# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208434Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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|---|---|
| **NDA#:** | 208,434 |
| **Drug Name:** | Alecensa® (alectinib) |
| **Indication(s):** | ALK+ locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib |
| **Applicant:** | F. Hoffmann-La Roche, Ltd. |
| **Date(s):** | Submission: 7/6/2015<br>PDUFA: 11/6/2015 |
| **Review Priority:** | Priority |
| **Biometrics Division:** | Division of Biometrics V |
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**Keywords:** ORR, 95% CI

## Table of Contents

# LIST OF TABLES

# 1 EXECUTIVE SUMMARY

In this original New Drug Application (NDA), the applicant is seeking an approval of Alecensa® (Alectinib) for 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. This submission was supported two open-label, single-arm, multicenter phase I/II trials (NP28761/AF-002JG) and NP28673.

Trial NP28761 was an open-label, multicenter phase I/II trial in ALK-positive NSCLC patients who progressed on prior crizotinib therapy, with or without prior chemotherapy. Trial NP28673 was an open-label, multicenter phase I/II trial of alectinib in patients with locally advanced NSCLC not amenable to curative therapy (AJCC Stage IIIB) or metastatic NSCLC, with documented ALK rearrangement based on an FDA-approved test, and disease progression following prior crizotinib.

Both trials used patients in activity-estimating part (NP28761: N=87; NP28673: N=138) to evaluate the efficacy of alectinib (600 mg BID). The primary efficacy endpoint was objective response rate (ORR) per central review (IRC) according to the RECIST 1.1. The secondary endpoints included duration of response (DoR), central never system (CNS) ORR (CORR) and CNS DoR (CDoR). In the Trial NP28673, the other co-primary efficacy endpoint was ORR in patients who had received prior chemotherapy (ORR-PC).

Trial NP28673 had ORR of 44% (95% confidence interval [CI]: 36%, 53%), consisting of 61 (44%) partial responses (PR). This trial had ORR-PC of 39% (95% CI: 30%, 49%). The CORR with baseline measurable lesions was 57% (95% CI: 39%, 74%).

Trial NP28761 had ORR of 38% (95% CI: 28%, 49%). The CORR with baseline measurable lesions was 69% (95% CI: 41%, 89%). Fifty one CNS patients with baseline measurable lesion in Trials NP28761 and NP28673 had ORR of 61% (95% CI: 46%, 74%), consisting of 9 (18%) complete responses (CR) and 22 (43%) PRs.

There are two issues. First, the clinical study reports (CSRs) use response evaluable set, a subset of protocol pre-specified primary analysis set, as treated population, for both trials. Second, the CSR reports and U.S. Package Insert (USPI) for Trial NP28673 use different clinical data cut-off dates.

Whether the data and analyses from the current submission in the NSCLC patients demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

# 2 INTRODUCTION

In this New Drug Application (NDA), the applicant is seeking an approval of Alecensa® (Alectinib, AF-802, CH5424802 or RO5424802) 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. This submission was primarily supported by results from two open-label, single-arm, multicenter phase I/II trials (NP28761/AF-002JG [hereafter called "NP28761"] and NP28673) under Investigational New Drug (IND) 111,723.

## 2.1 Overview

### 2.1.1 Class and Indication

As stated by the applicant, NSCLC is the leading cause of cancer-related mortality worldwide and represents a major health problem. Treatment options after failure of crizotinib are limited and mostly include cytotoxic chemotherapy, palliative radiotherapy, or supportive care. Sub-optimal control of central nervous system (CNS) metastases remains a concern with available ALK inhibitors. Significant morbidity is associated with brain metastases as a function of brain involvement. The presence of CNS metastases had also been shown to result in poor prognosis and shorter survival in patients with NSCLC. Therefore there is an unmet medical need for ALK-positive NSCLC patients who have progressed on or were intolerant to crizotinib treatment and the availability of effective new therapies with a manageable and well tolerated safety profile, as well as proven CNS activity.

According to the applicant's report, alectinib is a highly selective and potent ALK and rearranged during transmission tyrosine kinase inhibitor and is being developed for use in the treatment of patients with ALK-positive NSCLC. Alectinib inhibits ALK tyrosine kinase and blocks downstream signaling pathways, such as STAT3, PI3K/AKT and MAPK. Alectinib was approved in Japan for in patients with ALK-positive unresectable, recurrent or advanced NSCLC (approval date 04 July 2014). The approved dose is 300 mg twice daily (BID).

In the current NDA submission, the proposed indication is for the treatment of patients for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib.

### 2.1.2 Regulatory History

The following list summarizes the key statistical related regulatory history for trials NP28761 and NP28763:

- July 22, 2013: Type B End-of-Phase I Meeting held to seek the Agency's feedback and agreement on proposed development plans for alectinib.
    - FDA agreed on an overall response rate (ORR) of 50% with the 95% lower bound of confidence interval (CI) of 35%, based on the ongoing Trials NP28673 and NP28761, to support registry filing of alectinib.

