | 2070 (40) | 80 (48) |
| NP28991 - esomeprazole (n=24) | 3060 (28) | 162 (28) | 1750 (34) | 66 (40) |
| NP28991 - food effect (n=18) | 5320 (33) | 257 (32) | 3390 (22) | 122 (25) |

NA = not available
Source: Summary of Clinical Pharmacology, Appendices

Of note, alectinib concentrations measured as part of Study NP28761 were estimated using the Chugai assay and this assay measured on average 20% lower concentrations for alectinib compared to concentrations measured in the other studies using the (b) (4) assay (*Section 2.6*).

**2.2.5.3** *What are the characteristics of drug absorption?*

The absolute bioavailability of alectinib was 37% (90% CI: 34%, 40%) in healthy subjects (NP28989). Each subject received a single 600 mg oral dose (150 mg capsules x 4) within 30 minutes of a meal followed by a single 50 μg radiolabeled intravenous dose (~18.5 kBq, 500 nCi). The relative bioavailability and bioequivalence of different formulations is discussed in *Section 2.5*.

The median $T_{max}$ occurred about 4 hours after a dose of 600 mg BID under fed conditions in cancer patients (NP28761 and NP28673).

Alectinib is not a substrate of MDR1 or BCRP in vitro. M4 is a substrate of MDR1, but not

BCRP in vitro.

**2.2.5.4** *What are the characteristics of drug distribution?*

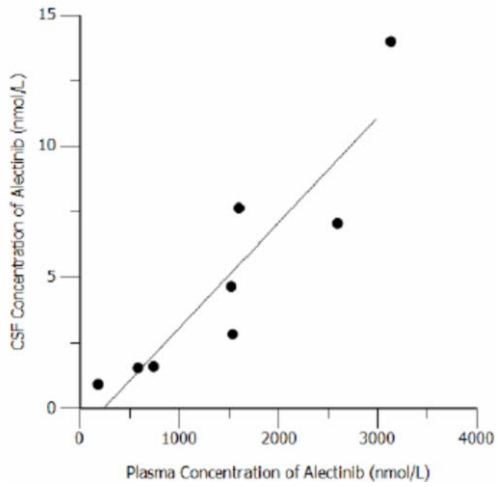
The population estimated apparent central volume of distribution (V/F) of alectinib was 4,016 L and of M4 was 10,093 L based on the final population PK model.

Alectinib and M4 are greater than 99% bound to human plasma proteins independent of their concentrations (report no. 1054086, 1057255). Alectinib demonstrated greater affinity for human serum albumin compared to human $\alpha_1$-acidic glycoprotein (report no. 1056250).

Alectinib and M4 predominantly distributed to blood cells. The average blood-to-plasma concentration ratio ranged from 1.3 to 2.9 for alectinib (report no. 1054086) and 2.5 to 2.6 for M4 (report no. 1057255).

Alectinib demonstrated penetration into the CNS in the 8 patients with CNS metastases who consented to an optional lumbar puncture (NP28761). A PK sample was collected immediately following the lumbar puncture in 6 of these patients. The alectinib concentration was estimated for the remaining two patients based on concentration measured at a similar time on another day. This approach appears reasonable as alectinib reaches steady-state concentrations within one week of the first dose. Alectinib concentrations in the cerebrospinal fluid (CSF) were 0.2% to 0.5% of alectinib concentrations in the plasma. The fraction of alectinib that reaches the CNS approximates the fraction unbound. Alectinib concentrations in the CSF correlate ($R^2$ = 0.83; Intercept = -0.95; Slope = 0.004) with alectinib concentrations in the plasma (**Figure 7**).

**Figure 7.** Alectinib concentrations in the cerebrospinal fluid correlates with alectinib concentrations in the plasma




Source: Study NP28761 Report, Figure 22

**2.2.5.5** *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

The mass balance study suggests that alectinib is primarily eliminated in the feces. Metabolism and biliary excretion likely contribute to the elimination of alectinib.

Clinical

Six healthy men were given a single oral dose of 600 mg of [$^{14}$C] alectinib (~2.5 MBq, 67 μCi)

as a suspension within 30 minutes of a standardized meal (NP28989). Serial PK samples were collected up to at least 72 hours after administration of the radiolabeled dose. Complete urine and fecal outputs were collected for at least 72 hours after administration. The overall mean recovery of radioactivity in urine and feces was 98% within 168 hours after administration. The percent of the radioactive dose recovered from pooled feces was 98% and from pooled urine was 0.47%; therefore, it is estimated that about 1% of the absorbed drug was eliminated in the urine and the remaining portion was eliminated in the feces (assuming about 37% of the dose was absorbed). A study in subjects with impaired hepatic function is planned *(Section 2.3)*.

Nonclinical

Following single oral administration of a 1 mg/kg radiolabeled dose to rats, about 42% ± 7% of the radiolabeled dose was identified in bile (report no. 1056247). The overall mean recovery of radioactivity was 55% ± 9% within 48 hours, suggesting about 76% of the dose was excreted into bile. The remaining portion of the dose was excreted in urine (< 1%) and feces (19%). Re-absorption rate excreted in bile was estimated to be at least 3%, suggesting that alectinib may undergo enterohepatic circulation.

**2.2.5.6** *What are the characteristics of drug metabolism?*

Alectinib is primarily metabolized by CYP3A4 to its major active metabolite M4 (**Figure 8**); the metabolism of alectinib to M4 accounts for about 40% of alectinib's metabolism based on the geometric mean metabolite to parent ratio estimated at steady-state using the final population PK model (0.40, 90% CI: 0.24, 0.71). M4 is subsequently metabolized by CYP3A4. M4 likely contributes to the observed safety and efficacy, since it is a major circulating metabolite with similar in vitro potency and activity; however, it is unlikely that the M1b metabolite will contribute to the observed efficacy or safety, as this metabolite accounted for < 10% of the radiolabeled dose identified in the plasma for a relatively short duration.

In vitro studies demonstrated that CYP3A4 is responsible for formation of M4, M1, M6 and other minor metabolites (report no. 1054089). Alectinib can also be metabolized by CYP2B6, 2C8, 2C9, and 2D6 (report no. 1054089). M4 is mainly metabolized by CYP3A4 (report no. 1062527).

In plasma, the metabolite profiles showed unchanged alectinib as the major circulating radiolabeled component, accounting for 61% of the $AUC_{0\text{-last}}$ of total radioactivity. Alectinib and M4 collectively accounted for 76% of the $AUC_{0\text{-last}}$ of total radioactivity. M1b was the only other metabolite detected in plasma; it accounted for 8% of the $AUC_{0\text{-last}}$ of total radioactivity, but it was only detected within the first 6 hours.

In urine, M1b was the major component in urine accounting for 0.2% of the radioactivity. M4 accounted for < 0.05% of the radioactivity and alectinib was not detected in urine.

In feces, alectinib accounted for 84% of the cumulative excretion of the radioactivity within 168 hours. The relatively high percentage of unchanged alectinib in the feces is consistent with relatively low solubility compared to the estimated concentration of alectinib in the stomach following a dose of 600 mg (*Section 2.1*). The other compounds identified in the fecal matter included M1a+M1b (7.2% of dose), M4 (5.8%) and M6 (0.2%).

The pharmacologic activity of the M4 metabolite was evaluated. M4 is an active metabolite that inhibits human recombinant ALK with an $IC_{50}$ value similar to alectinib (report no.1056380).

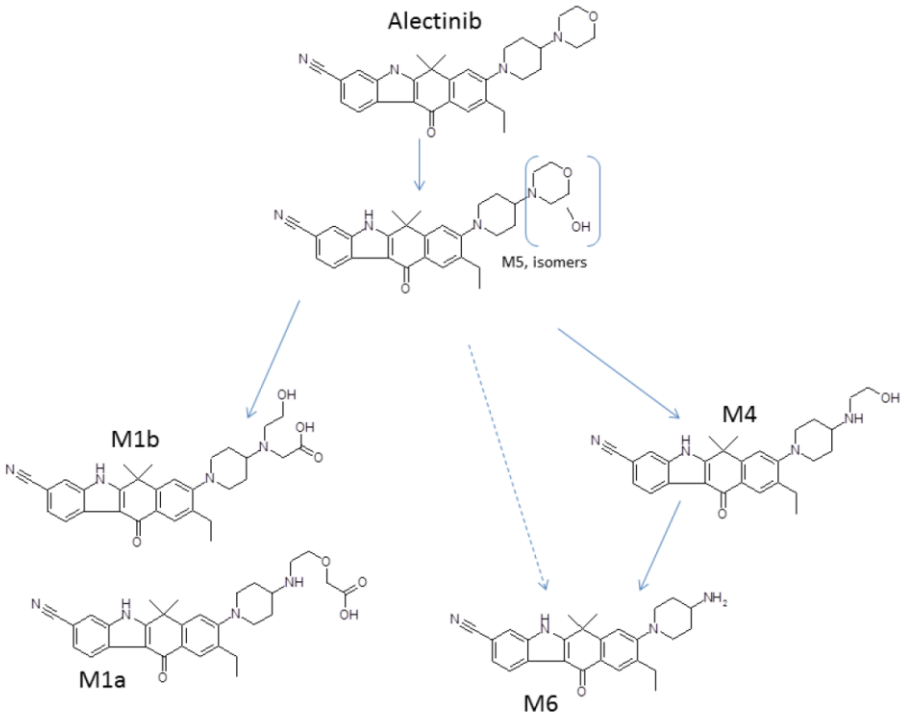
The kinase selectivity of M4 is very similar to the kinase selectivity of alectinib. M4 also inhibited the growth of an EML4-ALK fusion positive cell line with an $IC_{50}$ value of 37 nM (report no. 1056381). This metabolite likely contributes to the observed efficacy and safety, since it is a major circulating metabolite with comparable in vitro activity. These data support the Applicant's approach of using the combined average steady-state concentration of alectinib and M4 in the exploration of the exposure-safety and exposure-efficacy relationships and in the evaluation of the effect of various extrinsic factors on systemic exposures after administration of alectinib. The remaining human metabolites were identified at relatively low concentrations and the Applicant did not evaluate their in vitro activity.

**2.2.5.7** *What are the characteristics of drug excretion?*

Metabolism and biliary excretion followed by fecal elimination is the primary route of alectinib elimination as described above.

The estimated population geometric mean (CV, %) CL/F was 1,965 L/h (82%) for alectinib and was 5,205 L/h (217%) for M4. The geometric mean elimination half-life was 32 hours (36%) for alectinib and was 31 hours (46%) for M4 in cancer patients based on the final population PK model.

**Figure 8**. Proposed metabolism of alectinib in humans



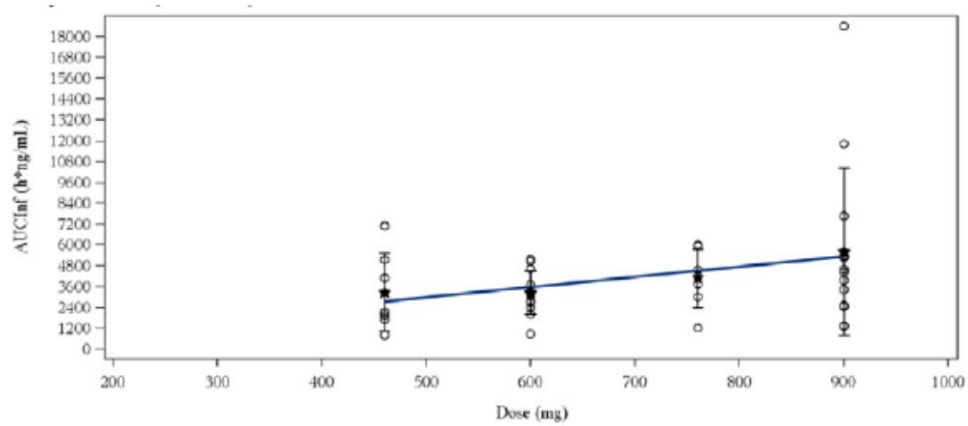

Source: Pharmacokinetics Written Summary, Figure 3

**2.2.5.8** *Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?*

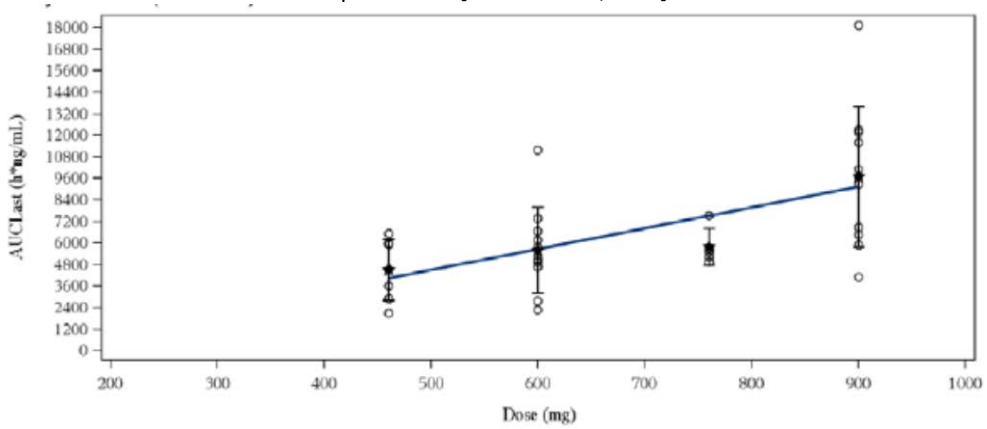
Alectinib demonstrated linear exposure over a dose range of 460 mg to 900 mg after a single dose or at steady-state under fed conditions (**Figure 9**). The Applicant could not exclude dose proportionality using the PK data from the dose finding study (NP28761), but confirmed dose

proportionality based on comparisons of the post hoc estimates for the PK parameters. From the final population PK model, alectinib does not demonstrate dose-dependent absorption.

**Figure 9**. Mean area under the curve after a single dose (top) and steady-state dose (bottom) of 460 mg to 900 mg under fed conditions in cancer patients




slope = 0.752 [90% CI: 0.06, 1.44]




slope = 1.110 [90% CI: 0.65, 1.57]

Source: Final Clinical Study Report NP28761, Figure 14.2-3.3

**2.2.5.9** *How do the PK parameters change with time following chronic dosing?*

Accumulation of alectinib and M4 at steady-state is about 6-fold. State-state concentrations were reached by day 7 based on the final population PK model. **Table 8** lists the predicted PK parameters for alectinib and M4 at steady-state following repeat doses of 600 mg BID. Accumulation is anticipated as alectinib is being administered twice daily and its elimination half-life is 32 hours.

**Table 8**. Summary of Pharmacokinetic Parameters of Alectinib and M4 at Steady-State based on Population PK Model

Alectinib

| Secondary PK Parameters | Mean | SD | Median | 5th Percentile | 95th Percentile | Geometric Mean | Geometric CV (%) |
|---|---|---|---|---|---|---|---|
| $T_{1/2}$ (hr) | 34.5 | 12.6 | 33.0 | 17.4 | 57.6 | 32.5 | 36.2 |
| $R_{acc}$ | 5.85 | 1.95 | 5.58 | 3.18 | 9.21 | 5.56 | 32.8 |
| $AUC_{ss,12hr}$ (ng×hr/mL) | 8130 | 3400 | 7640 | 3190 | 15000 | 7430 | 45.7 |
| $C_{ss,max}$ (ng/mL) | 723 | 292 | 688 | 297 | 1300 | 665 | 44.3 |
| $C_{ss,trough}$(ng/mL) | 630 | 275 | 592 | 242 | 1190 | 572 | 47.8 |
| $C_{ss,max}/C_{ss,trough}$ ratio | 1.17 | 0.073 | 1.15 | 1.08 | 1.32 | 1.16 | 6.10 |
| Time to steady-state (hr) | 173 | 63.2 | 165 | 87.2 | 288 | 162 | 36.2 |

M4

| Secondary PK Parameters | Mean | SD | Median | 5th Percentile | 95th Percentile | Geometric Mean | Geometric CV (%) |
|---|---|---|---|---|---|---|---|
| $T_{1/2}$ (hr) | 33.8 | 15.2 | 31.1 | 14.2 | 61.8 | 30.7 | 46.5 |
| $R_{acc}$ | 7.11 | 3.41 | 6.38 | 2.98 | 12.8 | 6.45 | 45.9 |
| $AUC_{ss,12hr}$ (ng×hr/mL) | 3060 | 1250 | 3040 | 1130 | 5310 | 2810 | 45.9 |
| $C_{ss,max}$ (ng/mL) | 268 | 108 | 262 | 103 | 460 | 246 | 45.4 |
| $C_{ss,trough}$ (ng/mL) | 243 | 101 | 242 | 90.5 | 424 | 222 | 46.6 |
| $C_{ss,max}/C_{ss,trough}$ ratio | 1.11 | 0.071 | 1.09 | 1.03 | 1.29 | 1.11 | 6.07 |
| Time to steady-state (hr) | 169 | 75.9 | 155 | 71.0 | 309 | 154 | 46.5 |
| M/P ratio | 0.420 | 0.154 | 0.400 | 0.242 | 0.708 | 0.399 | 34.3 |

Source: Population Pharmacokinetic Report, Tables 22 and 23

**2.2.5.10** *What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?*

The final population PK model incorporated data from 138 patients. For alectinib, the estimated between-patient variability in CL/F was 40% (RSE 6%) and in V/F was 40% (RSE 11%). For M4, the estimated between-patient variability in CL/F was 36% (RSE 7.6%) and in V/F was 59% (RSE 7.4%). Body weight was the only covariate found to significantly affect CL/F and V/F. After inclusion of the body weight effect on CL/F and V/F, the between-patient variability decreased from 42% to 36% on CL/F and from 60% to 58% on V/F. No other causes of variability were identified in the population PK model.

## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on effectiveness or safety responses?

The final population PK model included only one covariate. Body weight had a statistically significant effect on alectinib and M4 PK parameters. The remaining covariates assessed in the population PK model had no statistically significant effect on alectinib or M4 PK, including age, body mass index, body surface area, CNS metastases, mild hepatic impairment, mild to moderate renal impairment, performance status, ethnicity, sex, prior chemotherapy status, race, smoking

status, and tumor size.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups, healthy subjects vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?**

**2.3.2.1** *Geriatric*

None. The median (min, max) age was 53 (21, 83) years. The final model suggests age has no statistically meaningful effect on the PK of alectinib and M4. The clinical review team concluded that no overall differences in safety or efficacy were observed between patients 65 years and older (14% of patients enrolled in registration trials) and patients younger than 65 years.

