FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

April 12, 2016

NDA 208542
Rociletinib

Applicant: Clovis Oncology, Inc.

DISCLAIMER STATEMENT

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Glossary

AE	Adverse Events
ALK	Anaplastic lymphoma kinase
AUC	Area under the Curve
AUC_{ss}	Area under the Curve at Steady State
BID	Twice Daily
BSC	Best Supportive Care
C_{max}	Maximum Observed Plasma Concentration
$C_{max,ss}$	Maximum Observed Plasma Concentration at Steady State
CI	Confidence Intervals
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CYP	Cytochrome P450
DoR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal Growth Factor Receptor
EGFR-TKI	Epidermal Growth Factor Receptor- Tyrosine Kinase Inhibitor
EOT	End of Treatment
FB	Free Base
IND	Investigational New Drug Application
HBr	Hydrobromide
HR	Hazard Ratio
hERG	human Ether-à-go-go-Related Gene (also known as KCNH2)
IFG1R	Insulin-Like Growth Factor 1
ILD	Interstitial Lung Disease
INV	Investigator
INSR	Insulin Receptor
IR	Information Request
IRR	Independent Radiology Review
mOS	Median Overall Survival
msec	Millisecond
M460	One of Three Major Metabolites of Rociletinib
M502	One of Three Major Metabolites of Rociletinib
M544	One of Three Major Metabolites of Rociletinib
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NAT2	N-acetyltransferase 2
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NSCLC	Non-Small Cell Lung Cancer
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDUFA	Prescription Drug User Fee Act
PFS	Progression-Free Survival
PK	Pharmacokinetics
QTc	Corrected QT Interval
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SCLC	Small Cell Lung Cancer
SD	Stable Disease
TKI	Tyrosine Kinase Inhibitor
T790M	EGFR gene mutation: threonine to methionine at position 790
WNL	Within Normal Limits

1 Proposed Indication

Rociletinib is indicated for the treatment of patients with EGFR mutation positive metastatic NSCLC who have been previously treated with and EGFR-targeted therapy and who have the EGFR T790M mutation as detected by an FDA approved test.

2 Executive Summary

On 24 June 2015, Clovis Oncology, Inc. (Clovis) submitted New Drug Application (NDA) 208542 for rociletinib for the proposed indication. Clovis requested accelerated approval under the provisions of 21 CFR part 314 subpart H, based on the results of two non-randomized studies (CO-1686-008 and CO-1686-019) conducted in patients with EGFR T790M mutation-positive metastatic NSCLC with progressive disease while receiving at least one epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). In these studies, patients received rociletinib at doses ranging from 500 mg twice daily (BID) to 1000 mg BID. In the NDA submission, Clovis' proposed recommended dose was 500 mg BID. In patients who received this dose (N=79), the objective response rate (ORR) is 23% (95% confidence interval (CI): 14, 34) with a median duration of response (DoR) of 9.1 months. On 15 December 2015, Clovis notified FDA of plans to amend the proposed recommended dose to 625 mg BID; draft labeling reflecting this change was submitted to the NDA on 08 January 2016. In the 170 patients who received rociletinib 625 mg BID, the ORR is 32% (95% CI: 25, 40) with a median DoR of 8.8 months.

The most common adverse reactions in the pooled safety analysis of 400 patients receiving rociletinib at doses 500 mg, 625 mg, 750, or 1000 mg BID (>30%) were diarrhea, hyperglycemia, fatigue, nausea, decreased appetite, QT prolongation, and vomiting. The most common Grade 3-4 adverse reactions (>10%) were hyperglycemia and QTc prolongation. Dose reductions occurred in 51% patients. The most common adverse reactions leading to dose reductions across all dose levels were hyperglycemia (22%) and QTc prolongation (11%). The criteria for dose reduction were not clearly specified in the clinical protocol for Study CO-1686-008 and were inconsistently applied by investigators; this study enrolled 90% of the patients included in the safety population and 87% of the patients in the efficacy population. Dose interruptions occurred in 57% of patients across dose levels, most commonly due to hyperglycemia (22%), QTc prolongation (10%), and nausea (10%). Discontinuation due to adverse reaction occurred in 11% of patients, most commonly due to QTc prolongation (2%), and pneumonia/pneumonitis (2%). Serious adverse reactions occurred in 47% of patients, most commonly due to malignant neoplasm progression (16%), hyperglycemia (8%) and pneumonia (4%). Seventeen percent of patients had post-baseline QTc intervals of greater than 500 msec on at least one occasion. There were two sudden deaths (on day 4 and day 13) and one patient experienced Torsades de pointes.

Pharmacokinetic analyses revealed high variability of systemic exposure of rociletinib and its major metabolites. Rociletinib demonstrated non-linear pharmacokinetics, as systemic exposures did not increase when the dose increased from 500 mg to 1000 mg. Similar systemic exposure in terms of $C_{max,ss}$ and area under the curve at steady state (AUC_{ss}) was observed across

doses ranging from 500 mg to 1000 mg, likely due to the low solubility of rociletinib. Rociletinib has an elimination half-life of 3.7 hours, whereas the major rociletinib metabolites, M502 (which induces hyperglycemia) and M460 (which induces QTc prolongation), have half-lives of 20 hours and 51 hours, respectively. Compared to no apparent accumulation of rociletinib at steady state, M502 and M460 accumulated up to 5 fold and 58 fold, respectively, across doses ranging from 500 mg to 1000 mg BID with a meal. Exposure-response analyses indicate a plateau in ORR at exposures obtained with the 500 mg BID dose and above. Exposure-safety analyses suggest incidences of Grade 3 to 4 hyperglycemia and QTc prolongation increases with increased exposure of these metabolites. Additionally, as the acetylation of both M502 and M460 may be mediated by N-acetyltransferase (NAT2), patients who are classified as NAT2 slow acetylators based on NAT2 genotype have higher M502 and M460 exposures, and are at increased risk for QTc prolongation and hyperglycemia, although these risks also exist in patients who are classified as intermediate or fast NAT2 acetylators.