    - FDA encouraged Roche to discuss the clinical development plan [redacted] (b) (4)
- November 14, 2013: Type B Meeting held to discuss the clinical design of Trials NP8761, NP28763, and BO28984 for alectinib in patients with and without preexisting CNS metastases.
    - FDA agreed that these trials [redacted] (b) (4) CNS assessments were conducted more frequently (i.e., at least every 8 weeks) and that consistent use of a uniform image acquisition technique for evaluation of CNS disease with either CT or MRI scans were performed.
    - Roche acknowledged that time to CNS progression data in a single-arm trial was not interpretable.
    - Roche agreed to provide Independent review committee (IRC) determined CNS ORR (CORR) and CNS durations of response (CDoR) using both Response Evaluation Criteria in Solid Tumors (RECIST) and RANO criteria.
- September 30, 2014: FDA sent comments on the Type B Content and Format Pre-NDA Meeting which proposed the clinical and clinical pharmacology content and format of the NDA for alectinib.
    - FDA agreed on statistical analysis plans (SAP) for Trials NP28761 and NP28673 that the primary analysis would test the null hypothesis of ORR=35%.
    - FDA agreed on the proposed clinical data package including data cut-off dates for Trial NP28761 (data cutoff October 31, 2014, 85 patients in dose expansion cohort) and Trial NP28673 (data cutoff August 18, 2014, 138 patients in dose expansion cohort).
- April 7, 2015: Type B Clinical Pre-NDA meeting held on April 7, 2015 to discuss the results from the pivotal Phase I/II Trials NP28761 and NP28673 and any issues regarding the presentation of the clinical data to support the NDA for alectinib.
    - FDA stated that the secondary endpoint of disease control rate (DCR) was unlikely to be included in product labeling. DCR was not a measure of clinical benefit as the treatment effect could not be discerned in a single arm trial as compared to the natural history of CNS metastases in ALK-positive NSCLC.
    - FDA stated that it was unclear how DCR leads to patient benefit, in contrast to partial responses (PR) or complete responses (CR) where reduction in tumor size may be linked to a reduction in tumor-related symptoms.
    - FDA agreed that use of the new data cut-off date of January 8, 2015, for efficacy results from Trial NP28673, was acceptable. Roche stated that this would provide an additional four months of follow-up for these efficacy results.
- July 6, 2015: Rolling NDA submission was completed.

### 2.1.3 Trial Reviewed

Trial NP28761 was an ongoing two-part (dose-finding and activity-estimating), open-label, multicenter phase I/II trial of alectinib (600 mg BID fed or fast, 21 day per cycle) in ALK-positive NSCLC patients who progressed on prior crizotinib therapy, with or without prior chemotherapy. This trial was conducted at 27 centers within North America (26 sites in US and 1 in Canada) from May 3, 2012. The clinical data cutoff for the primary efficacy analysis was

October 24, 2014. The planned primary endpoint was ORR in the activity-estimating chohort (N=87) based on RECIST 1.1 per IRC assessment. The secondary endpoints included DoR, CORR, and CDoR.

Trial NP28673 was an ongoing three-part (dose-finding, activity-estimating, and access), open-label, multicenter phase I/II trial of alectinib (600 mg BID oral fed, 28 day per cycle) in patients with locally advanced NSCLC not amenable to curative therapy (AJCC Stage IIIB) or metastatic NSCLC, with documented ALK rearrangement based on an FDA-approved test, and disease progression based on RECIST 1.1 following prior crizotinib. Patients were also permitted but not required to have progressed following prior chemotherapy. This trial was conducted at 56 centers (10 U.S. sites) in 16 counties from June 20, 2013. The primary analysis population included patients in the activity-estimating cohort (n=138). The co-primary endpoints were ORR based on RECIST 1.1 as assessed by the IRC and ORR in the subset of patients with prior chemotherapy (ORR-PC). The secondary endpoints included CORR, DoR, and CDoR. In the CSR, the efficacy results were based on the clinical data cutoff date August 18, 2014. The U.S. Package Insert (USPI) efficacy results were based on new clinical data cut-off date, January 8, 2015.

### 2.2 Data Sources

The electronic submission including protocols, SAP, clinical study reports (CSR), and analysis datasets for this NDA submission are located on the network with network path: \\cdsesub1\evsprod\NDA208434\0001 and \\cdsesub1\evsprod\nda208434**0002**\m5 for trials NP28761 and NP28673 respectively.

## 3 STATISTICAL EVALUATION

Part of the text presented in this section is adapted from the applicant's CSR.

### 3.1 Data and Analysis Quality

The data and analysis quality were acceptable. This reviewer was able to duplicate the analysis variable derivation and summary statistics.

### 3.2 Evaluation of Efficacy in Trial NP28761 in the Part II

#### 3.2.1 Objective

The primary efficacy endpoint of the trial NP28761 was to access the efficacy of ORR per IRC assessment, according to RECIST 1.1. The key secondary efficacy objectives included CORR, DoR, and CDoR.

#### 3.2.2 Trial Design

Trial NP28761 was designed to evaluate the efficacy of alectinib in 85 patients ALK-positive NSCLC who have failed crizotinib. Patients received the recommended Phase II dose (RP2D) alectinib 600 mg BID (150 mg capsules) BID determined from the Phase I portion on Days 1 to

21 of each cycle. Patients continued treatment until progressive disease (PD), intolerable toxicity, withdrawal of consent, or death.

Tumor assessment was assessed every 6 weeks at the first 6 cycles and every 3 cycles thereafter until PD. Only IRC review was used for the analysis of the primary efficacy endpoint. The results of the investigator's review of radiographs were used to determine whether or not patients could be enrolled and remain on trial. All decisions during the trial were based on local investigator reads.

A separate IRC performed CNS assessments using CNS CT/MRI scans according to both RECIST v1.1 and RANO criteria (IRC CNS RECIST and IRC CNS RANO, respectively). The IRC CNS RECIST and IRC CNS RANO assessments were completely independent from the IRC systemic RECIST assessments, and from each other, being performed separately by neurological specialized readers according to pre-specified CNS RECIST and CNS RANO charters

The major inclusion criteria included patients:

- Age 18 years or older.
- WHO performance status $\leqslant 2$
- Patients with locally advanced (AJCC Stage IIIB) not amenable to curative therapy or metastatic (AJCC Stage IV) NSCLC
- Histologically-confirmed NSCLC that had progressed on crizotinib treatment. Patients needed to have a minimum 1-week washout period between the last dose of crizotinib and the first dose of alectinib
- ALK-rearrangement confirmed by a FDA-approved Test
- Measurable disease defined by RECIST 1.1 per INV assessment

### 3.2.3 Efficacy Measures

**ORR** was defined as the proportion of patients achieving a confirmed best overall response of CR or PR, per IRC based on RECIST 1.1.