**2.3.2.2** *Pediatric*

A disease specific waiver from pediatric studies for the proposed indication was requested. Alectinib has orphan designation for ALK-positive NSCLC (27 January 2015).

**2.3.2.3** *Sex*

None. Forty-six percent (46%) of the patients included in the population PK model were men. The final model suggests that sex has no statistically meaningful effect on the PK of alectinib and M4.

**2.3.2.4** *Race*

None. The final population PK model suggests that race has no statistically meaningful effect on the PK of alectinib and M4. Asian patients constituted 18% of the population included in the population PK model, but the remaining races constituted only a small portion of the population. **Table 9** provides a comparison of the PK parameters for each race category.

**Table 9**. Summary of pharmacokinetic parameters of alectinib and M4 based on the final population pharmacokinetic model for each race category

Alectinib

| | White | Black | Asian | American Indian or Alaska native | Other |
|---|---|---|---|---|---|
| No. of patients (% of Total) | 196 (74%) | 6 (2%) | 49 (18%) | 2 (1%) | 13 (5%) |
| CL/F [L/hr] | 88.5 ± 36.8 | 103.6 ± 38.4 | 67.8 ± 25.7 | 73.7 ± 6.68 | 91.6 ± 54.3 |
| V/F [L] | 4100 ± 1737 | 4232 ± 1503 | 3359 ± 1440 | 5365 ± 2117 | 4858 ± 2394 |
| KA [1/hr] | 1.39 ± 0.633 | 1.58 ± 0.366 | 1.29 ± 0.690 | 1.98 ± 0.898 | 1.29 ± 0.626 |
| D1 [hr] | 3.54 ± 1 | 3.53 ± 0.555 | 3.91 ± 1.32 | 2.58 ± 1 | 3.68 ± 1.17 |

M4

| | White | Black | Asian | American Indian or Alaska native | Other |
|---|---|---|---|---|---|
| No. of patients (% of Total) | 196 (74%) | 6 (2%) | 49 (18%) | 2 (1%) | 13 (5%) |
| CL/F [L/hr] | 208.5 ± 94.3 | 221.6 ± 134.2 | 200.3 ± 77 | 278.2 ± 87.5 | 270 ± 185.7 |
| V/F [L] | 11519 ± 6252 | 11288 ± 6852 | 10315 ± 5919 | 15731 ± 15262 | 15953 ± 9677 |
| $K_{formation}$ [1/hr] | 0.741 ± 0.327 | 0.717 ± 0.233 | 0.698 ± 0.458 | 0.657 ± 0.155 | 0.696 ± 0.408 |

Source: Population Pharmacokinetic Report, Tables 31 and 32

Alectinib and M4 exposure in Asian and White patients was compared in a planned substudy analysis. Serial PK samples were collected from 22 Asian (12 Korean, 10 Taiwanese) patients and 6 White patients enrolled into Study NP28673 following multiple doses of 600 mg BID with food. Alectinib geometric mean exposure in Asians was similar compared to the alectinib geometric mean exposure in Whites, but M4 geometric mean exposure was lower in Asians compared to Whites (**Table 10**). The relatively wide confidence intervals suggest that the observed differences are not statistically different. Although the M4 likely contributes to the observed anticancer activity, these differences are not likely clinically meaningful with no exposure-efficacy relationship observed with the combined exposure to alectinib and M4.

**Table 10**. Effect of Race on Alectinib and M4 Pharmacokinetic Parameters in Study NP28673 following a Single 600 mg Dose

| | White (n=6) | Asians (n=22) | Geometric Mean Ratio (90% CI) |
|---|---|---|---|
| **Alectinib** | | | |
| $C_{max}$ ng/mL | 236 | 196 | 83.2 (65.6, 134.4) |
| $AUC_{last}$ ng*h/mL | 1460 | 1300 | 87.5 (62.2, 137.8) |
| **M4** | | | |
| $C_{max}$ ng/mL | 73 | 54 | 73.2 (45.1, 119.1) |
| $AUC_{last}$ ng*h/mL | 529 | 345 | 65.2 (40.8, 104.3) |

Source: Final Study Report Study NP28673, Table 26

In contrast, a cross study comparison of alectinib exposure observed in a dose finding study conducted in Japan (AF-001JP) and in North America (NP28761) suggests that geometric mean alectinib exposure (defined as $AUC_{last}$) was 2.2-fold lower and geometric mean M4 exposure was 2.3-fold lower in the North American study compared to the Japanese study at a dose of 300 mg (as 20-mg and 40-mg capsules) administered with food (**Table 11**). The potential reasons for the apparent differences in exposure may include differences in meal, race, weight and sex. The evaluable PK population for the NP28671 cohort included three Whites, two Blacks and one Asian. More men (North American 67% vs. Japanese 17%) and heavier patients (North American, mean 76 kg vs. Japanese mean 50 kg) were enrolled into the NP28761 cohort than into the AF001JP cohort. Of these intrinsic factors, weight was the only covariate included in the final population PK model, but it had no clinically meaningful effect on alectinib and M4 PK parameters *(Section 2.3)*. The body weight range of patients in Study AF-001JP is encompassed by the body weight range of the population model. A high-fat, high-calorie meal increases alectinib exposure 3-fold (*Section 2.5*). The small study population and other potential

confounding factors, precludes drawing definitive conclusions from this analysis, but differences in weight and meal type likely contributed to the observed PK differences.

**Table 11.** Comparison of Alectinib and M4 Exposure in Japanese and North American Dose Finding Studies at a Dose of 300 mg twice daily under Fed Conditions

| Study | 300 mg | | 600 mg | |
|---|---|---|---|---|
| | $AUC_{0\text{-}10h}$ (ng*h/mL) | $C_{max}$ (ng/mL) | $AUC_{0\text{-}10h}$ (ng*h/mL) | $C_{max}$ (ng/mL) |
| **Alectinib** | | | | |
| AF001JP (n=6) | 4070 | 512 | - | - |
| NP28761 (n=6) | 1720 | 247 | 5880 | 747 |
| **M4** | | | | |
| AF001JP (n=6) | 1980 | 233 | - | - |
| NP28761 (n=5-6) | 838 | 105 | 2470 | 302 |

Source: Summary of Clinical Pharmacology, Appendices

### 2.3.2.5 *Renal impairment*

None. It is unlikely that renal impairment will have a clinically meaningful effect on alectinib exposure, since less than 1% of the absorbed drug was eliminated in the urine and an inactive metabolite was the major component of the urine. The population PK model suggests that mild or moderate renal impairment is unlikely to influence alectinib or M4 exposure. The population PK model evaluated creatinine clearance (CLcr) calculated using the Cockcroft-Gault formula as a covariate. Patients with normal renal function (CLcr ≥ 90 mL/min, n=141), as well as patients with mild (CLcr 60 to 89 mL/min, n=104), and moderate (CLcr 30 to 59 mL/min, n=21) renal impairment were included in the population analysis. Based on the final PK model, the results showed that baseline CLcr had no statistically significant effect on alectinib apparent oral clearance (**Table 12**). No additional studies are recommended to evaluate the effect of renal impairment on alectinib exposure.

**Table 12**. Effect of Renal Impairment on Alectinib and M4 Pharmacokinetic Parameters based on the Final Population Pharmacokinetic Model

Alectinib

| | Normal CrCL ≥ 90 | Mild Renal Impairment 60 ≤ CrRCL < 90 | Moderate Renal Impairment 30 ≤ CrCL < 60 | Severe Renal Impairment CrCL < 30 |
|---|---|---|---|---|
| No. of patients (% of Total) | 141 (53%) | 104 (39%) | 21 (8%) | 0 (0%) |
| CL/F [L/h] | 89.1 ± 38.8 | 81.2 ± 33.8 | 77.1 ± 35.7 | - |
| V/F [L] | 4284 ± 1763 | 3725 ± 1773 | 3610 ± 1162 | - |
| KA [1/hr] | 1.39 ± 0.641 | 1.34 ± 0.612 | 1.48 ± 0.785 | - |
| D1 [hr] | 3.53 ± 0.982 | 3.69 ± 1.13 | 3.66 ± 1.47 | - |

M4

| | Normal CrCL ≥ 90 | Mild Renal Impairment 60 ≤ CrRCL < 90 | Moderate Renal Impairment 30 ≤ CrCL < 60 | Severe Renal Impairment CrCL < 30 |
|---|---|---|---|---|
| No. of patients (% of Total) | 141 (53%) | 104 (39%) | 21 (8%) | 0 (0%) |
| CL/F [L/h] | 227.3 ± 99.9 | 199.6 ± 99.4 | 155.6 ± 55.3 | - |
| V/F [L] | 12325 ± 7088 | 10872 ± 5997 | 9586 ± 3913 | - |
| $K_{formation}$ [1/hr] | 0.745 ± 0.339 | 0.698 ± 0.337 | 0.781 ± 0.515 | - |

Source: Population Pharmacokinetic Report, Tables 33 and 34

The adverse event rates were similar in patients with renal impairment compared to patients with normal renal function with the following exceptions. Peripheral edema, weight changes and decreased appetite were observed more commonly in patients with moderate renal impairment compared to patients with normal renal function or mild renal impairment. Drug withdrawal more commonly occurred in patients with moderate renal impairment compared to patients with normal renal function or mild renal impairment.

**Table 13**. Effect of Renal Impairment on Adverse Events and Dose Modification

| | Normal Function (n=143) | Mild Impairment (n=92) | Moderate Impairment (n=18) |
|---|---|---|---|
| Adverse Events | | | |
| Constipation | 44 (31%) | 30 (33%) | 7 (39%) |
| Fatigue | 39 (27%) | 22 (24%) | 6 (33%) |
| **Peripheral Edema** | **33 (23%)** | **22 (24%)** | **6 (33%)** |
| Myalgia | 35 (24%) | 15 (16%) | 4 (22%) |
| AST Increased | 14 (10%) | 21 (23%) | 2 (11%) |
| CK Increased | 15 (10%) | 13 (14%) | 1 (6%) |
| Nausea | 21 (15%) | 9 (10%) | 5 (28%) |
| ALT Increased | 13 (9%) | 18 (20%) | 2 (11%) |
| **Weight Increase** | **12 (8.4%)** | **3 (3.3%)** | **3 (17%)** |
| Weight Decrease | 4 (2.8%) | 0 | 2 (11%) |
| | | | |
| Dose Modification | | | |
| Dose Interruption | 32 (22%) | 20 (22%) | 5 (28%) |
| **Withdrawal** | **3 (2.1%)** | **7 (7.6%)** | **3 (17%)** |

Source: FDA Request for Information dated 11 August 2015

### 2.3.2.6 *Hepatic impairment*

Alectinib is primarily eliminated by metabolism and biliary excretion with about 98% of the absorbed dose excreted in feces, so it is possible that alectinib or M4 exposure could increase in patients with hepatic impairment. No dose adjustment is needed for patients with mild hepatic impairment based on the population PK analysis, but it is not known if the dose needs to be reduced for patients with moderate to severe hepatic impairment. FDA will issue a postmarket requirement (PMR) for the final study report (*Section 1.2*).

Population Pharmacokinetic Analysis

The final population PK model suggests that mild hepatic impairment defined by the National Cancer Institute criteria does not affect alectinib or M4 exposure. The mean alectinib and M4 PK parameters are similar in cancer patients with mild hepatic impairment (n=59, total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to ≤ 1.5 × ULN and AST any value) compared to cancer patients with normal hepatic function (n=206, total bilirubin and AST ≤ ULN) (**Table 14**). No patients with moderate hepatic impairment were enrolled in the clinical trials with alectinib. Only one patient with severe hepatic impairment was enrolled in the clinical trials, but the CL/F was 1.5-fold higher for this patient compared to the mean CL/F for patients with normal hepatic function. Additional PK and safety data is needed to determine an appropriate dose for patients with moderate to severe hepatic impairment.

**Table 14**. Effect of Mild Hepatic Impairment on Alectinib and M4 Pharmacokinetic Parameters based on the Final Population Pharmacokinetic Model

Alectinib

| | Normal | Mild Hepatic Impairment | Moderate Hepatic Impairment | Severe Hepatic Impairment |
|---|---|---|---|---|
| No. of patients (% of Total) | 206 (77%) | 59 (22%) | 0 (0%) | 1 (0%) |
| CL/F [L/h] | 86.7 ± 38.3 | 78.6 ± 30.5 | - | 130.2 |
| V/F [L] | 4069 ± 1702 | 3740 ± 1805 | - | 8502 |
| KA [1/hr] | 1.42 ± 0.654 | 1.23 ± 0.568 | - | 0.497 |
| D1 [hr] | 3.53 ± 1.10 | 3.86 ± 0.995 | - | 4.32 |

M4

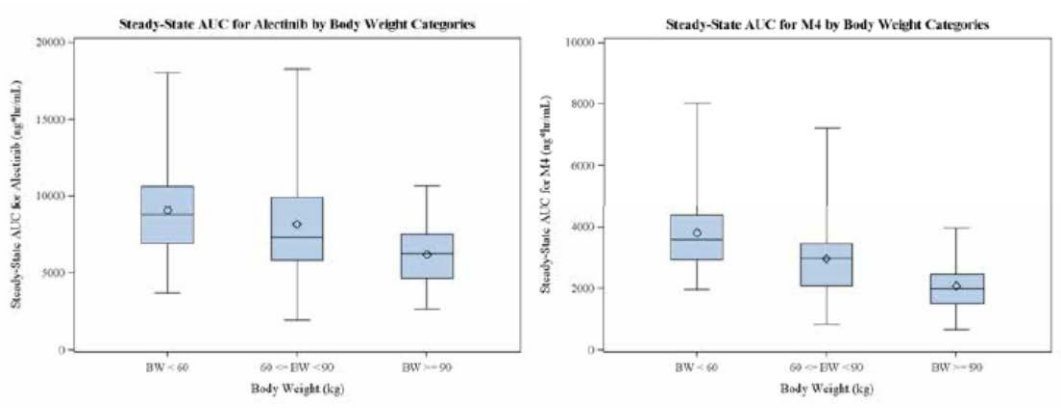
| | Normal | Mild Hepatic Impairment | Moderate Hepatic Impairment | Severe Hepatic Impairment |
|---|---|---|---|---|
| No. of patients (% of Total) | 206 (77%) | 59 (22%) | 0 (0%) | 1 (0%) |
| CL/F [L/h] | 214.7 ± 105 | 195.9 ± 73 | - | 289.9 |
| V/F [L] | 11868 ± 6754 | 10192 ± 5300 | - | 23675 |
| $K_{formation}$ [1/hr] | 0.752 ± 0.368 | 0.660 ± 0.289 | - | 0.269 |

Source: Population Pharmacokinetic Report, Tables 35 and 36

### 2.3.2.7 *Body weight*

None. Weight was included in the final population PK model as a covariate of CL/F and V/F with the effect incorporated in accordance with the principles of allometric scaling by using a coefficient of 0.75 for the CL/F and a coefficient of 1 for the V/F. The median body weight of the patients included in the model was 72 kg (min 38, max 128). **Figure 10** shows that exposure to alectinib and M4 declines with increasing body weight; however, no clinically meaningful differences were observed for the lower body weight or higher body weight category compared to the body weight category of ≤ 60 kg to 90 kg. The median exposure for patients < 60 kg is about 20% higher compared to patients with body weight of ≤ 60 to 90 kg and the median exposure for patients ≥ 90 kg is about 15% lower compared to patients with body weight of ≤ 60 to 90 kg.

**Figure 10**. Steady-state Exposure of Alectinib (left) and M4 (right) by Body Weight Category




Endpoint of upper whisker=maximum; upper edge of box=75th percentile; line inside box=median; diamond=mean; lower edge of box=25th percentile; endpoint of lower whisker=minimum.

Source: Population Pharmacokinetic Report, Figure 13

**2.3.2.8** *What pregnancy and lactation use information is there in the application?*

No clinical trials in pregnant or lactating women have been conducted, but alectinib was embryotoxic and fetotoxic in animals. It is not known whether alectinib is excreted in human milk. The labeling advises women of childbearing potential to avoid becoming pregnant while taking alectinib and for women of child bearing potential who are partners of men taking alectinib to use highly effective contraceptive methods.

## 2.4 EXTRINSIC FACTORS

### 2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No dose adjustment is recommended for patients taking alectinib with a CYP3A modulator. Coadministration with a strong CYP3A inhibitor or inducer did not affect the combined exposure of alectinib and M4 to a clinically meaningful extent.

### 2.4.2 Drug-drug interactions

**2.4.2.1** *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

Yes. As alectinib and M4 are determined to be CYP3A4 substrates in vitro, inducers and inhibitors of CYP3A4 could affect exposure of alectinib and M4 in humans. Alectinib and M4 inhibited CYP3A4 and induced CYP3A4 and CYP2B6 in vitro and alectinib inhibited CYP2C8 in vitro. Both alectinib and M4 also inhibited MDR1 and BCRP in vitro.

**2.4.2.2** *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

Alectinib undergoes metabolism by CYP3A4 (about 40% of its overall metabolism) to M4 (report no. 1064536 and 1054089). Genetic differences will likely have no effect on alectinib metabolism.

Two open-label studies were conducted in 47 healthy subjects to assess the effects of posaconazole (strong CYP3A inhibitor) and rifampin (strong CYP3A inducer) on alectinib and

M4 exposure after a single alectinib dose. Although changes in both alectinib and M4 exposure were observed, there was no clinically meaningful change in the combined exposure. Therefore, no dose adjustment is recommended for patients taking alectinib with a CYP3A modulator.

CYP3A4 Induction

A single open-label, three-period, fixed sequence study was conducted in 24 healthy subjects to investigate the effect of multiple rifampin doses on the PK of alectinib after a single dose (NP29042). Subjects received alectinib at a dose of 600 mg on days 1 and 17 and rifampin at a dose of 600 mg once daily on days 8 to 20. Alectinib was given within 30 minutes after eating a standardized meal consisting of about 500 calories with 30% of calories from fat. Serial PK samples were collected up to 96 hours after each alectinib dose. Rifampin decreased alectinib exposure 73% and increased M4 exposure by 1.8-fold; but no clinically meaningful changes in exposure to the combined exposure were observed (**Table 15**). Therefore, no dose modification is recommended for patients who are coadministered alectinib with a CYP3A inducer.