**DoR** was defined for responders (CR or PR) per IRC based on RECIST 1.1, and was calculated from the date of the first documentation of response (CR, or PR) to the date of first documentation PD or death due from any cause, whichever occurs first.

**CORR** was defined as the ORR in measurable CNS lesions in patients who have measurable disease in the CNS at baseline.

**CDOR** was defined as the time from the first observation of a CNS response until first observation of CNS PD or death from any cause, whichever occurs first.

### 3.2.4 Analysis Sets

**As-Treated population** (AT) was defined as all enrolled patients who received any dose of trial treatment. The AT was the primary analysis population for the efficacy analyses.

**Response Evaluable Population** (RE) was defined as patients with measurable disease at baseline who had a baseline tumor assessment and received trial treatment. This population would be used to analyze the primary endpoint of ORR as well as other response endpoints (DCR, duration of response).

*Reviewer's Comments:*

1. *The results of the investigator's review of radiographs were used to determine whether or not patients had measurable disease at baseline to determine whether or not patients could be enrolled and remain on trial. Due to discordance between IRC and INV determined measurable disease at baseline, the applicant defined RE as patients with measurable disease per IRC at baseline in the CSR. The refined RE population was used as the primary analysis set in CSR. The applicant only provided efficacy outcomes based RE population in the CSR, which was inconsistent with protocol pre-specified primary analysis population.*
2. *The primary analysis of ORR should be performed in the AT.*
3. *This reviewer focuses on the evaluation of efficacy results in the AT.*

### 3.2.5 Sample Size Considerations

A sample size of 85 has been chosen such that the lower limit of the 2-sided 95% CI (using Clopper-Pearson method) around the point estimate of the ORR will allow identifying a clinically relevant response in order to reject the null hypothesis that ORR=35%. With 85 patients, an observed response rate of 46% (39/85 responses) would have a lower limit of the two-sided 95% confidence interval of 35% which was considered to be clinically relevant and the null hypothesis would be rejected at the at a two-sided 5% significance level.

*Reviewer's Comments:*

1. *Without control arm, statistical inference cannot be drawn from this trial.*
2. *The sample size consideration was amended for hypothesis assumption and threshold to claim clinically relevant response on Protocol V5 dated on March 8, 2013. The original null hypothesis of the best ORR for alectinib was 50% in the protocol V1.*
3. *On July 22, 2013, FDA agreed on an ORR of 50% with the 95% lower bound of CI of 35%.*
4. *On September 30, 2014, FDA agreed on SAP for Trials NP28761 and NP28673 that the primary analysis would test the null hypothesis of ORR=35%.*

### 3.2.6 Interim Analysis

A non-binding interim futility analysis on ORR according to RECIST 1.1 per local investigator assessments in the AT was planned when the first 30 patients were enrolled. An 80% CI around 9/30 = 30% response rate would have an upper bound of 42%. If the ORR is not above or equal to 30%, then the trial would be considered futile and would be terminated.

*Reviewer's Comments:*

5. *The futility consideration was amended from Simon's Two Stage Design method on Protocol V5 dated on March 8, 2013. This reviewer did not find any discussion on this futility amendment in DARRTS.*

### 3.2.7 Statistical Methodologies

**Efficacy Analysis Method for ORR**

The point estimate of ORR and its 95% CI would be estimated by Clopper-Pearson method. If the lower bounds of the associated 95% CIs of ORR exceed 35%, then it would be considered clinical relevance. The primary analysis was planned to take place once all 85 patients from the Part II have been followed for a minimum of 12 weeks such that any observed response at Week 6 could be confirmed.

**Efficacy Analysis Method for CORR**

The analysis method for CORR was identical to ORR analysis.

**Efficacy Analysis Method for Time to Event Endpoints**

The DoR and CDoR would be estimated by the Kaplan-Meier method.

### 3.2.8 FDA Statistical Reviewer's Findings / Comments

In the CSR, the applicant provides efficacy results based on RE population per IRC assessment, which was inconsistent with protocol pre-defined primary trial population (AT). Due to the discordance between efficacy results based on different primary analysis sets, the review team sent multiple Information Requests (IRs) and held Teleconference (T-Con) with the applicant to get efficacy results based on the AT. In this review, all the efficacy results for Trial NP28761 were calculated by this reviewer based on the AT population.

#### 3.2.8.1 Patient Population and Disposition

A total of 87 patients were enrolled in the activity estimating part. Table 1 presents the trial populations and the primary reason for treatment discontinuation.

**Table 1 Patient Population and Disposition**

| | NP28761 (N=87) |
|---|---|
| AT | 87 (100%) |
| RE per IRC | 69 (79%) |
| Ongoing | 56 (64%) |
| Median follow up in month (Range) | 4.8 (1.1-13.7) |
| Median Treatment in month (Range) | 4.5 (0.7, 13.7) |
| CNS per IRC | 52 (60%) |
| Measurable lesion | 16 (18%) |
| Discontinued | 31 (36%) |
| AE | 2 (2%) |
| Death | 3 (3%) |
| PD | 22 (25%) |
| Withdrawal | 2 (2%) |
| Other | 2 (2%) |

*Reviewer's Comments:*

6. *Per Applicant's primary analysis set, 18 (21%) treated patients were excluded from trial population.*
7. *PD was the primary reason for treatment discontinuation.*
8. *There were only 16 (18%) CNS patients with measurable lesion at baseline assessment*

### 3.2.8.2 Baseline Demographic Characteristics

Table 2 presents the patient baseline demographic characteristics.

**Table 2 Baseline Demographics Characteristics in AT Population**

| | NP28761 (N=87) |
|---|---|
| Age: Median (Range) | 54 (29-79) |
| > = 65 | 16 (18%) |
| Race: White | 73 (84%) |
| Asian | 7 (8%) |
| Other | 7 (8%) |
| Sex: Female | 48 (55%) |
| Region: North America | 87 (100%) |

### 3.2.8.3 Baseline Disease Characteristics

Table 3 presents the important baseline disease characteristics and prior treatments in the AT population.

**Table 3 Baseline Disease Characteristics and Prior Treatments in AT Population**

| | NP28761 (N=87) |
|---|---|
| ECOG: 0 | 30 (35%) |
| 1 | 48 (55%) |
| 2 | 9 (10%) |
| Smoker: Non-Smoker | 54 (62%) |
| Current Stage: IV | 86 (99%) |
| Histology: Adenocarcinoma | 82 (94%) |
| Adenosquamous | 1 (1%) |
| Large cell carcinoma | 1 (1%) |
| Prior Chemo, n(%) | 64 (74%) |
| Prior Surgery, n(%) | 59 (68%) |
| Prior Radiotherapy: Brain | 36 (41%) |
| Bone | 11 (13%) |
| Lung | 8 (9%) |
| Prior Crizotinib | 87 (100%) |
| Time on crizotinib, Med. (range) days | 366 (16, 1622) |
| Time since last dose, Med. (range) days | 15 (7, 733) |
| ORR on crizotinib | 29 (33%) |
| PD on crizotinib | 27 (31%) |

### 3.2.8.4 ORR Analysis

Table 4 presents the results of ORR per IRC assessment using RECIST for the AT population at the 12 weeks.

**Table 4 ORR Results per IRC Assessment in AT Population**

| | NP28761 (N=87) |
|---|---|
| ORR, n (%) | 33 (37.9%) |
| CR, n (%) | 0 |
| PR, n (%) | 33 (37.9%) |
| 95% CI* | (27.7%, 49.0%) |

*Per Clopper-Pearson Method

*Reviewer's Comments:*

4. *The ORR is 37.9% (95% CI: 27.7%, 49.0%). The lower bound of 95% CI does not exceed 35%, the pre-specified threshold per the trial design operating characteristics.*
5. *The ORR sensitivity analyses based on RE set (Per IRC assessment), INV assessment in the AT, and INV assessment in the RE were 47.8% (95% CI: 35.7%, 60.2%), 46.0% (95% CI: 35.2%, 57.0%), and 42.0% (95% CI: 30.2%, 54.5%), respectively.*

### 3.2.8.5 DoR Analysis

Table 5 presents the median and 95% CI for DoR based on responders at the 12-week. The median DoR was 7.5 months (4.9, NE).

**Table 5 DoR Results per IRC Assessment**

| | NP28761 (N=87) |
|---|---|
| DoR (month) | N=33 |
| PD, n (%) | 6 (18.2%) |
| Median (95% CI) | 7.5 (4.9, NE) |

NE: not estimated

### 3.2.8.6 CORR Analysis

Table 6 presents the results of CORR based on the central review per RECIST.

**Table 6 CORR Results per IRC using RECIST**

| | NP28761 | |
|---|---|---|
| | Measurable or Non-Measurable CNS | Measurable CNS |
| | N=52 | N=16 |
| CORR, n (%) | 20 (38.5%) | 11 (68.8%) |
| CR, n (%) | 11 (21.2%) | 2 (12.5%) |
| PR, n (%) | 9 (17.3%) | 9 (56.3%) |
| 95 CI | (25.3%, 53.0%) | (41.3%, 89.0%) |

Table 7 presents the results of CORR based on the central review per RANO.

**Table 7 CORR Results per IRC using RANO**

| | NP28761 | |
|---|---|---|
| | Measurable or Non-Measurable CNS | Measurable CNS |
| | N=52 | N=16 |
| CORR, n (%) | 5 (9.6%) | 4 (25.0%) |
| CR, n (%) | 0 | 0 |
| PR, n (%) | 5 (9.6%) | 4 (25.0%) |
| 95 CI | (3.2%, 21.0%) | (7.3%, 52.4%) |

*Reviewer's Comments:*

6. *The CORR with or without measurable lesion was 39% (95% CI: 28%, 49%).*
7. *The measurable CORR was 69% (95% CI: 41%, 89%). The lower bound of 95% CI exceeds 35%, the pre-specified threshold per the trial design operating characteristics.*
8. *This reviewer did not find any discussion on which CORR result (measurable vs. measurable/non- measurable) would be included the USPI in the meeting minutes or IND reviewers. This is deferred to the medical review team reviewing this application.*

### 3.2.8.7 CDoR Analysis

The median CDoR per RECIST was not estimable in both all responders (N=20, 2 patients had PD) or in responders with measurable disease (N=11, 1 patient had PD).

The median CDoR per RANO was not estimable in both all responders (N=5, 0 patients had PD) or in responders with measurable disease (N=4, 0 patient had PD).

## 3.3 Evaluation of Efficacy in Trial NP28673 in the Part II

### 3.3.1 Objective

The co-primary efficacy endpoints were to access the efficacy of ORR per RECIST 1.1 as assessed by IRC and ORR-PC. The key secondary efficacy objectives included CORR, DoR, and CDoR.