**Table 15.** Effect of Rifampin on the Pharmacokinetics of Alectinib and M4

| Perpetrator | Perpetrator Dose | Alectinib Dose | Analyte | $C_{max}$ GMR% (90% CI)[a] | $AUC_{inf}$ GMR% (90% CI)[a] |
|---|---|---|---|---|---|
| Rifampin[b] | 600 mg QD fasted/fed [b] | 600 mg SD fed | Alectinib | 48.6 (43.5 – 54.3) | 26.8 (23.8 – 30.1) |
| | | | M4 | 220 (190 – 255) | 179 (158 – 202) |
| | | | Alectinib + M4[c] | 96.1 (87.7 – 105) | 81.6 (74.0 – 90.1) |

Source: Summary of Clinical Pharmacology Studies, Table 10

CYP3A4 Inhibition

A single open-label, three-period, fixed sequence study was conducted in 17 healthy subjects to investigate the effect of multiple posaconazole doses on the PK of a single alectinib dose (NP28990). Subjects received alectinib at a dose of 300 mg within 30 minutes of a high-fat meal (1000 calories, 50% fat) on days 1 and 15 and posaconazole at a dose of 400 mg BID on days 8 to 21. Serial PK samples were collected up to 96 hours after each alectinib dose. Posaconazole increased alectinib exposure 1.8-fold and decreased M4 exposure by 25% (**Table 16**). The combined exposure increased 1.4-fold. Despite a statistically significant increase in the combined exposure, no dose modification is recommended for patients who are coadministered alectinib with a CYP3A inhibitor. This recommendation is based on that no exposure-safety relationships were identified and alectinib is reasonably well-tolerated with few dose modifications for adverse events.

**Table 16.** Effect of Posaconazole on the Pharmacokinetics of Alectinib and M4

| Perpetrator | Perpetrator Dose | Alectinib Dose | Analyte | $C_{max}$ GMR% (90% CI)[a] | $AUC_{inf}$ GMR% (90% CI)[a] |
|---|---|---|---|---|---|
| Posaconazole[b] | 400 mg BID fed | 300 mg SD fed | Alectinib | 118 (102 – 137) | 175 (157 – 195) |
| | | | M4 | 28.7 (23.1 – 35.5) | 75.1 (64.4 – 87.7) |
| | | | Alectinib + M4[c] | 93.3 (80.8 – 108) | 136 (124 – 149) |

Source: Summary of Clinical Pharmacology Studies, Table 10

**2.4.2.3** *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Alectinib and M4 do not induce or inhibit CYP3A4 in humans based on the results of a substudy (of Study NP28673) conducted in patients with ALK-positive NSCLC who received a single midazolam dose with multiple alectinib doses. Alectinib does not appear likely to inhibit CYP2C8 in humans based on a PBPK model.

- Alectinib (inactivation constant KI ≥ 60 μM and inactivation rate $K_{inact}$ = 0.0624 $min^{-1}$; report no. 1054091, 1054093) and M4 (KI = 369 μM and $K_{inact}$ = 0.0620 $min^{-1}$ report no. 1057256) showed time-dependent inhibition of CYP3A4. A substudy demonstrated that alectinib or M4 is unlikely to inhibit CYP3A in humans.
- Alectinib at a concentration of 10 μM competitively inhibited CYP2C8 (Ki = 2.0 μM) (report no. 1054091, 1054093). Assuming a maximal concentration of alectinib of 1.3 μM following a dose of 600 mg BID, the $R_1$ value is 1.6, suggesting that alectinib may inhibit CYP2C8 in humans; subsequently, the Applicant showed that alectinib is unlikely to inhibit CYP2C8 in vivo using a PBPK model and that a drug interaction study in humans is not needed. The predicted median AUC ratio for the effect of alectinib on repaglinide (a sensitive CYP2C8 substrate) was 1.0 (report no. RDR106459).
- Alectinib did not competitively inhibit CYP1A2, 2B6, 2C9, 2C19, or 2D6 in vitro ($IC_{50}$ > 10 μM) (report no. 1054091) and M4 did not competitively inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 (report no. 1057256).
- Alectinib at concentrations up to 1 μM increased CYP2B6 and 3A mRNA 1.5- to 2.1-fold in three hepatocyte donors compared to positive controls in vitro (report no. report 1056251). It was assumed that M4 contributed to the observed induction, since M4 is formed in human hepatocytes. A substudy demonstrated that alectinib or M4 is unlikely to induce CYP3A in humans.

Midazolam Substudy

A single open-label, two-period, fixed sequence substudy was conducted in 10 patients with ALK-positive NSCLC to investigate the effect of multiple alectinib doses on the PK of a single midazolam dose (NP28673). Subjects received a 2 mg dose of midazolam (oral syrup) on day -1 and day 21 and a 600 mg dose of alectinib twice daily within 30 minutes of a meal on days 1 to 28. Midazolam was administered with a standard meal (500 calories with 30% from fat). Serial PK samples were collected up to 24 hours after each midazolam dose. No statistically significant change in midazolam exposure was observed, suggesting that alectinib and M4 do not inhibit or induce CYP3A enzyme activity in humans. No dose modification is recommended for patients

who are coadministered a sensitive CYP3A substrate or narrow therapeutic CYP3A substrate with alectinib.

PBPK Model

The Applicant developed an integrated PBPK model for alectinib and its M4 metabolite using the SimCYP® population-based simulator. The model considered clinical data from Studies NP28761, NP28673, NP28989, and NP28990 and multiple nonclinical studies. The Applicant used this model to predict the effect of multiple doses of alectinib on the PK of a sensitive CYP2C8 substrate (i.e. repaglinide) in patients with ALK-positive NSCLC. The simulations were performed using 12 patients (aged 20 to 50 years, 45% male) enrolled in 10 trials. Alectinib PK profiles were simulated for a dose of 600 mg BID x 16 days. On day 12, a single 0.25 mg dose of repaglinide was administered 3 hours after the alectinib morning dose to align the maximal concentration of both drugs. The model suggests that alectinib is unlikely to inhibit repaglinide metabolism in humans. Of note, repaglinide can be metabolized by CYP3A; however, alectinib is unlikely to affect the ability of CYP3A to metabolize repaglinide as multiple alectinib doses did not have a statistically significant effect on midazolam exposure in the drug interaction substudy described above. A clinical drug interaction study does not appear necessary to determine the effects of alectinib on the PK of a sensitive CYP2C8 substrates based on the PBPK model.

**2.4.2.4** *Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?*

Alectinib is not a MDR1 substrate (efflux ratio < 2) (report no. 1056252), but M4 is a MDR1 substrate in vitro (report no. 1061915).

Both alectinib ($IC_{50}$ = 1.1 μM) and M4 ($IC_{50}$ = 4.7 μM) inhibited MDR1 transport in vitro (report no. 1059474, 1056252). Assuming an alectinib mean steady-state concentration of 1.3 μM ($I_1/IC_{50}$ =1.2) and an M4 mean steady-state concentration of 0.5 μM ($I_1/IC_{50}$ = 0.1), alectinib and M4 may inhibit MDR1 in humans.

**2.4.2.5** *Are there other metabolic/transporter pathways that may be important?*

Yes. Alectinib and M4 may inhibit BCRP transport activity in vivo and alectinib may inhibit BSEP activity in vivo.

- Alectinib is not a BCRP substrate (efflux ratio < 2) in vitro, but it may inhibit BCRP in vivo ($IC_{50}$ 0.10 μM; $I_1/IC_{50}$ =13; report no. 1056253) assuming an alectinib mean steady-state concentration of 1.3 μM.
- M4 is not a BCRP substrate (efflux ratio < 2) in vitro (report no. 1061915), but it may inhibit BCRP in vivo ($IC_{50}$ 2.6 μM; $I_1/IC_{50}$=0.2; report no. 1059473) assuming a M4 mean steady-state concentration of 0.5 μM.
- Alectinib ($IC_{50}$ 0.9 μM; $I_1/IC_{50}$=1.4), but not M4 ($IC_{50}$ 22 μM; $I_1/IC_{50}$=0.02) inhibited BSEP transport activity in vitro (report no. 1059476).
- Alectinib and M4 did not inhibit MRP2 mediated uptake in vitro (report no. 1059476).
- Alectinib and M4 are not OATP1B1 or OATP1B3 substrates in vitro (report no. 1063003).
- Alectinib did not inhibit OATP1B1, OAT1, OAT2, or OCT2 transport activity in vitro (report no. 1056253, 1059475).
- The Applicant did not determine if alectinib or M4 is a substrate of the renal transporters in vitro or if M4 is an inhibitor of other transporters.

**2.4.2.6** *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

Alectinib is to be given as monotherapy.

**2.4.2.7** *What other co-medications are likely to be administered to the target population?*

Patients taking alectinib will likely be taking other medications to prevent or treat adverse events or other illnesses.

**2.4.2.8** *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

No. Alectinib is a weak base that demonstrates low solubility and pH dependent solubility (*Section 2.2*). The Applicant completed a single two-period, fixed-sequence cross-over study to assess the effects of esomeprazole on the PK of alectinib in 24 healthy subjects (NP28991). Alectinib was given as a single 600 mg dose on days 1 and 16 and esomeprazole was given at a dose of 40 mg once daily on days 11 to 16. Alectinib was given within 30 minutes of a standard meal of 500 calories with 30% of the calories from fat. PK samples were collected up to 96 hours after each alectinib dose. No clinically meaningful effect on the individual exposures or the combined exposure of alectinib and M4 when esomeprazole was coadministered with alectinib (**Table 17**). Similarly, simulations performed using GastroPlus™ predicted no impact of esomeprazole on alectinib exposures (report no. 1064595). The Applicant postulated that gastric pH changes did not affect alectinib exposure, because alectinib does not undergo relevant dissolution in the stomach. This postulation may be supported by the fact that the solubility of alectinib at typical gastric pH is much lower than 2.4 mg/mL (600 mg dose / 250 mL), even though the solubility decreases as gastric pH increases to a pH of 6 (Zhang et al. Clin Pharm Ther 2014;96:266), this pH change would not have the effect on the absorption of alectinib. No dose modification is recommended for patients taking alectinib with an acid-reducing agent.

**Table 17**. Geometric Mean Ratios at Steady-state in Patients taking Alectinib with an Acid-Reducing Agent compared to Patients taking Alectinib without an Acid-Reducing Agent

| Perpetrator | Perpetrator Dose | Alectinib Dose | Analyte | $C_{max}$ GMR% (90% CI)[a] | $AUC_{0\text{-last}}$ GMR% (90% CI)[a] | $AUC_{inf}$ GMR% (90% CI)[a] |
|---|---|---|---|---|---|---|
| Esomeprazole | 40 mg QD | 600 mg SD fed | Alectinib | 116 (103 – 132) | 122 (110 – 136) | 122 (109 – 136) |
| | | | M4 | 102 (87.0 – 119) | 109 (95.3 – 126) | 110 (96.3 – 126) |
| | | | Alectinib + M4[b] | 113 (100 – 128) | — | 117 (104 – 131) |

Source: Summary of Clinical Pharmacology, Table 9

**2.4.2.9** *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

No.

**2.4.2.10** *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

No.

### 2.4.3 What issues related to dose, dosing regimens or administration is unresolved and represents significant omissions?

None.

## 2.5 General Biopharmaceutics

### 2.5.1 Based on Biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Alectinib appears to be a low-solubility, low permeability (BCS Class IV) compound. It demonstrates moderate permeability in vitro, but its absolute bioavailability is only 37%.

### 2.5.2 What is the relative bioavailability of the proposed 'to-be-marketed' formulation to the pivotal clinical trial?

No relative bioavailability study was needed, since the drug product used in the registration trials is the same drug product as the to-be-marketed product; however, two relative bioavailability studies were conducted during the drug development.

Hard gelatin capsules at dose strengths of 20-mg, 40-mg and **150-mg** were used in dose escalation portion of Study NP28671. The Applicant states that no differences were observed in the dissolution profiles between the 20-mg and 40-mg capsules compared to the 150-mg capsules. The applicant compared the relative bioavailability of alectinib following the administration of a 600 mg and 900 mg dose given with 20-mg and 40-mg capsules and 150-mg capsules in this trial. No clinically meaningful differences in alectinib exposure at a dose of 600 mg BID following the 20-mg and 40-mg or the 150-mg capsules was observed, as the geometric mean ratio was within bounds of 80, 125 (**Table 18**).

**Table 18**. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of Alectinib and M4 at Steady-state following administration of Different Capsule Strengths

| Dose | Alectinib | | M4 | |
|---|---|---|---|---|
| | $AUC_{last}$ (ng*h/mL) | $C_{max}$ (ng/mL) | $AUC_{last}$ (ng*h/mL) | $C_{max}$ (ng/mL) |
| **600 mg** | | | | |
| 20 or 40-mg capsules (n=6) | 5800 (20) | 747 (25) | 2470 (42) | 302 (44) |
| 150-mg capsules (n=7) | 4620 (62) | 607 (49) | 2250 (45) | 284 (37) |
| **900 mg** | | | | |
| 20 or 40-mg capsules (n=7) | 8880 (52) | 1060 (41) | 4540 (41) | 515 (40) |
| 150-mg capsules (n=6) | 9180 (32) | 1160 (30) | 4720 (35) | 565 (39) |

A randomized single, four sequence, four period crossover study was conducted in healthy subjects to compare the relative bioavailability (n=48) and bioequivalence (n=49) of capsules containing different amounts of SLS compared to the to-be marketed hard gelatin capsule (NP29040). No clinically meaningful differences in alectinib exposure was observed for the (b)(4)% w/w SLS capsules compared to the to-be-marketed (b)(4)% w/w SLS capsules under fasted and fed conditions (data not shown). (b)(4)

(b) (4)

.

**2.5.2.1** *What data support or do not support a waiver of in vivo BE data?*

Not applicable.

**2.5.2.2** *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?*

Not applicable.

**2.5.2.3** *If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the 'to-be-marketed' product?*

Not applicable.

**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

It is recommended that alectinib be given with food as patients were instructed to take alectinib within 30 minutes of the start of a meal in the registration trials. The meal content was not specified in the clinical trial protocols. A FDA specified high-calorie, high-fat meal increased combined exposure of alectinib and M4 3-fold following a single 600 mg dose in healthy subjects. This observed food effect is anticipated based on the physiochemical properties (poor solubility and moderate bioavailability) of alectinib.

Food Effect Study

A single two-period, randomized study was conducted in 18 healthy subjects to determine the effects of an FDA specified high-calorie, high-fat breakfast on alectinib exposure following a single 600 mg dose (NP28991). Serial PK samples to measure alectinib and M4 plasma levels were collected up to 96 hours after alectinib administration. The individual and combined exposures of alectinib and M4 were about 3-fold higher when alectinib was taken with a high-fat meal compared to those when alectinib was taken under a fasted state (**Table 19**). The M/P ratios of $AUC_{inf}$ were similar for fasted and fed conditions indicating that food does not affect alectinib's metabolism to M4. The $T_{max}$ was delayed from a median of 4 hours in the fasted state to a median of 8 hours in the fed state for alectinib and from a median of 8 hours in the fasted state to a median of 10 hours in the fed state for M4. It is recommended that alectinib be taken in the fed state as food increases alectinib exposure and alectinib was administered with food in the registration trials. No exposure-safety relationships were observed at the proposed clinical dose and alectinib appears well-tolerated based on the adverse event profile and dose modification rate.

**Table 19.** Effect of High-fat Breakfast on the Pharmacokinetics of Alectinib and M4

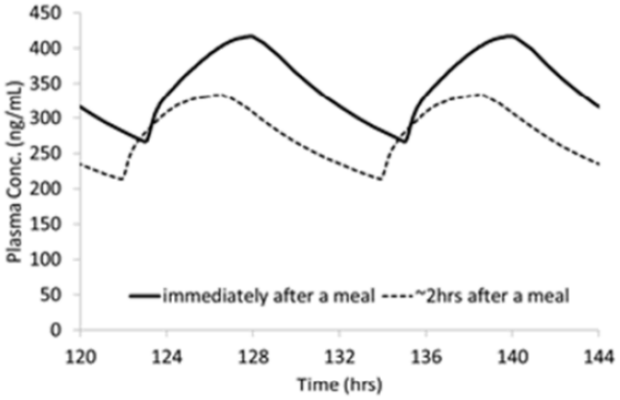
| Analyte | Parameter | Fed/Fasted GMR%[a] | 90% CI for the Ratio |
|---|---|---|---|
| Alectinib | $AUC_{inf}$ (ng•h/mL) | 292 | 258, 329 |
| | $AUC_{0\text{-}last}$ (ng•h/mL) | 306 | 269, 348 |
| | $C_{max}$ (ng/mL) | 270 | 228, 320 |
| M4 | $AUC_{inf}$ (ng•h/mL) | 328 | 276, 389 |
| | $AUC_{0\text{-}last}$ (ng•h/mL) | 349 | 288, 422 |
| | $C_{max}$ (ng/mL) | 377 | 303, 468 |
| Alectinib + M4 | $AUC_{inf}$ (h•nmol/L) | 311 | 273, 355 |
| | $C_{max}$ (nmol/L) | 331 | 279, 393 |

Source: Summary of Clinical Pharmacology, Table 6

PBPK Model

The Applicant developed a PBPK model for alectinib using GastroPlus™ to support recommendations for the relative time of an alectinib dose with respect to a meal. The applicant used the human-physiological-fed or -fasted model and incorporated relevant parameters from Studies NP28989, NP28990, NP28991 and NP29040 and various in vitro and in silico studies and demonstrated that alectinib PK is not substantially sensitive (within 20% changes in exposure) to moderate variations in the time of dosing with respect to a meal (**Figure 11**). The adequacy of PBPK model to support dosing recommendation with respect to timing of food intake was not reviewed by the FDA; however, because no exposure-efficacy relationship was identified for alectinib in the registration trials, it appears that alectinib can be administered with food without specifying a dosing time relative to meal administration.

**Figure 11**. Model Simulations of the Effect of Dosing Time relative to Meal Administration following administration of Alectinib at a Dose of 600 mg Twice Daily




Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 5

### 2.5.4 When would a fed BE study be appropriate and was one conducted?

No BE study is necessary as the registration trials (NP28761 and NP28673) used the to-be-marketed drug product.

### 2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Refer to the review by Office of Product Quality (OPQ).

### 2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the 'to-be-marketed' product?

Not applicable; only one dose strength of 150-mg will be marketed.

### 2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

### 2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

### 2.5.9 What other significant, unresolved issues relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

## 2.6 ANALYTICAL SECTION

### 2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

High performance liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) methods were developed and validated for the identification and quantification of alectinib and M4 in human plasma from patients and healthy subjects. Alectinib was also measured in cerebrospinal fluid from patients enrolled into Study NP28673.

### 2.6.2 Which metabolites have been selected for analysis and why?

Alectinib is metabolized by CYP3A4 to its active metabolite M4. Plasma concentrations of M4 were measured, as this metabolite's exposure accounts for about 40% of alectinib's exposure (based on the M/P ratio at steady-state) in human plasma and demonstrates similar potency and activity in vitro.

### 2.6.3 For all moieties measured is free, bound or total measured?

Total concentrations were measured for alectinib and M4. Alectinib and its major active metabolite M4 are highly bound to human plasma proteins (>99%), independent of drug concentration.

### 2.6.4 What bioanalytical methods are used to assess concentrations?

**Table 20** lists the validated bioanalytical methods used to measure alectinib and M4 for each study that included PK sampling. Two different methods were used for the quantification of alectinib and M4 in human plasma. The Applicant showed that the two assays were not

comparable. A negative bias was seen for alectinib and M4 using the Chugai assay compared to the [redacted] assay. The mean bias between the two methods was -21% (22% CV) for alectinib and -21% (20%) for M4. To account for the known 20% lower concentration on average measured by the Chugai assay, a relative bioavailability was fixed to 0.8 for Study NP28761 in population PK model. The parameters described for the various methods indicate that the methods were adequate to estimate the concentration data.

**Table 20.** Bioanalytical methods

| Bioanalytical Method | Study | Analyte |
|---|---|---|
| CBG712 (Chugai)<br>Report no. RDR1058284 and RDR1063680 (stability) | AF-001JP<br>NP28761 | Alectinib |
| CBG715 (Chugai)<br>Report no. RDR1063987 and RDR 1063383 | AF-001JP<br>NP28761 | M4 and M6 |
| 121321HBS4802HPL_S [redacted])<br>Report no. RDR1057698 | NP28673<br>NP28990<br>NP29042<br>NP28991<br>NP29040<br>NP28989 | Alectinib and M4 |

Source: Summary of Biopharmaceutic Studies and Associated Analytical Studies

**2.6.4.1** *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

**Table 21** lists the range of the standard curve and the curve fitting techniques applied to measure alectinib and M4 in human plasma for each method. These standard curve ranges were adequate for the purposes of determining plasma concentrations of alectinib and M4 in the clinical studies.

**Table 21.** Summary of Bioanalytical Methods

| Parameter | CBG712 (Chugai) | CBG715 (Chugai) | 121321HBS4802HPL_S [redacted]) |
|---|---|---|---|
| **Standard Curve** | | | |
| - Range | 0.1 to 20 ng/mL | 1 to 200 ng/mL | 1.5 to 500 ng/mL |
| - Model | Linear | Linear | Linear |
| - Weighting Factor | $1/x^2$ | $1/y^2$ | $1/x^2$ |
| **Lower Limit of Quantification** | 0.1 ng/mL | 1 ng/mL | 0.5 ng/mL |
| **Upper Limit of Quantification** | 10,000 ng/mL | 10,000 ng/mL | 6000 ng/mL |
| **Accuracy** | Intra- and inter-assay precision and accuracy<br>Mean bias within ±15% (±20% at LLOQ) | | |
| **Precision** | <15% (<20% at LLOQ) | | |

| | | | |
|---|---|---|---|
| **Sample Stability**<br>Freeze-Thaw<br>In plasma<br>- Room temperature<br>- - 20 °C<br>- - 70 °C<br>Stock Solution<br>- Room temperature<br>- 4 °C<br>Working Solution<br>- Room temperature<br>- 4 °C | 5 times<br><br><br>27 days<br>27 days<br><br><br>92 days | 8 times<br><br><br>91 days<br><br><br><br>104 days | 5 times<br><br>24 hours<br>396 days<br>721 days<br><br><br>21 hours<br>325 days<br><br>21 hours<br>325 days |
| **QC Concentrations** | 0.1 ng/mL<br>0.3 ng/mL<br>2 ng/mL<br>16 ng/mL | 3 ng/mL<br>20 ng/mL<br>160 ng/mL | 1.5 ng/mL<br>4.5 ng/mL<br>50 ng/mL<br>600 ng/mL<br>1200 ng/mL<br>6000 ng/mL |

**2.6.4.2** *What are the lower and upper limits of quantification?*

**Table 21** provides the lower and upper limits of quantification for each method.

**2.6.4.3** *What are the accuracy, precision and selectivity at these limits?*

**Table 21** provides the accuracy and precision for each method. The specificity or selectivity of the assay was demonstrated by evaluating the apparent peak area in blank samples and in LLOQ samples for alectinib, M4 and the internal standard. Minimal carryover was adequately demonstrated.

**2.6.4.4** *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

**Table 21** provides the sample stability under multiple conditions.

**2.6.4.5** *What is the QC sample plan?*

**Table 21** provides the QC concentrations. QC samples were prepared from pooled plasma as needed for each run. Chugai analytical method required at least two replicates be included in each validation run. The QC samples compromised about 5% of the number of study samples analyzed in each run. The (b) (4) analytical method required at least six replicates be included in each validation run.

## 3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Agency's suggested changes to the proposed labeling are shown in underline blue text and removal of content shown by red strikethroughs. Of note, the Agency's labeling modifications have not been agreed upon by the Applicant as of the date of this review.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

#### 1.1.1 Do the exposure-response (E-R) relationships for efficacy and safety support the proposed dose of 600 mg twice daily (BID)?

Yes. The E-R relationship for efficacy endpoints (i.e., best overall response [BOR], central nervous system [CNS] BOR) appeared to be flat based on multivariate logistic regression analysis. The E-R relationship for adverse events (AE) which are not gastrointestinal (GI) related appeared to be flat. There was an apparent inverse E-R relationship for constipation, diarrhea, nausea and vomiting. The reasons for such apparent inverse E-R relationship for GI disorders are unknown. Overall, the proposed dose of 600 mg BID dosing is supported by E-R relationships for efficacy and safety.

#### 1.1.2 What are the findings based on population PK analysis?

Body weight was identified as statistically significant covariate for the clearance (CL/F) and volume of distribution (V/F) for both alectinib and it major active metabolite M4. For patients with body ranging from 37.8 Kg to 128 Kg, the change in clearance from typical value (BW=75 Kg) is - 40.2 and +49.3%, respectively. Given the flat E-R relationship for efficacy and safety, body weight will not have a clinically meaningful impact on efficacy and safety. No other covariate had a statistically significant effect on the PK of alectinib and M4. Dose proportionality was confirmed for both alectinib and M4 from 300 mg to 900 mg. For alectinib, the apparent half-life was estimated to be 32 hours, and the accumulation ratio (Racc) for a BID regimen was estimated to be 5.6. For M4, the apparent half-life was estimated to be 31 hours, and the Racc for a BID regimen was estimated to be 6.4.

### 1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in NDA 208434. This NDA is considered acceptable from a pharmacometrics perspective.

## 2 RESULTS OF SPONSOR'S ANALYSIS

### 2.1 Results of Population PK analysis

The number of alectinib and M4 plasma concentrations per study is provided in **Table 1**.

**Table 1**: Number of Alectinib and M4 Plasma Concentrations by Study

| | No. serum concentration[a] /No. patients | |
|---|---|---|
| **Study no.** | **Alectinib** | **M4** |
| NP28673 | 1982 / 138 | 1941 / 138 |
| NP28761 | | |
| Phase 1 | 860 / 41 | 808 / 41 |
| Phase 2 | 445 / 87 | 439 / 87 |
| Total | 3287 / 266 | 3188 / 266 |

[a] BLQ concentrations were not included in this tabulation.

*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 41*

The summary of covariates used in the population PK analyses is summarized in **Table 2**.

**Table 2:** Summary of Covariates used in Population PK Analysis

| Covariate | All Patients | NP28673 | NP28761 Phase 1 | NP28761 Phase 2 |
|---|---|---|---|---|
| | Mean (SD)<br>Median (Min/Max) | Mean (SD)<br>Median (Min/Max) | Mean (SD)<br>Median (Min/Max) | Mean (SD)<br>Median (Min/Max) |
| Age (years) | 52.8 (11.2)<br>53.0 (21.0/83.0) | 51.4 (11.1)<br>52.0 (21.0/79.0) | 55.7 (10.7)<br>55.0 (38.0/83.0) | 53.6 (11.5)<br>54.0 (29.0/79.0) |
| Body Mass Index ($kg/m^2$) | 26.1 (5.38)<br>25.5 (13.6/44.6) | 25.6 (5.37)<br>25.4 (16.9/44.6) | 26.8 (5.49)<br>25.7 (15.1/40.3) | 26.5 (5.31)<br>25.6 (13.6/42.9) |
| Body Surface Area ($m^2$) | 1.83 (0.241)<br>1.81 (1.27/2.51) | 1.81 (0.233)<br>1.80 (1.31/2.51) | 1.87 (0.260)<br>1.88 (1.38/2.44) | 1.85 (0.244)<br>1.83 (1.27/2.42) |
| Height (cm) | 168 (10.1)<br>168 (145/197) | 168 (10.1)<br>168 (145/197) | 169 (9.68)<br>168 (152/190) | 169 (10.3)<br>168 (148/191) |
| Body Weight (kg) | 74.2 (17.9)<br>72.0 (37.8/128) | 72.4 (17.2)<br>71.1 (41.0/122) | 77.0 (19.6)<br>74.1 (39.8/128) | 75.9 (18.0)<br>72.1 (37.8/123) |

| Covariate | Categories | All Patients N (%) | NP28673 N (%) | NP28761 Phase 1 N (%) | NP28761 Phase 2 N (%) |
|---|---|---|---|---|---|
| Ethnicity | 0: Non-Hispanic | 247 (93) | 130 (94) | 39 (95) | 78 (90) |
| | 1: Hispanic | 19 (7) | 8 (6) | 2 (5) | 9 (10) |
| Race | 0: White | 196 (74) | 93 (67) | 30 (73) | 73 (84) |
| | 1: Black | 6 (2) | 1 (1) | 2 (5) | 3 (3) |
| | 2: Asian | 49 (18) | 36 (26) | 6 (15) | 7 (8) |
| | 3: American Indian | 2 (1) | 1 (1) | 1 (2) | 0 (0) |
| | 4: Other | 13 (5) | 7 (5) | 2 (5) | 4 (5) |
| Gender | 0: Female | 143 (54) | 77 (56) | 18 (44) | 48 (55) |
| | 1: Male | 123 (46) | 61 (44) | 23 (56) | 39 (45) |
| Smoking Status | 0: Non-Smoker | 182 (68) | 96 (70) | 32 (78) | 54 (62) |
| | 1: Past Smoker | 79 (30) | 39 (28) | 7 (17) | 33 (38) |
| | 2: Active Smoker | 5 (2) | 3 (2) | 2 (5) | 0 (0) |

| Covariate | All Patients Mean (SD) Median (Min/Max) | NP28673 Mean (SD) Median (Min/Max) | NP28761 Phase 1 Mean (SD) Median (Min/Max) | NP28761 Phase 2 Mean (SD) Median (Min/Max) |
|---|---|---|---|---|
| Alkaline Phosphatase (U/L) | 123 (103)<br>98.0 (40.0/997) | 132 (105)<br>103 (40.0/722) | 115 (55.0)<br>105 (51.0/333) | 114 (117)<br>88.0 (47.0/997) |
| Alanine Amino Transferase(U/L) | 39.2 (34.2)<br>30.0 (5.00/310) | 38.9 (31.7)<br>31.0 (6.00/243) | 42.6 (31.3)<br>36.0 (11.0/177) | 38.0 (39.1)<br>29.0 (5.00/310) |
| Aspartate Amino Transferase(U/L) | 30.6 (16.4)<br>27.0 (8.00/135) | 29.8 (13.9)<br>26.5 (8.00/77.0) | 34.6 (20.9)<br>28.0 (12.0/123) | 30.1 (17.6)<br>26.0 (10.0/135) |
| Creatinine Clearance (mL/min) | 99.2 (33.1)<br>94.3 (33.4/244) | 99.5 (33.3)<br>94.9 (46.3/244) | 91.0 (32.0)<br>81.3 (33.4/168) | 103 (33.1)<br>97.7 (42.2/218) |
| Gamma Glutamyl Transferase(U/L) | 59.9 (109)<br>37.0 (3.00/1350) | 51.1 (65.2)<br>37.0 (10.0/548) | 84.7 (112)<br>37.0 (12.0/494) | 62.2 (153)<br>31.0 (3.00/1350) |
| Serum Creatinine (µmol/L) | 77.2 (21.0)<br>72.5 (35.4/168) | 76.0 (20.6)<br>70.7 (35.4/146) | 86.5 (25.0)<br>79.6 (35.4/168) | 74.8 (18.5)<br>70.7 (37.1/119) |
| Total Bilirubin (µmol/L) | 8.54 (5.28)<br>7.00 (1.71/68.0) | 8.32 (6.44)<br>6.84 (3.00/68.0) | 9.38 (3.69)<br>8.55 (3.42/18.8) | 8.49 (3.61)<br>8.55 (1.71/20.5) |

| Covariate | All Patients<br>Mean (SD)<br>Median (Min/Max) | NP28673<br>Mean (SD)<br>Median (Min/Max) | NP28761 Phase 1<br>Mean (SD)<br>Median (Min/Max) | NP28761 Phase 2<br>Mean (SD)<br>Median (Min/Max) |
|---|---|---|---|---|
| Baseline Tumor Size (mm) | 58.4 (48.3)<br>44.0 (10.0/273) | 51.5 (38.9)<br>40.0 (10.0/238) | 69.9 (60.6)<br>44.0 (12.5/228) | 64.0 (53.9)<br>52.0 (11.0/273) |

| Covariate | Categories | All Patients<br>N (%) | NP28673<br>N (%) | NP28761 Phase 1<br>N (%) | NP28761 Phase 2<br>N (%) |
|---|---|---|---|---|---|
| Prior Chemotherapy | 0: No | 59 (22) | 28 (20) | 8 (20) | 23 (26) |
| | 1: Yes | 207 (78) | 110 (80) | 33 (80) | 64 (74) |
| CNS Metastasis | 0: No | 216 (81) | 104 (75) | 41 (100) | 71 (82) |
| | 1: Yes | 50 (19) | 34 (25) | 0 (0) | 16 (18) |
| ECOG | 0: ECOG = 0 | 93 (35) | 44 (32) | 19 (46) | 30 (34) |
| | 1: ECOG = 1 | 148 (56) | 81 (59) | 19 (46) | 48 (55) |
| | 2: ECOG = 2 | 25 (9) | 13 (9) | 3 (7) | 9 (10) |

*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 42-44*

The PK of alectinib was described by one-compartment open model with first-order elimination and with a sequential zero and first order absorption. The estimates of final model were provided in **Table 3**. Body weight is the only statistically significant covariate for alectinib PK.

**Table 3**: Parameter Estimates for the Final PK Model for Alectinib

| Parameter | Unit | Estimate | RSE (%) |
|---|---|---|---|
| **Fixed Effects** | | | |
| CL/F | L/day (L/hr) | 1965 (81.9) | 3.50 |
| V/F | L | 4016 | 4.30 |
| KA | 1/day (1/hr) | 31.2 (1.30) | 18.1 |
| D1 | day (hr) | 0.143 (3.44) | 8.50 |
| **Random Effects BPV** | | | |
| CL/F | CV% | 40.2 | 6.10[b] |
| V/F | CV% | 40.1 | 11.2[b] |
| KA | CV% | 63.1 | 28.5[b] |
| D1 | CV% | 42.2 | 17.9[b] |
| Correlation CL-V | – | 0.487 | 11.0[c] |
| **Covariate Effects** | | | |
| Effect of WT on CL/F | – | 0.75[a] | - |
| Effect of WT on V/F | – | 1[a] | - |
| **Error Model** | | | |
| $\sigma_1$ (additive) | ng/mL | 41.9 | 17.3 |
| $\sigma_2$ (proportional) | % | 19.0 | 5.80 |

RUNID: RUN822, OFV: 19645.878

BPV = between-patient variability; σ = residual error; RSE = relative standard error of estimate; CV = coefficient of variation; OFV = objective function value; WT = body weight.

[a] Allometric coefficients: fixed.

[b] RSE computed for the corresponding variance.

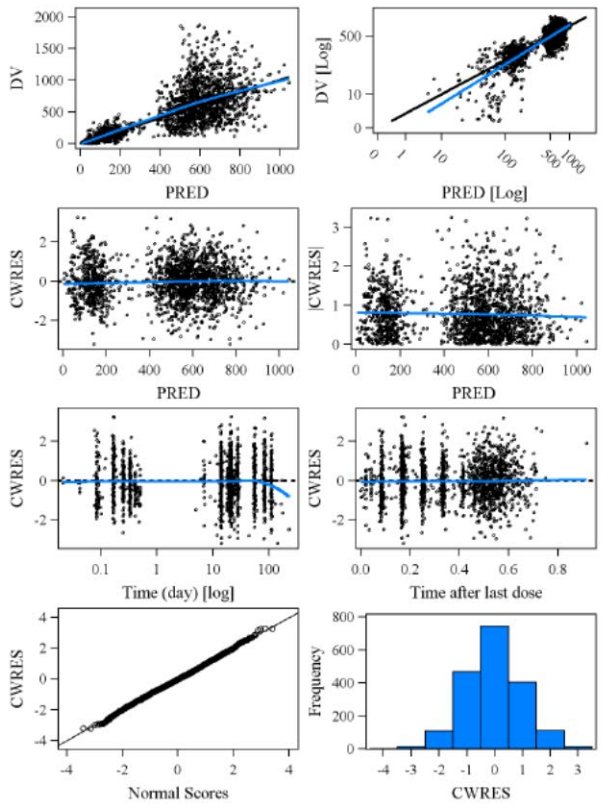
[c] RSE computed for the corresponding covariance.