### 3.3.2 Trial Design

Trial NP28673 was designed to evaluate the efficacy of alectinib in 130 patients with locally advanced NSCLC not amenable to curative therapy (AJCC Stage IIIB) or metastatic NSCLC, with documented ALK rearrangement based on an FDA-approved test, and PD based on RECIST 1.1 following prior crizotinib. Patients received the recommended RP2D alectinib dose within 30 minutes after meals in the morning and evening on Days 1 to 28 of each cycle for 5 cycles. Patients continued treatment until PD, death, or withdrawal for any other reasons. Upon PD in Part 2, patients were offered to continue to receive alectinib in Part 3.

Tumor assessment was assessed every 8 weeks in the first year, every 12 weeks (3 cycles) in the secondary, and every 16 weeks (4 cycles) subsequently until PD. Only IRC review was used for the analysis of the primary efficacy endpoint. The results of the investigator's review of radiographs were used to determine whether or not patients could be enrolled and remain on trial. All decisions during the trial were based on local investigator reads.

A separate IRC performed CNS assessments using CNS CT/MRI scans according to both RECIST v1.1 and RANO criteria (IRC CNS RECIST and IRC CNS RANO, respectively). The IRC CNS RECIST and IRC CNS RANO assessments were completely independent from the IRC systemic RECIST assessments, and from each other, being performed separately by neurological specialized readers according to pre-specified CNS RECIST and CNS RANO charters

The major inclusion criteria included patients:

- Age 18 years or older.
- WHO performance status $\leqslant 2$
- Patients with locally advanced (AJCC Stage IIIB) not amenable to curative therapy or metastatic (AJCC Stage IV) NSCLC
- Histologically-confirmed NSCLC that had progressed on crizotinib treatment. Patients needed to have a minimum 1-week washout period between the last dose of crizotinib and the first dose of alectinib
- ALK-rearrangement based on a FDA-approved Test
- Measurable disease defined by RECIST 1.1 per INV assessment
- Adequate hematologic, hepatic and renal function

*Reviewer's Comments:*

9. *During the conduct of Part 1 for this trial, the RP2D (600 mg BID) was confirmed in Trial NP28761. Hence, this trial's Part 1 and Part 2 were combined as the activity estimating part for reporting purposes. FDA acknowledged applicant's proposal at the pre-NDA meeting.*

### 3.3.3 Efficacy Measures

**ORR** was defined as the proportion of patients achieving a confirmed best overall response of CR or PR, per IRC assessment based on RECIST 1.1.

**ORR-PC** was defined as the ORR in the subset of patients who have been treated with prior chemotherapy.

**DoR** was defined for responders (CR or PR), and was calculated from the date of the first documentation of response (CR, or PR) to the date of first documentation PD or death due to any cause, whichever occurs first.

**DoR-PC** was defined as the DoR in patients who have been treated with prior chemotherapy

**CORR** was defined as the ORR in patients who have measurable disease in the CNS at baseline.

**CDOR** was defined as the time from the first observation of a CNS response until first observation of CNS progression or death from any cause.

### 3.3.4 Analysis Sets

**AT population** was defined as all enrolled patients who received any dose of trial treatment. The AT was the primary analysis population for the efficacy analyses.

**RE Population** was defined as patients with measurable disease at baseline who had a baseline tumor assessment and received trial treatment. This population would be used to analyze the primary endpoint of ORR as well as other response endpoints.

*Reviewer's Comments:*

*10. The applicant only provided efficacy outcomes based RE population in the CSR.*

*11. This reviewer focuses on the evaluation of efficacy results in the AT. In response to FDA's information request, the applicant only provided ORR and CORR results in the AT population.*

### 3.3.5 Sample Size Considerations

Assuming a null hypothesis of the best ORR for alectinib was 35%, a sample size of 85 patients who have been treated with prior chemotherapy had been chosen such that the lower limit of the 2-sided 95% CI (using Clopper-Pearson method) around the point estimate of the ORR would allow identifying a clinically relevant response in order to reject the null hypothesis that ORR=35%. With 85 patients, an ORR of 46% (39/85 responses) would have a lower limit of the

two-sided 95% CI of 35% which was considered to be clinically relevant and the null hypothesis would be rejected at the at a two-sided 5% significance level.

A total of 130 patients would be enrolled, with a maximum of 45 chemo-naïve patients enrolled to ensure reaching the minimum number of 85 prior-chemotherapy patients. With 130 patients an observed rate of 44% (57/130 responses) would have a lower limit of the two-sided 95% confidence interval of 35.2% which was considered to be clinically relevant and the null hypothesis would be rejected.

*Reviewer's Comments:*

12. *Without control arm, statistical inference cannot be drawn from this trial.*
13. *The sample size consideration was amended for hypothesis assumption and threshold to claim clinically relevant response on Protocol V4 dated on Nov 19, 2013. The original null hypothesis of the best ORR for alectinib was 50% in the original protocol.*
14. *On July 22, 2013, FDA agreed on an overall response rate (ORR) of 50% with the 95% lower bound of CI of 35%.*
15. *On September 30, 2014, FDA agreed on statistical analysis plans (SAP) for Trials NP28761 and NP28673 that the primary analysis would test the null hypothesis of ORR=35%.*

### 3.3.6 Interim Analysis

A non-binding interim futility analysis on ORR according to RECIST 1.1 per local investigator assessments in the AT population was planned when the first 30 patients had a tumor assessment at 8 weeks post -treatment. If the non-binding futility analysis result shown that the response rate did not achieve 30%, then the trial might be terminated due to futility. Otherwise, enrollment would stop when approximately 130 ALK-positive NSCLC patients in total were enrolled into the trial.

*Reviewer's Comments:*

16. *The futility consideration was amended on Protocol V4 dated on Nov 19, 2013. A Simon two- stage study design was proposed for futility analysis at the original trial design. This reviewer did not find any discussion on this futility amendment in DARRTS.*

### 3.3.7 Statistical Methodologies

**Efficacy Analysis Method for ORR**

The point estimate of ORR and its 95% CI based on Clopper-Pearson would be provided. The primary analysis would take place once all 130 patients have been followed for a minimum of 16 weeks, i.e. two tumor assessments in order that any observed CR or PR can be confirmed, unless patients progressed or withdrew sooner. The end of the trial was defined as the date when the last patient, last visit occurs.

**Efficacy Analysis Method for ORR-PC**

The analysis method for ORR-PC was identical to ORR analysis.

**Efficacy Analysis Method for CORR**

The analysis method for CORR was identical to ORR analysis.

**Efficacy Analysis Method for Time to Event Endpoints**

The DoR and CDoR would be estimated by the Kaplan-Meier method.

### 3.3.8 FDA Statistical Reviewer's Findings / Comments

In the CSR, the applicant provides efficacy results based on the clinical data cutoff date August 18, 2014 on the RE population. The new FDA agreed clinical cut-off date was January 8, 2015 which provided an additional four months of follow-up for these efficacy results. Only brief summary based on the new clinical cut-off date was provided in the Clinical Overview. Furthermore, the USPI was also based on the new clinical cut-off date on RE population.

Due to the discordance between efficacy results based on different clinical data cut date and primary analysis sets, the review team sent multiple IRs and held T-con with applicant. In this review, the entire efficacy results for Trial NP28673 were calculated by this reviewer using updated clinical data cut-off date in the AT population.

#### 3.3.8.1 Patient Population and Disposition

A total of 138 patients were enrolled in the Part II. Table 8 presents the trial populations and the primary reason for treatment discontinuation.

**Table 8 Patient Population and Disposition**

| | **NP28673 (N=138)** |
|---|---|
| AT | 138 (100%) |
| RE per IRC | 122 (88%) |
| Ongoing | 89 (65%) |
| Median follow up in month (Range) | 10.4 (0.6, 16.8) |
| Median Treatment in month (Range) | 10.9 (0.6, 16.8) |
| CNS per IRC | 84 (60%) |
| Measurable | 35 (25%) |
| Discontinued | 72 (52%) |
| AE | 12 (9%) |
| Death | 7 (5%) |
| PD | 48 (35%) |
| Withdrawal | 4 (3%) |
| Other | 1 (<1%) |

Clinical data cut-off date: January 8, 2015

*Reviewer's Comments:*

*17. Six patients from dose finding part were combined with the activity estimating part.*

18. *Per Applicant's primary analysis set, 12% treated patients were excluded from this trial population.*
19. *Disease progression was the primary reasons for treatment discontinuation.*
20. *There were only 35 (25%) CNS patients with measurable lesion at baseline assessment.*
21. *Comparing to Trial NP28761, patients in Trial NP28673 got longer treatment, more patients with measurable CNS disease, more PD caused withdraw and less RE per IRC assessment.*

### 3.3.8.2 Baseline and Demographic Characteristics

Table 9 presents the patient baseline demographic characteristics.

**Table 9 Baseline Demographics Characteristics in AT Population**

| | **NP28673 (N=138)** |
|---|---|
| Age: Median (Range) | 52 (22-79) |
| > = 65 | 14 (10%) |
| Race: White | 93 (67%) |
| Asian | 36 (26%) |
| Other | 9 (7%) |
| Sex: Female | 77 (56%) |
| Region: USA | 23 (17%) |
| Asia | 29 (21%) |
| West EU | 78 (57%) |
| Other | 8 (6%) |

Clinical data cut-off date: January 8, 2015

Table 10 presents the important baseline disease characteristics and prior treatments in the AT.

**Table 10 Baseline Disease Characteristics and Prior Treatments in AT Population**

| | **NP28673 (N=138)** |
|---|---|
| ECOG: 0 | 44 (32%) |
| 1 | 81 (59%) |
| 2 | 13 (9%) |
| Smoker: Non-Smoker | 96 (70%) |
| Current Stage: IV | 136 (99%) |
| Histology: Adenocarcinoma | 133 (96%) |
| Adenosquamous | 2 (1%) |
| Large cell carcinoma | 3 (2%) |
| Prior Chemo, n(%) | 110 (80%) |
| Prior Brain Radiation, n (%) | 42 (30%) |
| Prior Radiotherapy: Brain | 69 (50%) |
| Bone | 30 (22%) |
| Lung | 17 (12%) |
| Prior Crizotinib | 138 (100%) |
| Time on crizotinib, Med. (range) days | 364 (1, 1428) |
| Time since last dose, Med. (range) days | 15 (3, 676) |
| ORR on crizotinib | 75 (54%) |
| PD on crizotinib | 27 (20%) |

Clinical data cut-off date: January 8, 2015

*Reviewer's Comments:*

*22. Due to different regimen, tumor assessment, and baseline characteristics between Trials NP28761and NP28673, the efficacy results from Trials NP28761and NP28673 should not be pooled.*

### 3.3.8.3 ORR Analysis

Table 11 presents the results of ORR per IRC assessment.