* D1: duration of zero-order absorption

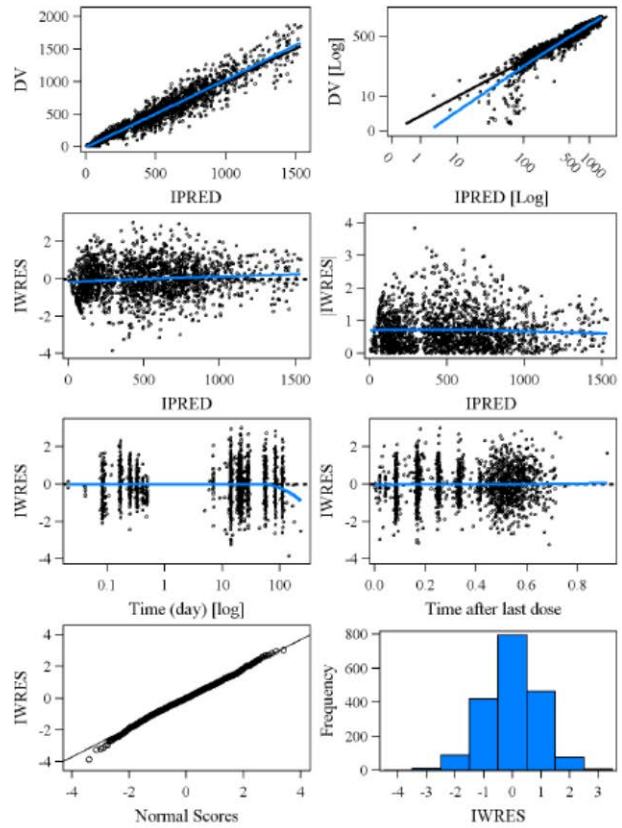
*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 51*

As shown in the goodness-of-fit plots (**Figure 1**), the model appeared to be adequate in describing the observed PK data of alectinib.

**Figure 1:** Goodness of Fit for the Final Model for Alectinib




DV – Observed alectinib concentrations [ng/mL], PRED (IPRED) – NONMEM predicted alectinib concentrations [ng/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], TAD – time after last drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.




DV – Observed alectinib concentrations [ng/mL], PRED (IPRED) – NONMEM predicted alectinib concentrations [ng/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], TAD – time after last drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.

*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 52-53*

The base structural PK model for M4 was a one-compartment open model with first order elimination and with a sequential zero and first-order formation. Similar to alectinib, the final PK model for M4 also retained the effect of body weight on clearance and volume of distribution, with the effect incorporated in accordance with the principles of allometric scaling by using a coefficient of 0.75 for the CL/F and a coefficient of 1 for the V/F. The estimates of final model were provided in **Table 4**. As shown in the goodness-of-fit plots (**Figure 2**), the model appeared to be adequate in describing the observed PK data of alectinib.

**Table 4:** Parameter Estimates for the Final PK Model for M4

| Parameter | Unit | Estimate | RSE (%) |
|---|---|---|---|
| **Fixed Effects** | | | |
| CL/F | L/day (L/hr) | 5205 (217) | 3.10 |
| V/F | L | 10093 | 6.20 |
| $K_{formation}$ | 1/day (1/hr) | 14.2 (0.592) | 13.6 |
| $D1_{formation}$ | day (hr) | 0.209 (5.02) | 4.80 |
| **Random Effects BPV** | | | |
| CL/F | CV% | 36.0 | 7.60[b] |
| V/F | CV% | 58.9 | 7.40[b] |
| $K_{formation}$ | CV% | 72.7 | 23.9[b] |
| Correlation CL-V | – | 0.475 | 12.3[c] |
| **Covariate Effects** | | | |
| Effect of WT on CL/F | – | 0.75[a] | - |
| Effect of WT on V/F | – | 1[a] | - |
| **Error Model** | | | |
| $\sigma_1$ (additive) | ng/mL | 10.9 | 11.1 |
| $\sigma_2$ (proportional) | % | 15.9 | 4.40 |
| RUNID: RUN925, OFV: 14844.401 | | | |

BPV = between-patient variability; σ = residual error; RSE = relative standard error of estimate; CV = coefficient of variation; OFV = objective function value; WT = body weight.

[a] Allometric coefficients: fixed.

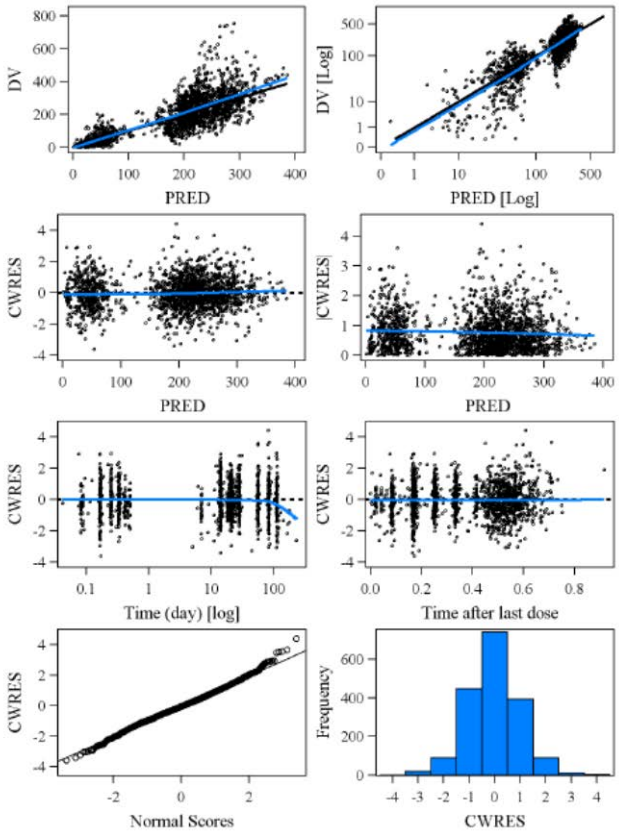
[b] RSE computed for the corresponding variance.

[c] RSE computed for the corresponding covariance.

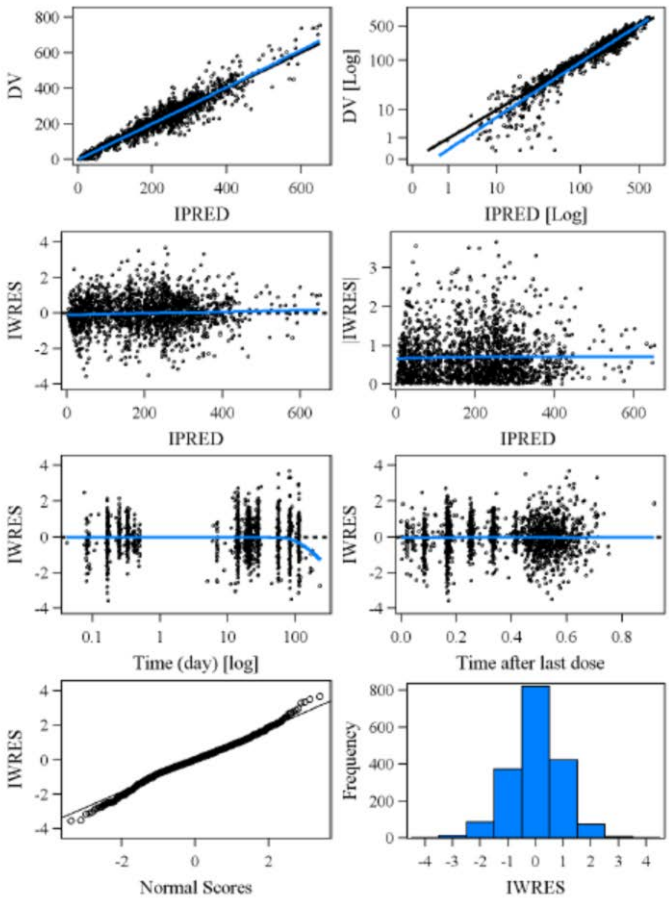
* D1: duration of zero-order absorption

*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 63*

**Figure 2:** Goodness of Fit For the Final Model for M4




DV – Observed M4 concentrations [ng/mL], PRED (IPRED) – NONMEM predicted M4 concentrations [ng/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], TAD – time after last drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.




DV – Observed M4 concentrations [ng/mL], PRED (IPRED) – NONMEM predicted M4 concentrations [ng/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], TAD – time after last drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.

*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 64-65*

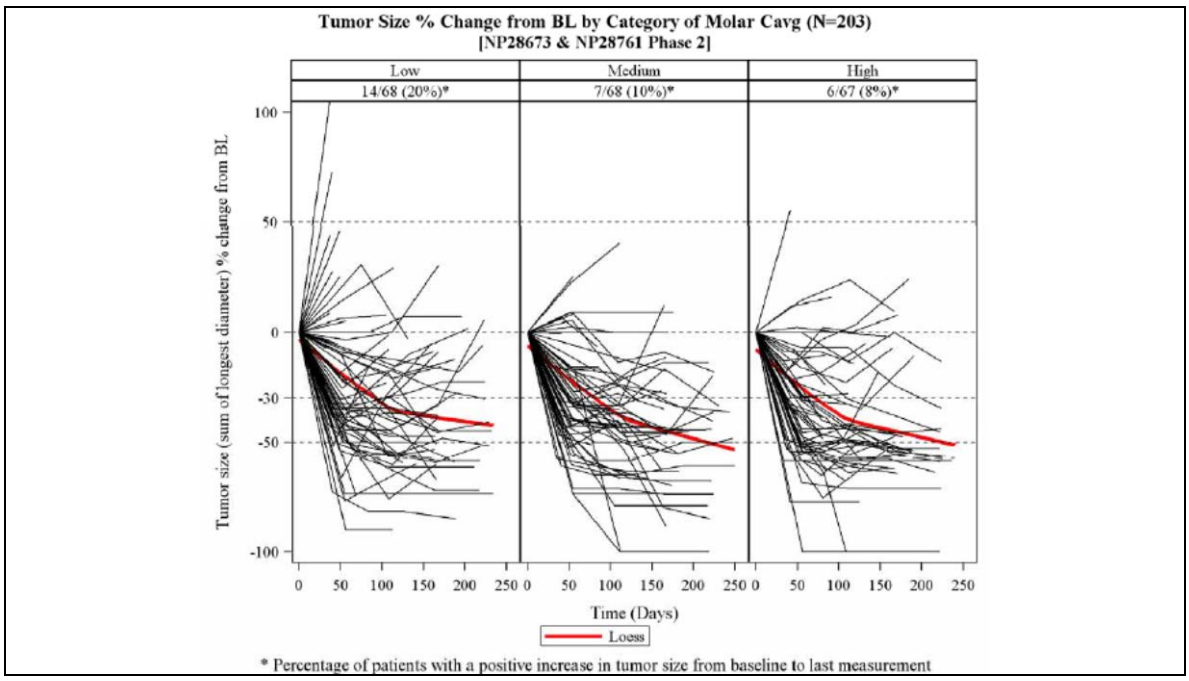
*Reviewer's comments: Body weight was identified as statistically significant covariate for PK of alectinib and M4, for subjects with body ranging from 37.8 Kg to 128 Kg, the change in clearance from typical value is - 40.2 and +49.3%, respectively. Given the flat E-R relationship for efficacy and safety, body weight will not result in a clinically meaningful impact on efficacy and safety.*

## 2.2 Results of exposure-response analysis

### 2.2.1 Results of E-R analysis for efficacy

For patients treated with the 600 mg BID dose (NP28673 and NP28761 Phase 2), the average-decline in tumor size was similar across exposure categories (**Figure 3**). A higher percentage of patients with a positive increase in tumor size at the end of treatment compared to baseline were observed in the low exposure category (20%) versus the medium and high exposure categories (10% and 8%, respectively). However, those patients also had a higher tumor size at baseline compared to the other patients. In general, the decrease in tumor size across time appeared to plateau with increasing alectinib exposure.

**Figure 3:** Change in Tumor Size from Baseline by Category of Combined Alectinib and M4 Exposure Following 600 mg BID (NP28673 and NP28761 Phase 2)



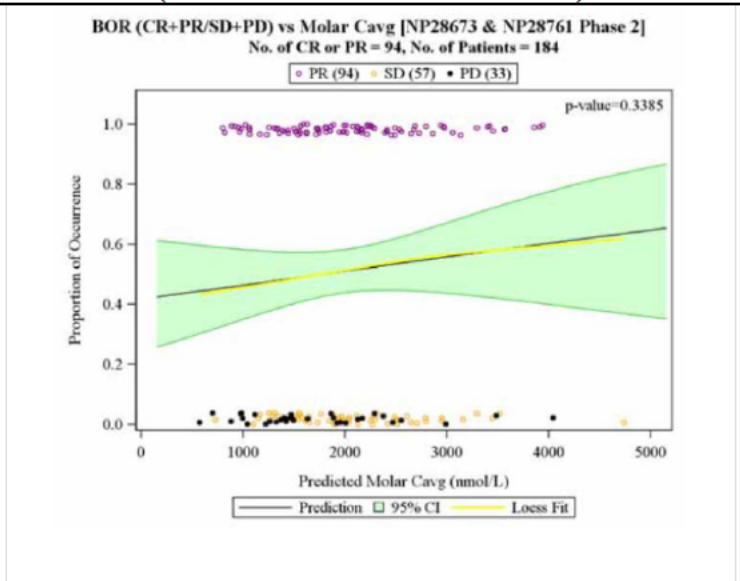

Exposure-efficacy analyses were conducted for systemic BOR by independent review committee (IRC) and CNS BOR by IRC in patients with measurable CNS disease at baseline using multivariate logistic regression analyses (Studies NP28673 and NP28761 Phase 2). The analyses were conducted by accounting for the potential influence of 12 possible prognostic factors, including baseline disease status factors (i.e., tumor size, Eastern Cooperative Oncology Group [ECOG] score [0/1, 2], CNS metastases status [yes, no], prior chemotherapy [yes, no], prior crizotinib treatment duration), demographic factors (i.e., body weight, age, gender, race, ethnicity, smoking status [never, past/present]), and the combined molar concentration of alectinib and M4 up to the efficacy assessment. Using a stepwise forward inclusion followed by a backward deletion process, the final multivariate logistic regression model which includes the statistically significant prognostic factors is referred to as the final logistic regression model.

For BOR, the combined molar concentration of alectinib and M4 (Caverage) was not found to be significantly correlated with the probability of having a complete response (CR) or partial response (PR) for patients who were treated with the 600 mg BID dose (**Figure 4**). Multivariate logistic regression analysis identified baseline tumor size as only significant covariate for BOR (**Table 5**).

For CNS BOR in patients with measurable CNS disease at baseline, multivariate analysis showed that none of the 12 possible prognostic factors tested were significant in predicting the probability of having a CNS BOR. The combined molar concentration of alectinib and M4 (Caverage) was not found to be significantly correlated with the

probability of having a CNS BOR for patients with measurable CNS disease at baseline who were treated with the 600 mg BID dose (**Figure 5**).

**Figure 4:** Systemic Best Overall Response (CR+PR/SD+PD) versus Combined Alectinib and M4 Exposure Following 600 mg BID (NP28673 and NP28761 Phase 2)




*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 90*
*SD = stable disease and PD = progressive disease*

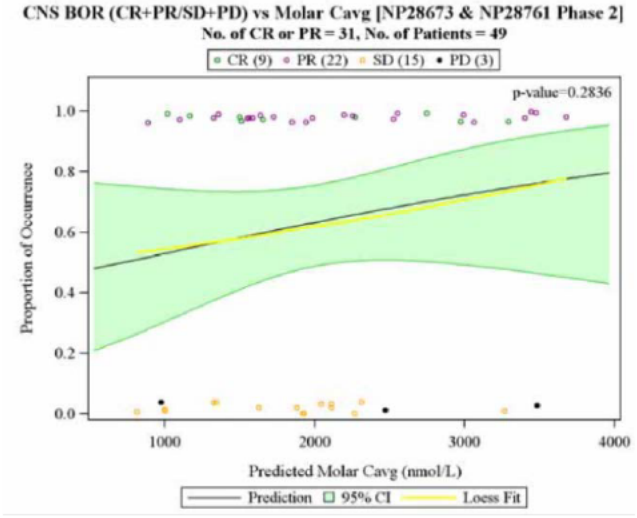
**Table 5**: Parameter Estimates for the Final Logistic Regression Model for Systemic Best Overall Response (CR+PR/SD+PD) by IRC Following Alectinib 600 mg BID (NP28673 and NP28761 Phase 2)

| Parameter | Parameter Estimate | Standard Error | p-value | Odds Ratio | Odds Ratio Lower 95% CI | Odds Ratio Upper 95% CI |
|---|---|---|---|---|---|---|
| Baseline tumor size (mm) | $-9.25 \times 10^{-3}$ | $3.73 \times 10^{-3}$ | 0.013 | 0.991 | 0.983 | 0.998 |

CI = confidence interval; BID = twice daily; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

*Sources: Responses, FDA Request for Information (Reference ID: 3813882) dated 31 August 2015, Page 4*

**Figure 5:** CNS Best Overall Response (CR+PR/SD+PD) versus Combined Alectinib and M4 Exposure Following 600 mg BID (NP28673 and NP28761 Phase 2)

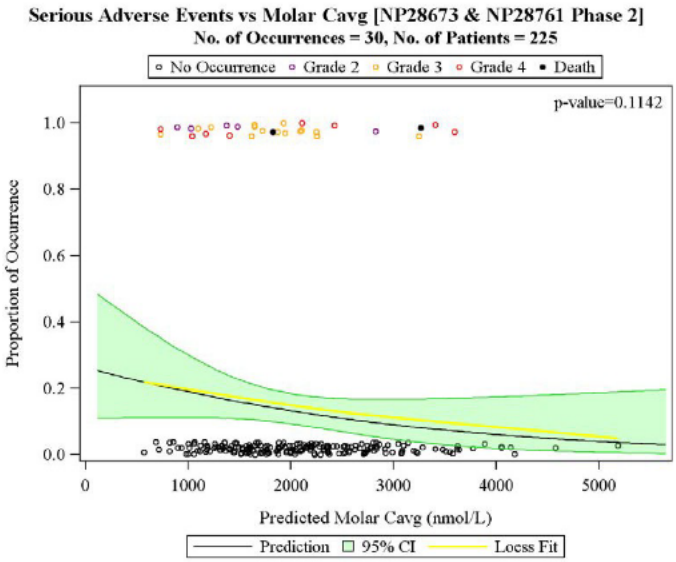



*Sources: Population PK and PK-PD Analyses Report 1064536 (alectinib), page 92*

### 2.2.2 Results of E-R analysis for safety

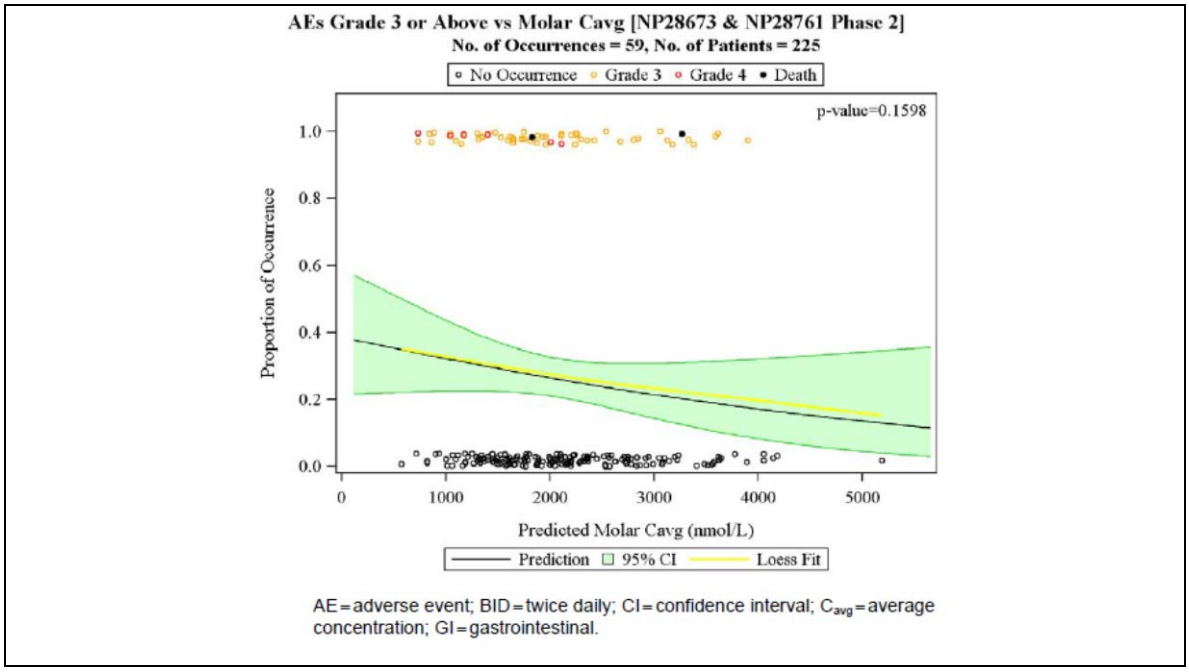
E-R analyses were conducted for serious adverse events (SAEs) and AEs for patients from Studies NP28673 and NP28761 Phase 2. For patients receiving alectinib 600 mg BID, logistic regression analyses have shown that there was no significant relationship between combined molar concentration of alectinib and M4 (Caverage) up to the safety events and the occurrences of SAEs that are not GI disorders (**Figure 6**). There was also no significant relationship between Caverage and the occurrences of AEs Grade 3 or above that are not GI disorders (**Figure 7**).