**Table 11 ORR Results per IRC Assessment in AT Population**

| | **NP28673 (N=138)** |
|---|---|
| ORR, n (%) | 61 (44.2%) |
| CR, n (%) | 0 |
| PR, n (%) | 61 (44.2%) |
| 95% CI* | (35.8%, 52.9%) |

Clinical data cut-off date: January 8, 2015
*Per Clopper-Pearson Method

*Reviewer's Comments:*

*23. The ORR was 44.2% (95% CI: 35.8%, 83.0%). The lower bound of the associated Clopper-Pearson 95% CI exceeds 35%, the pre-specified threshold per the trial design operating characteristics.*

*24. The ORR sensitivity analyses based in RE (Per IRC assessment), INV assessment in the AT, and INV assessment in the RE were 50.0% (95% CI: 40.8%, 59.2%), 50.0% (95% CI: 41.4%, 58.6%) and 52.5% (95% CI: 43.2%, 61.6%). The lower bounds of the associated Clopper-Pearson 95% CI exceed 35%, the pre-specified threshold per the trial design operating characteristics.*

### 3.3.8.4 DoR Analysis

Table 12 presents the median and its 95% CI for DoR based on the central review at the updated clinical data cut-off date. The median DoR was 11.2 months (9.6, NE).

**Table 12 DoR Results per IRC Assessment**

| | **NP28673 (N=138)** |
|---|---|
| DoR (month) | N=61 |
| PD, n (%) | 20 (32.8%) |
| Median (95% CI) | 11.2 (9.6, NE) |

NE: not estimated
Clinical data cut-off date: January 8, 2015

### 3.3.8.5 ORR-PC Analysis

Table 13 presents the results of ORR-PC per IRC assessment.

**Table 13 ORR-PC Results per IRC Assessment**

| | NP28673 (N=110) |
|---|---|
| ORR-PC, n (%) | 43 (39.1%) |
| 95% CI* | (29.9%, 48.9%) |

Clinical data cut-off date: January 8, 2015
*Per Clopper-Pearson Method

### 3.3.8.6 DoR-PC Analysis

Table 14 presents the median and its 95% CI for DoR based on the central review at the updated clinical data cut-off date. The median DoR was 11.9 months (9.6, NE).

**Table 14 DoR-PC Results per IRC Assessment**

| | NP28673 (N=138) |
|---|---|
| DoR-PC (month) | N=43 |
| PD, n (%) | 15 (34.9%) |
| Median (95% CI) | 10.9 (9.2, NE) |

Clinical data cut-off date: January 8, 2015
NE: not estimated

### 3.3.8.7 CORR Analysis

Table 15 presents the results of CORR based on the central review.

**Table 15 CORR Results per IRC Assessment using RECIST**

| | NP28673 | |
|---|---|---|
| | Measurable or Non-Measurable CNS | Measurable CNS |
| | N=84 | N=35 |
| CORR, n (%) | 36 (42.9%) | 20 (57.1%) |
| CR, n (%) | 23 (27.4%) | 7 (20.6%) |
| PR, n (%) | 13 (15.5%) | 13 (38.2%) |
| 95% CI | (32.1%, 54.1%) | (39.4%, 73.7%) |

Clinical data cut-off date: January 8, 2015

Table 16 presents the results of CORR based on the central review per RANO.

**Table 16 CORR Results per IRC using RANO**

| | NP28673 | |
|---|---|---|
| | Measurable or Non-Measurable CNS | Measurable CNS |
| | N=84 | N=35 |
| CORR, n (%) | 17 (20.2%) | 17 (48.6%) |
| CR, n (%) | 5 (6.0%) | 5 (14.3%) |
| PR, n (%) | 12 (14.3%) | 12 (34.3%) |
| 95% CI | (12.3%, 30.4%) | (31.4%, 66.0%) |

Clinical data cut-off date: January 8, 2015

*Reviewer's Comments:*

*25. The CORR was 42.9% (95% CI: 32.1%, 54.1%).*

26. *The CORR with baseline measurable disease was 57.1% (95% CI: 39.4%, 73.7%). The lower bound of the associated Clopper-Pearson 95% CI exceeds 35%, the pre-specified threshold per the trial design operating characteristics.*
27. *This reviewer did not find any discussion on which CORR result (measurable vs. measurable/non- measurable) would be included the USPI in the meeting minutes or IND reviewers. This is deferred to the medical review team reviewing this applicant.*
28. *There were discordance between CSR, Clinical Summary, and Response to FDA's IR for CORR results. Hence, this reviewer reported the FDA's CORR results based on the individual trial data submission.*

#### 3.3.8.8 CDoR Analysis

Table 17 presents the median and its 95% CI for CDoR per RECIST.

**Table 17 CDoR Results per IRC Assessment per RECIST**

| | NP28673 | |
|---|---|---|
| | **Measurable or Non-Measurable CNS** | **Measurable CNS** |
| DoR (month) | N=36 | N=20 |
| PD, n (%) | 18 (50.0%) | 11 (55.0%) |
| Median (95% CI) | 10.3 (7.6, 11.2) | 9.1 (5.8, NE) |

Clinical data cut-off date: January 8, 2015
NE: not estimated

Table 18 presents the median and its 95% CI for CDoR per RANO.

**Table 18 CDoR Results per IRC Assessment per RANO**

| | NP28673 | |
|---|---|---|
| | **Measurable or Non-Measurable CNS** | **Measurable CNS** |
| DoR (month) | N=17 | N=17 |
| PD, n (%) | 8 (47.1%) | 8 (47.1%) |
| Median (95% CI) | 9.1 (7.4, NE) | NE |

Clinical data cut-off date: January 8, 2015
NE: not estimated

### 3.4 Evaluation of Safety

Please refer to the clinical review of this application for safety evaluation.

### 3.5 Benefit/Risk Ratio

The lower bounds of the associated Clopper-Pearson 95% CI of ORR and measurable CNS-ORR in the trials NP28673 and NP28761exceed 35%, the pre-specified threshold per the trial design operating characteristics. Whether the submission demonstrated an overall favorable benefit vs. risk profile for alectinib in trials NP28673 and NP28761is deferred to the clinical team reviewing this submission.