**Figure 6:** SAEs that are not GI Disorders versus Combined Alectinib and M4 Exposure Following Alectinib 600 mg BID (NP28673 and NP28761 Phase 2)



*Sources: Responses, FDA Request for Information (Reference ID: 3813882) dated 31 August 2015, Page 7*

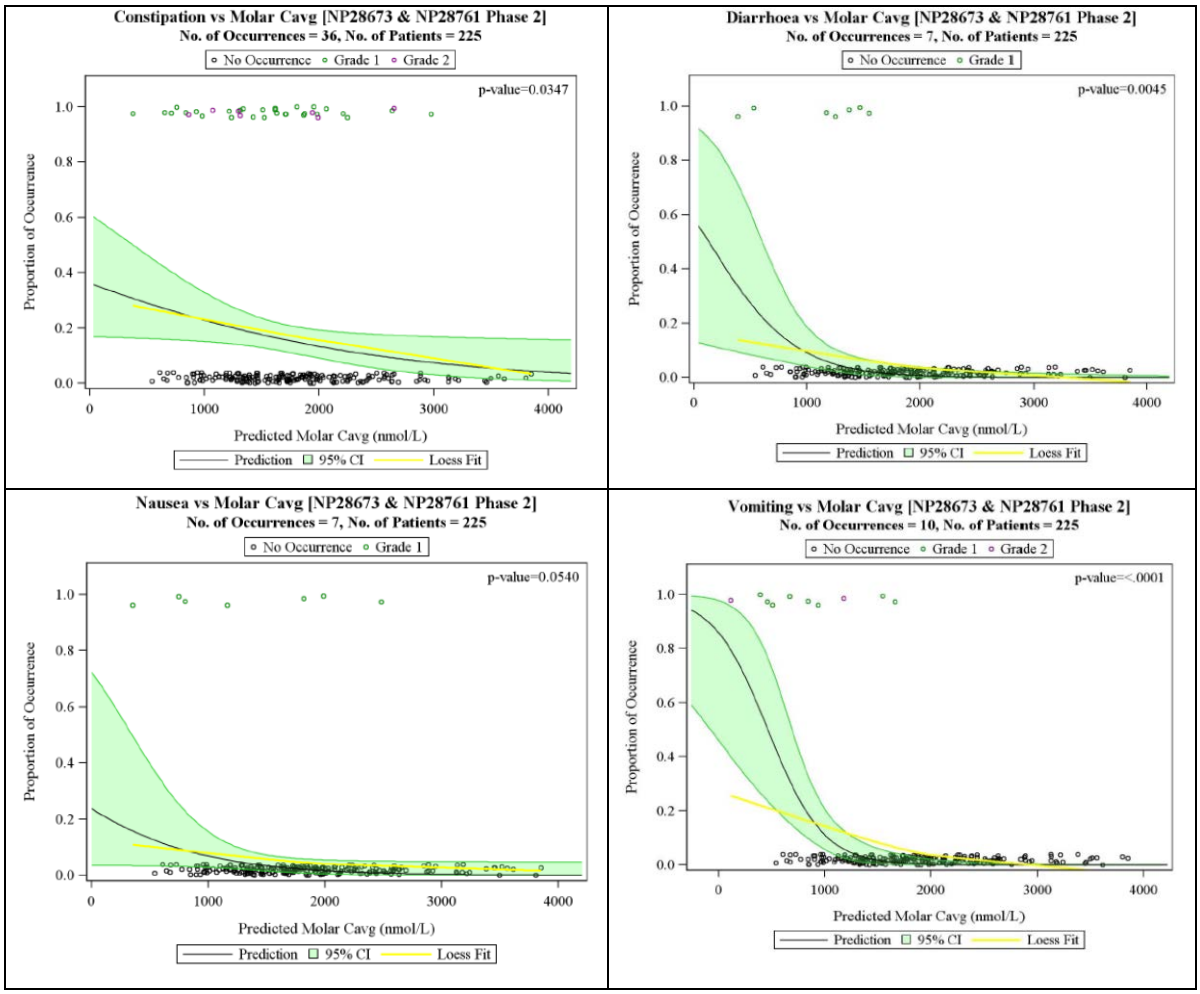
**Figure 7:** AEs Grade 3 or Above that are not GI Disorders versus Combined Alectinib and M4 Exposure Following Alectinib 600 mg BID (NP28673 and NP28761 Phase 2)




*Sources: Responses, FDA Request for Information (Reference ID: 3813882) dated 31 August 2015, Page 8*

In Studies NP28673 and NP28761 Phase 2, constipation, diarrhea, nausea, and vomiting were the 4 most frequent GI disorders. Therefore, the exposure-safety analyses were conducted for these 4 specific GI disorders. Results showed that an increase in exposure did not appear to be associated with an increase in the occurrence of each of these specific GI disorders during the first 14 days following alectinib 600 mg BID. There is an apparent inverse relationship between exposure and each of these 4 specific GI disorders during the first 14 days following alectinib 600 mg BID (**Figure 8**).

**Figure 8:** E-R Relationship for Each Specific GI Disorder, Including Constipation, Diarrhea, Nausea and Vomiting




*Sources: Responses, FDA Request for Information (Reference ID: 3813882) dated 31 August 2015, Page 11-14*

*Reviewer's comments: The reasons for apparent inverse E-R relationship for GI disorders are unknown. One possible explanation is that GI disorders are caused by unabsorbed portion of the drug in the GI tract. Both low systemic exposure and high probability of GI disorders is associated with high unabsorbed fraction in GI tract, which resulted in the observed apparent inverse E-R relationship for GI disorders.*

# Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

| | |
|---|---|
| **Application Number** | NDA208434 |
| **Drug Name** | Alectinib |
| **Proposed Indication** | Kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. |
| **Clinical Division** | DOP2 |
| **Primary PBPK Reviewer** | Ping Zhao, Ph.D. |
| **Secondary PBPK Reviewer** | Vikram Sinha, Ph.D. |
| **Applicant** | Roche |

## 1. *Objectives*

The main objective of this review is to evaluate the submitted physiologically-based pharmacokinetic (PBPK) modeling information that predicted the potential drug-drug interaction (DDI) potential of alectinib as an inhibitor of CYP2C8.

To support its conclusion that alectinib does not inhibit CYP2C8 at clinically relevant doses, the applicant provided the following PBPK modeling and simulation information:

a) Alectinib (RO5424802) - Physiologically based pharmacokinetic modeling using SimCYP® [1]
b) Alectinib (RO5424802) - Physiologically based pharmacokinetic modeling using GastroPlus™ [2]
c) Response to FDA Request for Information dated 11 August 2015 [3]

## 2. *Background*

### 2.1. Regulatory history on PBPK submission

Alectinib (RO5424802) is an oral anaplastic lymphoma kinase (ALK) inhibitor for the treatment of patients with ALK-positive, locally advanced or metastatic, non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib [4]. Alectinib is mainly metabolized by CYP3A. Its major metabolite M4 (RO5468924) has a similar in vitro potency to alectinib [5].

The applicant developed PBPK models of alectinib and its metabolite M4 to predict the effect of alectinib on the PK of CYP2C8 substrate repaglinide. (b) (4) On Aug 11, 2015, FDA issued information request (08112015IR, section 6.2.1) to the applicant.

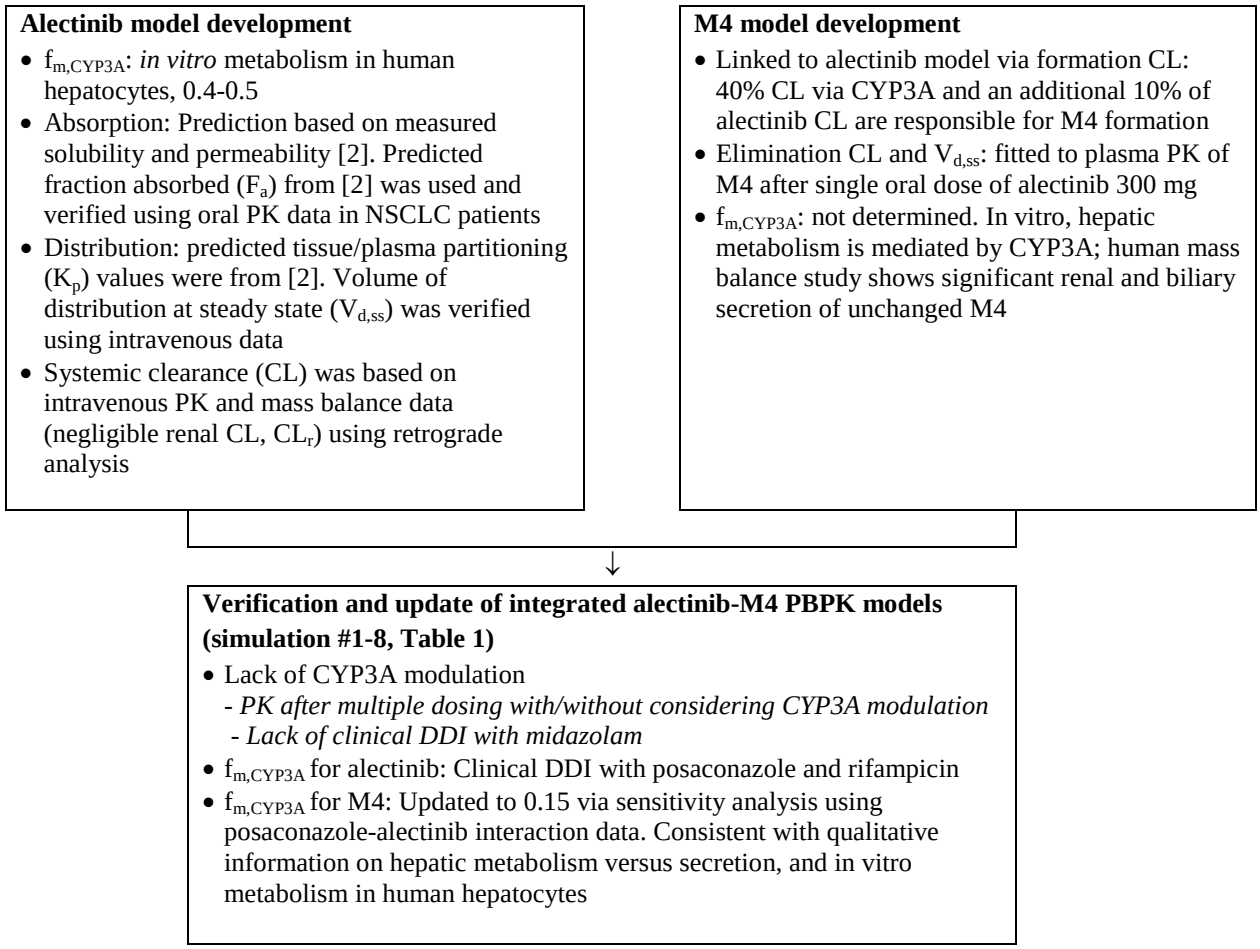
This review evaluates the adequacy of the applicant's PBPK models of alectinib and M4 to predict the potential of alectinib as an inhibitor of CYP2C8 in humans.

## *3. Methods*

A population based PBPK software SimCYP® (V13, release 1, Sheffield, UK) was used by the applicant to develop drug PBPK models and conduct simulations to predict potential DDIs. The concept and construct of SimCYP have been described by Jamei et al [6]. A workflow of applicant's PBPK modeling is summarized in **Figure 1**. Physico-chemical parameter values and sources for alectinib and M4 are summarized in **Appendix Table 1**. Drug absorption and disposition parameters for alectinib and M4 are summarized in **Appendix Tables 2 and 3**, respectively. For repaglinide, the applicant either used software's built-in "SV-repaglinide" model with a fraction of total clearance by CYP2C8 ($f_{m,CYP2C8}$) of 0.55, or modified the built-in model with $f_{m,CYP2C8}$ =0.79 ($f_{m,CYP3A}$=0.21). In this review, we refer to these two models as default repaglinide and high-$f_{m,CYP2C8}$ repaglinide models, respectively. For alectinib-midazolam DDI simulations, applicant directly used software built-in "Sim-midazolam" model. For rifampicin-alectinib DDI simulations, applicant either directly used built-in "Sim-rifampicin" model [1], or two other models modified with stronger CYP3A induction potency [3], and model parameters are compared in **Appendix Table 4**. For posaconazole-alectinib DDI simulation, applicant developed and verified a posaconazole model and the parameters are summarized in **Appendix Table 5**.

The software "Healthy volunteers" population and a NSCLC virtual population were used by the sponsor. The later was established according to [7]. **Table 1** summarizes conditions for simulations related to model verification/update and model application (Simulation #1-10), including simulation design, virtual population used, modifications of integrated alectinib-M4 PBPK model, and models of co-medications.

**Figure 1. Workflow of the development and verification of final integrated alectnib-M4 PBPK models [3]**



## Table 1. Summary of simulations for model verification/update and model application

| | Model verification/update | | | | | | | | Model application | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Simulation #** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| Simulation objectives | To demonstrate the negligible effect of CYP3A auto inhibition/induction on alectinib PK and negligible PK differences between healthy subjects and NSCLC subjects | | | To simulate alectinib-midazolam DDI | To simulate rifampicin-alectinib DDI using different rifampicin models | | | To simulate posaconazole-alectinib DDI | To Predict alectinib-repaglinide DDI. Alectinib-M4 model modified with 30% lower total clearance | To Predict alectinib-repaglinide DDI. |
| Design | 10 trials, n=50/trial, 600 mg oral alectinib twice daily (b.i.d.), 54 doses | | | 10 trials, n=14/trial, midazolam single 2 mg oral dose on day 10 at 9 am, alectinib, oral 600 mg b.i.d. starting on day 1 at 9 am, 30 doses | 10 trials, n=24/trial, alectinib single oral 600 mg on day 10 at 9 am; rifampicin oral 600 mg once daily (q.d.) starting on day 1 at 9 am, 13 doses | | | 10 trials, n=17/trial, alectinib single oral 300 mg on day 8 at 9 am; posaconazole oral 400 mg b.i.d., starting day 1 at 9 am, 30 doses | 10 trials, n=12/trial, repaglinide single oral 0.25 mg, day 12 at 12:00 pm, alectinib oral 600 mg b.i.d. starting on day 1 at 9 am, 30 doses | |
| Population | Sim-Healthy volunteer 20-60 years old, female 55%, fed | NSCLC [7]. 31-79 years, female 55%, fed | | | Sim-Healthy volunteers. 21-52 years, female 8%, fed | | | Sim-Healthy volunteers. 20-52 years, female 20%, fed | NSCSC [7]. 31-79 years, female 55%, fed | |
| Integrated alectinib-M4 PBPK model | | | No CYP3A interaction considered | Total clearance (and intrinsic clearance, $CL_{int}$) reduced by 30%[a] | | | | | Total clearance (and intrinsic clearance, $CL_{int}$) reduced by 30%[a] Unbound Ki 0.0049 µM was also tested | Unbound Ki 0.0049 µM was also tested |
| Co-medication models | NA | | | SV-Midazolam | Sim-Rifampicin (V13 1) | Sim-Rifampicin (V13 1) $I_{ndMax}$ [b] of CYP3A of 16 | Sim-Rifampicin (V13 1) modified according to [8] | Appendix Table 4 | SV-repaglinide or SV-repaglinide with higher $f_{m,CYP2C8}$ | SV-repaglinide or SV-repaglinide with higher $f_{m,CYP2C8}$ |

*[a] To bring simulated steady state alectinib concentrations into agreement with the clinical data obtained in NSCLC patient population [3]; [b] $I_{nd,max}$, maximal fold induction.*

## *4. Results*

### 4.1. Can the integrated alectinib-M4 PBPK models predict the effect of CYP3A modulators on the PK of alectinib and M4?

Yes. Two factors are critical for a substrate PBPK model to predict the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumption of $f_{m,CYP3A}$ for alectinib), and capability of the model to predict the PK profile under different dosing regimens. For M4, assumption on $f_{m,CYP3A}$ cannot be quantitatively made (**Figure 1**). As such, model of M4 was updated using observed DDI caused by posaconazole.