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race, Age, and Country

Table 19 presents the subgroup analysis of ORR by baseline demographic characteristics for Trials NP28673 and NP28761.

**Table 19 Demographic Characteristics Subgroup Analyses of ORR per Central Review, n (%), (95%CI**

| | NP28673* | | NP28761 | |
|---|---|---|---|---|
| | n (%) | 95% CI* | n (%) | 95% CI* |
| Age: <65 | 56 (45.2%) | (36.2%, 54.4%) | 25 (35.2%) | (24.2%, 47.5%) |
| > = 65 | 5 (35.7%) | (12.8%, 64.9%) | 8 (50%) | (24.7%, 75.4%) |
| Race: White | 40 (43.0%) | (32.8%, 53.7%) | 28 (38.4%) | (27.2%, 50.5%) |
| Asian | 18 (50%) | (32.9%, 67.1%) | 4 (57.1%) | (18.4%, 90.1%) |
| Other | 3 (33.3%) | (7.5%, 70.1%) | 1 (14.3%) | (0. 3%, 57.9% |
| Sex: Female | 32 (41.6%) | (30.4%, 53.4%) | 17 (35.4%) | (22.2%, 50.5%) |
| Male | 29 (47.5%) | (34.6%, 60.7%) | 16 (41.2%) | (35.6%, 57.9%) |

Clinical data cut-off date: January 8, 2015
*Per Clopper-Pearson Method

## 4.2 Pooled Measurable CNS

An assessment of the measurable CORR and CDoR for CNS metastases in 51 pooled patients from Trials NP28673 and NP28761 are summarized in Table 20.

**Table 20 Pooled CORR and CDoR in Patients with Measurable CNS Lesions in Trials NP28673 and NP28761**

| | Per RECIST | Per RANO |
|---|---|---|
| CORR (95% CI) | 60.8% (46.1%, 74.2%) | 41.2% (27.6%, 55.8%) |
| CR, n (%) | 9 (17.6%) | 5 (9.8%) |
| PR, n (%) | 22 (43.1%) | 16 (31.4%) |
| CDoR in months (95% CI) | 9.1(5.8, NE) | 9.1 (7.4, NE) |
| PD | 12 (30.7%) | 8 (30.1%) |

NE: not estimated

## 4.3 Pooled Measurable CNS by Prior Brain Radiation (RT)

The measurable CORR and CDoR analysis results per RECIST for pooled patients by prior brain radiation status are summarized in Table 21.

**Table 21 Pooled CORR and CDoR in Patients with Measurable CNS Lesions in Trials NP28673 and NP28761, By Prior Brain RT**

| | With prior Brain RT | Without prior Brain RT |
|---|---|---|
| | N=35 | N=16 |
| CORR (95% CI) | 57.1% (39.4%, 73.7%) | 68.8% (41.3%, 89.0%) |
| CDoR in months (95% CI) | 9.2 (5.6, NE) | 9.1 (7.1, NE) |

NE: not estimated

*Reviewer's comment:*

29. *These subgroup analyses are exploratory and comparative analyses cannot be conducted. These results should be viewed with caution due to small sample size.*

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

There are two issues. First, CSR, Clinical Overview, and USPI were based on RE population, a subset of protocol pre-specified AT population for both trials. Second, CSR reported efficacy outcomes and USPI used different clinical data cut-off dates for Trial NP28673.

Whether the data and analyses from the current submission in the NSCLC patients demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

## 5.2 Collective Evidence

Trial NP28673 had ORR of 44% (95% confidence interval [CI]: 36%, 53%), consisting of 61 (44%) PRs. This trial had ORR-PC of 39% (95% CI: 30%, 49%). The CORR with baseline measurable lesions was 57% (95% CI: 39%, 74%).

Trial NP28761 had ORR of 38% (95% CI: 28%, 49%). The CORR with baseline measurable lesions was 69% (95% CI: 41%, 89%). Fifty one CNS patients with baseline measurable lesion in Trials NP28761 and NP28673 had ORR of 61% (95% CI: 46%, 74%), consisting of 9 (18%) CRs and 22 (43%) PRs.

## 5.3 Conclusions and Recommendations

Without control arm, statistical inference cannot be drawn from this trial. All statistical summaries presented are for descriptive purposes only. Furthermore, only data and analyses in trial NP28761 met the predefined criteria for point estimates to meet or exceed 35% of ORR. The lower bounds of the associated 95% confidence intervals (CIs) also exceed 35%, the pre-specified threshold as per the trial design operating characteristics.

Whether alectinib demonstrated an overall favorable benefit vs. risk profile for patients with NSCLC is deferred to the clinical team reviewing this submission.

## 5.4 Labeling recommendation

1. The results of ORR analysis for each trial should be included in the label.
2. The DoR results should be included in the label.
3. The results of CORR analysis in patients with measurable disease may be included in the label.
4. The results of CDoR analysis in patients with measurable disease may be included in the label.

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HUANYU CHEN
11/06/2015

KUN HE
11/06/2015

RAJESHWARI SRIDHARA
11/06/2015

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 208434** **Applicant: Roche** **Stamp Date: 6/19/2015**

**Drug Name: Alectinib** **NDA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter | Yes | No | NA | Comments |
|---|---|---|---|---|---|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc. | √ | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | √ | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable). | √ | | | |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | √ | | | |

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|---|---|---|---|
| Designs utilized are appropriate for the indications requested. | √ | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | √ | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | √ | | | |
| Appropriate references for novel statistical methodology (if present) are included. | √ | | | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | √ | | | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | √ | | | |

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HUANYU CHEN
08/07/2015

KUN HE
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