**Figure 2** shows that integrated alectinib and M4 PBPK models are able to describe observed data in healthy subjects taking a single oral dose of alectinib. **Figure 3** shows that model simulations tended to under-predict steady-state exposures of alectinib and M4 in NSCLC subjects taking 600 mg b.i.d. orally (Simulation #1-3, **Table 1**), regardless if the model has considered modulation of CYP3A by alectinib and M4. In order to ensure sufficient parent/M4 exposures for simulations of the effect of multiple doses of alectinib on single dose PK of a CYP substrate, the applicant's reduced intrinsic clearance ($CL_{int}$) values of all elimination pathways of alectinib and M4 by 30% to match the observed steady state exposures of alectinib and M4 (**Appendix Tables 2 and 3**).

**Figure 2. PBPK simulated and observed plasma concentration-time profiles of alectinib (left) and M4 (right) after a single oral dose of alectinib 300 mg in healthy subjects. Simulation used integrated alectinib-M4 models**
Source: Figure 1, ref [3]

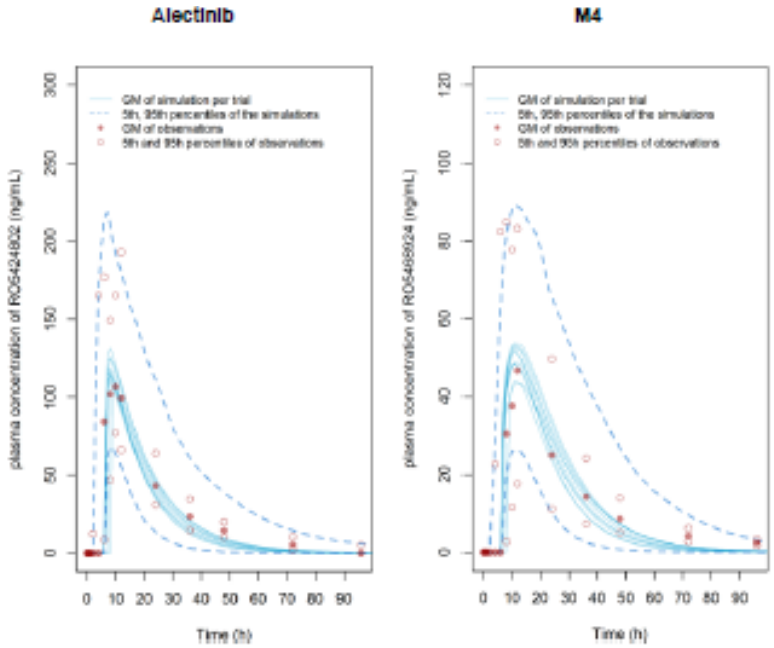
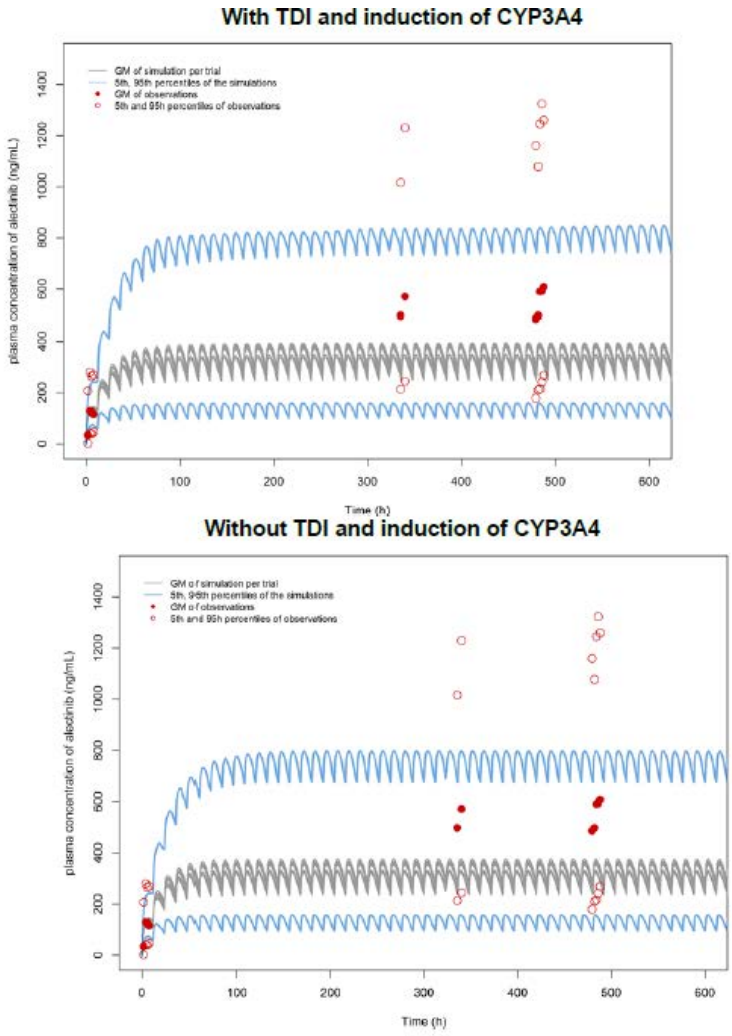


**Figure 3. Simulations of multiple dose pharmacokinetics with the final integrated alectinib-M4 model in patients using the NSCLC population model with no adjustment of intrinsic clearance and including (top) or not including (bottom) TDI and induction of CYP3A based on in vitro data (V14.1)**

TDI: time-dependent inhibition; Source: Figure 4, ref [3]




### *4.1.1. Effect of posaconazole on alectinib and M4 exposures*

The assumption on $f_{m,CYP3A}$ for alectinib was verified because the simulated magnitude of exposure changes of alectinib (Simulation #8, **Table 1**) are comparable to that observed in healthy subjects (**Table 2**).

The observed DDI between posaconazole and alectinib was used to inform $f_{m,CYP3A}$ value for PBPK model of M4. Simulation using integrated model with $f_{m,CYP3A}$=0.15 for M4 model reasonably captured the observed magnitude of Cmax ratio and AUC ratio of M4 (**Table 2**). The relatively low value of $f_{m,CYP3A}$ for M4 appears plausible and is consistent with significant biliary and urinary secretions of unchanged M4 (**Figure 1**).

**Table 2.Comparison of PBPK simulated (geometric mean [5th-95th percentiles]) and observed (geometric mean [90% confidence interval]) Cmax and AUC ratios of alectinib and M4 in clinical drug-drug interaction study with posaconazole**

| | | Cmax ratio | AUC ratio |
|---|---|---|---|
| Alectinib | Simulated with CYP3A modulation [3] | 1.18 [1.09 – 1.32] | 1.64 [1.31 – 2.25] |
| | Observed [a] | 1.18 [1.02 - 1.37] | 1.75 [1.57 - 1.95] |
| M4[b] | Simulated with CYP3A modulation [3] | 0.345 [0.233 – 0.511] | 0.495 [0.343 – 0.679] |
| | Observed [a] | 0.287 [0.231 – 0.355] | 0.751 [0.644 – 0.877] |

*Simulation #8, Table 1. Source, Table 3 [3] and Appendix 4, table 3 [1]. [a.] study NP28990, n=17 subjects. [b.] $f_{m,CYP3A}$ for M4 = 0.15 was informed by sensitivity analysis using posaconazole DDI data. The simulated Cmax ratio and AUC ratio (with and without posaconazole) using integrated alectinib-M4 models considering CYP3A modulation are not different from those simulated using models without CYP3A modulation (Data not shown).*

### *4.1.2. Effect of rifampicin on alectinib and M4 exposures*

The assumption on $f_{m,CYP3A}$ for alectinib was further assessed using clinical DDI data with rifampicin as modulator. **Table 3** compares observed Cmax and AUC ratios of alectinib and M4 to those simulated using PBPK models. Simulation using default rifampicin model in SimCYP Version 13.1 appears to underestimate the magnitude of effect on alectinib exposure by rifampicin *in vivo* (higher simulated Cmax and AUC ratios, Simulation #5, **Table 1**). This is consistent with under-prediction observed by others using SimCYP software [8, 9]. Increasing CYP3A induction potency within rifampicin model resulted in closer prediction of the observed magnitude of DDI for alectinib (Simulations #6 and 7, **Table 1**).

The integrated alectinib-M4 PBPK models assuming $f_{m,CYP3A}$ of 0.15 for M4 (see 4.2.1 above, **Table 2**) were not able to capture the observed Cmax ratio and AUC ratio for M4, regardless the potency of CYP3A induction in rifampicin model. The applicant suggested that pathways not recognized for the elimination of M4 in integrated models (**Appendix Table 3**) may be subject to modulation by rifampicin.

**Table 3. Comparison of PBPK simulated (geometric mean [5th-95th percentiles]) and observed (geometric mean [90% confidence interval]) Cmax and AUC ratios of alectinib and M4 in clinical drug-drug interaction study with rifampicin**

| | | Cmax ratio | AUC ratio |
|---|---|---|---|
| Alectinib | Simulation #5 [a] | 0.753 [0.607 – 0.880] | 0.462 [0.287 – 0.674] |
| | Simulation #7 [b] | 0.620 [0.441 – 0.797] | 0.326 [0.183 – 0.561] |
| | Simulation #6[c] | 0.573 [0.397, 0.758] | 0.269 [0.149, 0.449] |
| | Observed [d] | 0.486 [0.435 – 0.543] | 0.268 [0.238 – 0.301] |
| M4 | Simulation #5 [a] | 1.63 [1.28 – 2.13] | 1.00 [0.711 – 1.31] |
| | Simulation #7 [b] | 1.68 [1.23 – 2.41] | 0.851 [0.507 – 1.26] |
| | Simulation #6[c] | 1.74[1.229, 2.463] | 0.778 [0.421, 1.235] |
| | Observed [d] | 2.20 [1.90 – 2.55]] | 1.79 [1.58 – 2.02] |

*Source, Table 6 [3]; Appendix Table 4 [1]. [a.] Default rifampicin model in SimCYP V13.1 [1]; [b.] Default rifampicin model updated according to [8] (see more in **Appendix Table 4**); [c.] Default rifampicin model updated with 2-fold higher $I_{ndMax}$ (see more in **Appendix Table 4**) . [d.] Study NP29042, n=24 subjects. The simulated Cmax ratio and AUC ratio (with and without rifampicin) using integrated alectinib-M4 models considering CYP3A modulation are not different from those simulated using models without CYP3A modulation (Data not shown).*

### 4.2. Can integrated alectinib-M4 PBPK models predict minimal CYP inhibition in humans?

Yes.

Alectinib and M4 showed inhibition and induction potential of CYP3A in vitro. Simulations of steady state alectinib and M4 PK profiles were conducted using integrated alectinib-M4 PBPK models considering time-dependent inhibition (TDI) and induction of CYP3A, and models without considering CYP3A modulation. Simulations using these two models appear similar (Simulation #1-3, **Table 1**), suggesting that inhibition and induction of CYP3A by alectinib and M4 are minimal (**Appendix Figure 2**). The applicant used integrated models to simulate the effect of alectinib on the exposure of midazolam (Simulation #4, **Table 1**), and the results are shown in **Table 4**. When integrated models consider TDI of CYP3A only (e.g., without CYP3A induction mechanism), the simulated Cmax ratio and AUC ratio of midazolam are 1.27 and 1.42 respectively. These values are slightly above a pre-defined no-effect boundary of 1.25 [10]. When integrated models consider both TDI and induction of CYP3A, the simulated Cmax ratio and AUC ratio of midazolam become slightly lower. In comparison, the observed Cmax ratio and AUC ratio are 0.92 and 0.97, respectively.

**Table 4. Model simulated and observed geometric mean Cmax and AUC ratios of midazolam in the presence and absence of multiple doses of alectinib 600 mg BID using the integrated alectininb-M4 model (with adjustment in $CL_{int}$ Values for the NSCLC Population).**

| Midazolam PK Parameter | Predicted Ratio (TDI only) Ref [1] | Predicted Ratio (TDI + induction) Ref [3] | Observed Ratio |
|---|---|---|---|
| Cmax | 1.27 | 1.17 | 0.92 |
| AUC | 1.42 | 1.26 | 0.97 |

*Source, Table 7 [3]*

The applicant used integrated alectinib-M4 models to predict changes in repaglinide exposure by alectinib (Simulation #9 and 10, **Table 1**). Model predicted repaglinide Cmax ratio and AUC ratio are summarized in **Table 5**. The simulated median Cmax ratio and AUC ratio of repaglinide are 1.05 and 1.06, respectively. To remain conservative, the applicant conducted sensitivity analyses either by increasing the contribution of CYP2C8 to the metabolism of repaglinide (from 0.55 to 0.79), or by increasing alectinib inhibition potency towards CYP2C8 (e.g., by decreasing in vitro unbound $K_i$ by a factor of 30). Under the condition with both a stronger alectinib inhibition of CYP2C8 and a higher $f_{m,CYP2C8}$ for repaglinide, the model predicted median repaglinide Cmax ratio and AUC ratio are 1.11 and 1.29, respectively. These simulations suggested minimal effect of alectinib on the exposure of repaglinide.

**Table 5. PBPK model predicted median (5-95$^{th}$ percentiles) Cmax and AUC ratios of repaglinide in the presence and absence of multiple doses of alectinib 600 mg BID using the integrated alectininb-M4 model (with adjustment in $CL_{int}$ for the NSCLC population, Simulation #9, Table 1).**

| | **Default model ($f_{m,CYP2C8}$=0.55)** | | **High $f_{m,CYP2C8}$ model ($f_{m,CYP2C8}$=0.79)** | |
|---|---|---|---|---|
| *Alectinib $K_i$ for CYP2C8* | Cmax ratio | AUC ratio | Cmax ratio | AUC ratio |
| *In vitro* $K_i$ = 0.0147 μM | 1.06 (1.02-1.13) | 1.08 (1.03-1.21) | 1.03 (1.01-1.07) | 1.05 (1.01-1.11) |
| *In vitro* $K_i$/30 | 1.15 (1.06-1.28) | 1.32 (1.11-1.63) | 1.15 (1.07-1.28) | 1.40 (1.16-1.76) |

*Source, Table 1 [3], $f_{mCYP2C8}$ values are median $f_m$ of the virtual population simulated (simulation output), reflecting initial values according to references [11] (in vitro finding) and [12] (based on in vivo DDI with repaglinide as substrate), respectively. . Smaller exposure ratios were predicted in Simulation #10, where no adjustment of $CL_{int}$ of alectinib-M4 was made.*

### 4.3. What are the limitations of applicant's PBPK models?

As described in 4.1, prediction of the effect of rifampicin on the exposure of M4 by integrated alectinib-M4 PBPK models was not satisfactory. If one were to use PBPK to predict the effect of various patient factors on the PK of M4, additional elimination mechanisms of M4 need to be understood and be quantitatively incorporated into the model of M4.

The applicant also conducted PBPK modeling and simulation to understand oral absorption of alectinib and to evaluate the effect of the timing of alectinib dosing with respect to a meal [2]. This report was not reviewed.

## *5. Conclusion*

The applicant's integrated alectinib-M4 PBPK models accounting for CYP inhibition mechanisms (TDI and induction of CYP3A, and reversible inhibition of CYP2C8) predicted no effect on CYP2C8 substrate repaglinide at clinical doses. Simulations using integrated alectinib-M4 PBPK models are determined to be adequate to support the applicant's proposed labeling language regarding the lack of CYP2C8 inhibition potential.

## *6. Appendices*

### *6.1. Abbreviations*

ALK, anaplastic lymphoma kinase; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; b.i.d., twice daily dosing; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, systemic clearance; $CL_{int}$, intrinsic clearance; $CL_{po}$, oral clearance; $CL_r$, renal clearance; CV, coefficient of variation; DDI: drug-drug interaction; F, bioavailability; $f_a$, fraction absorbed; $f_{mj}$, fraction of total clearance mediated by j CYP isoform or renal elimination; $f_{up}$, fraction unbound in plasma; $f_{u,gut}$, apparent unbound fraction in enterocytes; $I_{nd,max}$, maximal fold induction; $k_a$, first order absorption rate constant; $K_i$, reversible inhibition constant; $K_I$, inactivator concentration that supports half maximal rate of inactivation; $k_{inact}$, maximal inactivation rate; $K_p$, tissue/plasma partitioning; $LogP_{o:w}$, logarithm of the

octanol-water partition coefficient; NA, not applicable; NSCLC, non-small cell lung cancer; NDA: new drug application; $P_{app}$, apparent passive permeability; $P_{eff,man}$, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; q.d., once daily dosing; $T_{max}$: time at maximal concentration in plasma; $V_{d,ss}$, volume of distribution at steady state.

### *6.2. Information requests*

6.2.1. Clinical Pharmacology (dated Aug 11, 2015)

Repeat alectinib-repaglinide drug-drug interaction (DDI) physiological-based pharmacokinetic (PBPK) simulations using final integrated alectinib-M4 model. Presentation of the final integrated model can be organized in a step-wise manner.

Model development in healthy subjects

Develop alectinib and M4 models using in vitro metabolism data, in-silico data (e.g., Kp from Gastroplus modeling), and results from human mass-balance study (including oral and intravenous data). Assumptions on fm,CYP3A for alectinib can be based on hepatocyte data, mass balance data, and differential absolute bioavailability data (capsule vs suspension). Clarify if assumptions on fm,CYP3A for M4 can be made based on in vitro data.

Conduct multiple dose simulations in patients using the NSCLC populations to justify the need to (1) adjust intrinsic clearance values in patients (or: Can pharmacokinetic (PK) differences be represented by simulations using the same drug model in healthy subjects and NSCLC patients?) and (2) consider time-dependent inhibition (TDI) and/or induction of CYP3A in the integrated model. At this stage, a model with no CYP3A interaction mechanisms by alectinib and M4 and a model with concurring TDI and induction potential are expected to predict similar PK profiles of alectinib and M4.

Verify and confirm the model regarding assumptions on fm,CYP3A of alectinib, fm,CYP3A of M4 and autoinhibition and/or induction of CYP3A.

Prospectively simulate the effects of posaconazole and rifampin. Modify rifampin model using the strategy for posaconazole model and refer to Xu et al (Drug Metabo Dispo, 39:1139-48; 2011).

Prospectively simulate the effect of alectinib/M4 on midazolam in NSCLC patients.

Submit model files and excel output files being used to generate final results of above simulations. Software specific files (.cmp, .lbr, and .wks) should be executable by FDA reviewer using SimCYP software (version 13, release 2).

*6.3. Appendix Tables and Figures*

**Appendix Table 1. Physico-chemical parameters of alectinib and M4 used in SimCYP (V13.1) (extracted from excel output submitted together with reference [3])**

| | **Alectinib** | **M4** | **Notes** |
|---|---|---|---|
| Molecular Weight (g/mol) | 482.6 | 456.6 | |
| log P | 1.96 | 1.96 | Alectinib: initial reported value 3.60; modified to 1.96 based on sensitivity analysis to match $V_{d,ss}$ |
| Compound type | Monoprotic Base | Monoprotic Base | |
| pKa | 7.05 | 7.35 | |

**Appendix Table 2. Input parameters of alectinib using SimCYP (V13.1). Each alectinib model was integrated with respective M4 model (extracted from excel output submitted together with reference [3])**

| Parameter name (units) | Parameter values | | | | | | | | | | Source |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model verification and update | | | | | | | | Model application | | |
| Model number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| B/P ratio | 2.64 | | | | | | | | | | In vitro study 1054086 (Table 1, [1]) |
| Unbound fraction in plasma $f_{u\,p}$ | 0.003 | | | | | | | | | | In vitro study 1054086 (Table 1, [1]) |
| 1st order absorption | | | | | | | | | | | |
| fa | 0.216 | | | | | | | 0.319[b] | 0.216 | | Fitted to PK in healthy subjects, study NP29042 (Table 14, [1]) |
| ka (1/h) | 0.163 | | | | 0.79[a] | | | 0.497[b] | 0.163 | | Fitted to study NP28673 (Table 14, [1]) |
| lag time (h) | 0.000 | | | | 3.18[a] | | | 3.81[b] | 0.00 | | |
| apparent unbound fraction in enterocytes $F_{u\,gut}$ | 0.010 | | | | | | | | | | Optimized according to Cmax after oral dosing. Predicted Qgut of 8.49 L/h (Table 14, [1]) |
| Full PBPK distribution [13] | | | | | | | | | | | |
| Elimination | | | | | | | | | | | |
| $CL_{int,\,CYP3A4}$ (µL/min/pmol) | 9.98 | | | 6.99[c] | 9.98 | | | | 6.99[c] | 9.98 | Retrograde analysis based on CYP portioning in human hepatocytes and in vivo study NP28989 (mass balance study with intravenous tracer dose and oral dose). $f_{m,CYP3A}$ =0.4. 40-50% from hepatocyte study with specific inhibitors [1]. The pathway forms M4 in integrated model $f_{m,CYP2J2}$ =0.1. Assumed non-CYP3A pathway that forms M4 in integrated model (See **Appendix Table 3** below) |
| $CL_{int,\,CYP2J2}$ (µL/min/pmol) | 285 | | | 199[c] | 285 | | | | 199[c] | 285 | |
| Unspecified HLM $CL_{int}$ | 1710 | | | 1196[c] | 1710 | | | | 1196[c] | 1710 | |
| $CL_r$ (L/h) | 0.000 | | | | | | | | | | Human mass-balance study |
| Interactions | | | | | | | | | | | |
| CYP2C8 $K_i$ (µM) | N/A[d] | | | | | | | | 0.147 | | In vitro unbound Ki. |
| CYP3A4 $K_I$ (µM) | 8.29 | | N/A[d] | 8.29 | 8.29 | N/A[d] | | 8.29 | | | In vitro unbound value for $K_I$, Table 15 of reference [1] |
| CYP3A4 $K_{inact}$ (1/h) | 3.74 | | N/A[d] | 3.74 | 1.87 | N/A[d] | | 3.74 | | | |
| CYP3A4 Ind Slope (1/µM) | 3.52 | | N/A[d] | 3.52 | 3.52 | N/A[d] | | 3.52 | | | At 0.38 µM unbound concentration alectinib caused 16.5% maximal induction generated by rifampicin (positive control) in hepatocytes. IndMax of rifampin in SimCYP was 8-fold. A slope was calculated as 8*0.165/0.38 = 3.47/µM (not 3.52 /µM) |
| Drug model name (software ".cmpx" file) | RO5424802_logP1.96 | RO5424802_logP1.96 | RO5424802_logP1.96 | RO5424802_logP1.96 | RO5424802_LogP1.96 | RO5424802_LogP1.96 | RO5424802_LogP1.96 | RO5424802_LogP1.96 | NP28673_Ka_30PlowCL | Integrated_PBPK_MD_TDI_Ind_NSCLC | |

[a.] Fitted to the NP29042 study data (Source, appendix 4, Table 1 [1]); [b.] Gastroplus™ prediction [2] for the dose of 300 mg. [c.] Adjusted for steady state clearance in NSCLC patients; [d.] NA, not applicable.

**Appendix Table 3. Input parameters of M4 using SimCYP (V13.1). Each M4 model was integrated with respective alectinib model (extracted from excel output submitted together with reference [3])**

| Parameter name (units) | Parameter values | | | | | | | | | | Source |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Model number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| B/P | 2.52 | | | | | | | | | | |
| fup | 0.006 | | | | | | | | | | |
| Absorption fu(Gut) | 0.01 | | | | 1.00 | | | 0.01 | | | Not applicable. Fu,gut assumed to be the same as parent (Appendix Table 2). Formation of M4 was via CYP3A4 and CYP2J2 (See Appendix Table 2). |
| Input Vd,ss (L/kg) | 2.28 | | | | 2.28 | | | 2.28 | | | Fitted to clinical data from control arm of posaconazole study, where alectinib was dosed 300 mg |
| Elimination | | | | | | | | | | | Apparent CL was fitted to clinical data from control arm of posaconazole study, where alectinib was dosed 300 mg |
| $CL_{int,CYP3A4}$ (µL/min/pmol) | 1.71 | | | 1.198[a] | 1.712 | | | | 1.198[a] | 1.710 | Informed from posaconazole DDI study, with fm,CYP3A=0.15. Retrograde analysis based on apparent CL |
| Additional HLM $CL_{int}$ | 1330 | | | 930[a] | 1329 | | | | 930[a] | 1330 | Retrograde analysis based on apparent CL |
| $CL_R$ (L/h) | 0.000 | | | | | | | | | | Assumed. |
| Interaction | | | | | | | | | | | |
| CYP3A4 $K_I$ (µM) | 7.01 | | N/A[b] | 7.01 | | N/A[b] | N/A[b] | 7.01 | | | In vitro unbound value for $K_I$. Table 15 of reference [1] |
| CYP3A4 $k_{inact}$ (1/h) | 3.72 | | N/A[b] | 3.72 | | N/A[b] | N/A[b] | 3.72 | | | |
| CYP3A Ind Slope (1/µM) | 17.6 | | N/A[b] | 17.6 | | N/A[b] | N/A[b] | 17.6 | | | Same approach as alectinib (Appendix Table 2). M4 in incubation is about 20%. Unbound concentration = 0.2*0.38 µM. |

[a.] Adjusted for steady state clearance in NSCLC patients; [b.] NA, not applicable.

**Appendix Table 4. Summary of interaction parameters used in rifampicin PBPK models using SimCYP (V13.1) (extracted from excel output submitted together with reference [3])**

| Rifampin model comparison for CYP3A induction | Default | Default updated according to [9] | Default updated according to induction parameters in V14 |
|---|---|---|---|
| $K_i$ (µM) | 11 | 19 | 11 |
| $I_{nd\ max}$ | 8 | 13 | 16 |
| Inducer concentration causing half $I_{nd,max}$ (µM) | 0.3 | 0.5 | 0.3 |
| Unbound fraction in incubation | 1.0 | 0.4 | 1.0 |
| Hill coefficient | 1.0 | 1.2 | 1.0 |

**Appendix Table 5. Summary of parameters for posaconazole PBPK model in SimCYP (V13.1) (extracted from excel output submitted together with reference [3], notes from Appendix 3 in [1])**

| Parameter (unit) | Value | Notes |
|---|---|---|
| Model name | MG_Posaconazole_SS | Compartmental model based on literature reported PK parameters to derive absorption, distribution, and elimination parameters |
| Molecular Weight (g/mol) | 700.790 | |
| log P | 4.000 | |
| Compound Type | Diprotic Base | |
| pKa 1, pKa 2 | 2.880, 4.110 | |
| B/P | 0.620 | |
| fu | 0.010 | |
| Absorption Model | 1st order | |
| fa | 0.850 | Single dose 0.5, multiple dose 0.85 to account for decreased CL/F after multiple dosing |
| ka (1/h) | 0.550 | |
| lag time (h) | 0.800 | |
| fu(Gut) | 1.000 | |
| Q(Gut) Input | Predicted from polar surface area of 50.000(Å²) | |
| Distribution Model | Minimal PBPK Model, $V_{d,ss}$ of 2.960 L/kg | |
| Intravenous CL (L/h) | 7.320 | |
| $CL_r$ (L/h) | 0.000 | |
| CYP3A4 and CYP3A5 $K_i$ (µM) | 0.005 | Lowest value in vitro (range from 0.005-0.013 mm) selected based on simulation of reported outcomes of posaconazole-midazolam DDI studies (Table 4, Appendix 3, [1]) |

*References*


1. Roche. Report NO. 1064597. ClearyY, Gertz M, Parrott, N. Alectinib (RO5424802) - Physiologically based pharmacokinetic modeling using SimCYP®, June 2015
2. Roche, Report NO. 1064595. Parrott N. Alectinib (RO5424802) - Physiologically based pharmacokinetic modeling using GastroPlus™
3. Genentech. RESPONSES FDA Request for Information dated 11 August 2015 (Received via email from Gina M. Davis, M.T.). 21 August 2015
4. Genentech. Draft product insert.
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/s/

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STACY S SHORD
11/05/2015

JINGYU YU
11/05/2015

YANING WANG
11/05/2015

PING ZHAO
11/05/2015

VIKRAM P SINHA
11/06/2015

HONG ZHAO
11/06/2015
I concur.

NAM ATIQUR RAHMAN
11/06/2015
I concur with the recommendation of the review team.

# CLINICAL PHARMACOLOGY FILING FORM

## Application Information

| | | | |
|---|---|---|---|
| **NDA/BLA Number** | 208434 | **SDN** | 003 |
| **Applicant** | Roche | **Submission Date** | 6 Jul 2015 |
| **Generic Name** | Alectinib | **Brand Name** | Alecensa |
| **Drug Class** | Tyrosine Kinase Inhibitor | | |
| **Indication** | Anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib | | |
| **Dosage Regimen** | 600 mg orally twice daily with food | | |
| **Dosage Form** | 150-mg capsules | **Route of Administration** | Oral |
| **OCP Division** | DCP V | **OND Division** | DOP 2 |

| **OCP Review Team** | **Primary Reviewer(s)** | **Secondary Reviewer/ Team Leader** |
|---|---|---|
| **Division** | Stacy S Shord | Hong Zhao |
| **Pharmacometrics** | Jingyu Yu<br>Ping Zhao | Yaning Wang |
| **Genomics** | Stacy S Shord | Rosane Charlab Orbach |
| **Review Classification** | ☐ Standard ☐ Priority ☑ Expedited | |
| **Filing Date** | 9/4/2015 | **74-Day Letter Date** 9/18/2015 |
| **Review Due Date** | 11/6/2015 | **PDUFA Goal Date** 3/2/2016 |

## Application Fileability

**Is the Clinical Pharmacology section of the application fileable?**

☑ Yes

☐ No

If no list reason(s)

**Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?**

☑ Yes

☐ No

If yes list comment(s)

- You should resubmit all files submitted along with the population pharmacokinetic and exposure-response study report with a ".txt" extension, as the files with this extension appear damaged and not readable.

- We have conducted initial review of your PBPK report that predicts the effect of alectinib on CYP2C8 substrate repaglinide. You should repeat alectinib-repaglinide DDI simulations using final integrated alectinib-M4 model. Presentation of the final integrated model can be organized in a step-wise manner:
    1. Model development in healthy subjects:
        1a. Develop alectinib and M4 models using in vitro metabolism data, in-silico data (e.g., $K_p$ from Gastroplus modeling) and results from human mass-balance study (including oral and intravenous data). Assumptions on fm,CYP3A for alectinib can be based on hepatocyte data, mass balance data, and differential absolute bioavailability data (capsule vs suspension). Clarify if assumptions on fm,CYP3A for M4 can be made based on in vitro data.
        1b. Conduct multiple dose simulations in patients using your NSCLC population to justify the need to (1) adjust intrinsic clearance values in patients (or: can PK differences be represented by

simulations using the same drug model in healthy subjects and NSCLC patients?) and (2) consider time-dependent inhibition and/or induction of CYP3A in the integrated model. At this stage, a model with no CYP3A interaction mechanisms by alectinib and M4 and a model with concurring TDI and induction potential are expected to predict similar PK profiles of alectinib and M4.

2. Verify and confirm the model regarding assumptions on fm,CYP3A of alectinib and M4, and autoinhibition and/or induction of CYP3A.
   2a. Prospectively simulate the effects of posaconazole and rifampin. Modify rifampin model using the strategy for posaconazole model and refer to Xu et al (Drug Metabo Dispo, 39:1139-48; 2011).
   2b. Prospectively simulate the effect of alectinib/M4 on midazolam in NSCLC patients.

Submit model files and excel output files being used to generate final results of above simulations. Software specific files (.cmp, .lbr, and .wks) should be executable by FDA reviewer using SimCYP software (version 13, release 2).

**Is there a need for clinical trial(s) inspection?**

☐ Yes

☑ No

If yes explain

## Clinical Pharmacology Package

| | | | |
|---|---|---|---|
| Tabular Listing of All Human Studies | ☑ Yes ☐ No | Clinical Pharmacology Summary | ☑ Yes ☐ No |
| Bioanalytical and Analytical Methods | ☑ Yes ☐ No | Labeling | ☑ Yes ☐ No |

**Clinical Pharmacology Studies**

| Study Type | | Count | Comment(s) |
|---|---|---|---|
| **In Vitro Studies** | | | |
| ☑ Metabolism Characterization | | 7 | 1054088, 1054089, 1056249, 1056535, 1062030, 1062527, 1063389 |
| ☑ Transporter Characterization | | 3 | 1056252, 1056253, 1063003 |
| ☑ Distribution | | 3 | 1054086, 1056250, 1057255 |
| ☑ Drug-Drug Interaction | | 9 | 1054091, 1054093, 1056251, 1056252, 1056253, 1057256, 1059473, 1059474, 1059475, 1059476, 1061915 |
| **In Vivo Studies** | | | |
| **Biopharmaceutics** | | | |
| ☑ Absolute Bioavailability | | 1 | NP28989 |
| ☐ Relative Bioavailability | | | |
| ☑ Bioequivalence | | 2 | NP29040, 1064595 (PBPK) |
| ☑ Food Effect | | 1 | NP28991, NP29040, 1064595 (PBPK), AF001JP |
| ☐ Other | | | |
| **Human Pharmacokinetics** | | | |
| Healthy Subjects | ☐ Single Dose | | |
| | ☐ Multiple Dose | | |
| Patients | ☑ Single Dose | 3 | NP28671, NP28673, AF001JP |
| | ☑ Multiple Dose | | NP28671, NP28673, AF001JP |
| ☑ Mass Balance Study | | | NP28989 |

| | | |
|---|---|---|
| ☐ Other (e.g. dose proportionality) | | |
| **Intrinsic Factors** | | |
| ☑ Race | | Population PK, NP28673 |
| ☑ Sex | | Population PK |
| ☑ Geriatrics | | Population PK |
| ☐ Pediatrics | | |
| ☑ Hepatic Impairment | | Population PK |
| ☑ Renal Impairment | | Population PK |
| ☐ Genetics | | |
| **Extrinsic Factors** | | |
| ☑ Effects on Primary Drug | 2 | NP28990, NP29042, NP28991 |
| ☑ Effects of Primary Drug | 1 | NP28991, 1064597 (PBPK), NP28673 |
| **Pharmacodynamics** | | |
| ☐ Healthy Subjects | | |
| ☐ Patients | | |
| **Pharmacokinetics/Pharmacodynamics** | | |
| ☐ Healthy Subjects | | |
| ☐ Patients | | |
| ☑ QT | 1 | 1060441 |
| **Pharmacometrics** | | |
| ☑ Population Pharmacokinetics | 1 | 1064536 |
| ☑ Exposure-Efficacy | | 1064536 |
| ☑ Exposure-Safety | | 1064536 |

| | | | | |
|---|---|---|---|---|
| **Total Number of Studies** | **In Vitro** | 22 | **In Vivo** | 12 |
| **Total Number of Studies to be Reviewed** | | 22 | | 12 |

| **Criteria for Refusal to File (RTF)** | | |
|---|---|---|
| **RTF Parameter** | **Assessment** | **Comments** |
| **1.** Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | ☐Yes ☐No ☑N/A | The 150-mg commercial capsule was given in Studies NP28763 and NP28761. The original 20-mg and 40-mg capsules were used in Studies AF-001JP and portions of NP28761. |
| **2.** Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information) | ☑Yes ☐No ☐N/A | |
| **3.** Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request? | ☑Yes ☐No ☐N/A | |
| **4.** Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application? | ☐Yes ☐No ☑N/A | |
| **5.** Did the applicant submit data to allow the evaluation of the validity of the analytical assay | ☑Yes ☐No ☐N/A | |

| | | |
|---|---|---|
| for the moieties of interest? | | |
| **6.** Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment? | ☑Yes ☐No ☐N/A | |
| **7.** Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)? | ☑Yes ☐No ☐N/A | The text files appear damaged. See information request above. |
| **8.** Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)? | ☑Yes ☐No ☐N/A | |
| **9.** Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices? | ☑Yes ☐No ☐N/A | |
| **Complete Application**<br>**10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission? | ☑Yes ☐No ☐N/A | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist** | | |
| **Data** | | |
| **1.** Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | ☑Yes ☐No ☐N/A | |
| **2.** If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | ☐Yes ☐No ☑N/A | |
| **Studies and Analysis** | | |
| **3.** Is the appropriate pharmacokinetic information submitted? | ☑Yes ☐No ☐N/A | |
| **4.** Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | ☑Yes ☐No ☐N/A | |
| **5.** Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | ☑Yes ☐No ☐N/A | |
| **6.** Is there an adequate attempt by the applicant to | ☑Yes ☐No ☐N/A | |

| | | |
|---|---|---|
| use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | |
| **7.** Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | ☐Yes ☐No ☑N/A | |
| **General** | | |
| **8.** Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | ☑Yes ☐No ☐N/A | |
| **9.** Was the translation (of study reports or other study information) from another language needed and provided in this submission? | ☐Yes ☐No ☑N/A | |

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/s/

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STACY S SHORD
08/07/2015

HONG ZHAO
08/07/2015
I concur.