According to Clovis, the ongoing Study CO-1686-020 (TIGER-3) will confirm the clinical benefit of rociletinib, should it receive accelerated approval. It is an open-label, randomized, multi-national study of rociletinib versus single agent chemotherapy (pemetrexed, docetaxel, or gemcitabine) in patients with EGFR-mutation positive NSCLC with disease progression following both an EGFR-TKI and platinum doublet chemotherapy.

The key issues for this application are whether the activity of rociletinib as reflected by the ORR and DoR are reasonably likely to predict clinical benefit and are superior to available therapy, if so, whether Clovis' proposed recommended dose of 625 mg BID is supported by the clinical and clinical pharmacology data, whether the risks (particularly with respect to QTc prolongation leading to Torsades de pointes) are acceptable in the intended population, and whether the dose modification strategy to mitigate the toxicities of rociletinib has been adequately characterized.

The Division of Oncology Products 2 seeks the advice of the ODAC regarding the pending NDA for rociletinib on the following issues:

Efficacy: Is the observed ORR and DoR for patients treated with rociletinib better than available therapy for the proposed patient population, and is it likely to predict clinical benefit?

Safety: Are the risks of rociletinib, particularly with respect to QTc prolongation leading to Torsades de pointes and other serious ventricular arrhythmias, acceptable?

Overall Benefit-Risk Assessment: Is the benefit-risk profile favorable for the proposed patient population?

3 Background

3.1 Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the United States (U.S.) and worldwide. In the U.S., in 2015, there were an estimated 224,390 new cases and 158,080 deaths due to lung cancer.[i] The two major histological subtypes of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for nearly 85% of all cases of lung cancer, and at diagnosis, 57% of cases are unresectable (Stage IIIb or Stage IV). In these patients, prognosis is poor with an estimated median survival of 10 to 12 months when treated with platinum-based chemotherapy and 3 to 6 months with supportive care.[ii,iii,iv,v]

The treatment of NSCLC is guided by both the histologic subtype and the presence of actionable mutations, such as driver mutations in the kinase domain of the epidermal growth factor receptor (EGFR) gene or alterations of the anaplastic lymphoma kinase (ALK) gene.[vi] EGFR belongs to a family of tyrosine kinase receptors that mediate tumor proliferation, invasion, metastasis, resistance to apoptosis, and angiogenesis.[vii] EGFR mutations occur with a frequency of 10-15% in Western/Caucasian patients and 30-50% in Asian patients. Additionally, these mutations are associated with distinct clinico-pathologic features such as a higher proportion of females, never or light smokers, and the adenocarcinoma histology than in patients without actionable mutations.[viii] Most patients with EGFR mutations possess the exon 19 (in-frame) deletion (45%) or the exon 21 L858R point mutation (40-45%).[ix] The presence of these mutations predicts for sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKI) at diagnosis.

Multiple randomized controlled studies have demonstrated superior outcomes for patients with metastatic NSCLC who harbor EGFR activating mutations, when they receive first- or second-line treatment with EGFR-TKIs compared to patients treated with chemotherapy. Objective response rates (ORR) ranging from 60 to 70% and median progression-free survival (PFS) times ranging from 9 to 14 months have been reported in patients treated in the first-line setting with gefitinib [IRESSA™], erlotinib [TARCEVA®], or afatinib [GILOTRIF™]). However, most patients treated with EGFR-TKIs subsequently develop acquired resistance to these agents.[x,xi] The T790M mutation is the most common resistance mutation and is observed in approximately 60% of patients. This mutation occurs when the methionine is substituted for threonine at position 790 at exon 20, rendering first and second generation EGFR-TKIs ineffective.[xii]

3.2 Approved Therapies for EGFR-positive NSCLC

The FDA-approved systemic first-line treatment for patients with metastatic NSCLC whose tumors harbor EGFR mutations are erlotinib, gefitinib, or afatinib. After disease progression, the treatment of these patients has followed the treatment paradigm in unselected patients with NSCLC who have progressed following doublet chemotherapy. In this group of patients, treatment options include nivolumab, pemetrexed, and docetaxel as a single agent or in combination with ramucirumab.

Docetaxel as a single agent received FDA approval based on the demonstration of an OS advantage in one of two randomized, open-label, active-controlled trials. The first trial

demonstrated an improvement in OS as compared to best supportive care [HR 0.56 (95% CI: 0.35, 0.88)] and the second showed similar survival (5.7 months vs. 5.6 months) for patients receiving docetaxel as compared to either vinorelbine or ifosfamide [HR: 0.82 (0.63, 1.06)]. The ORR in patients who received docetaxel in randomized trials has ranged from 6% to 14%, with median DoR of 6 to 8 months. The efficacy of docetaxel in the subgroup of patients with EGFR T790M mutation-positive NSCLC has not been studied.

Ramucirumab is a human vascular endothelial growth factor receptor 2 antagonist approved for use in combination with docetaxel. Approval was based on the demonstration of a significant improvement in overall survival (OS) [HR 0.86 (95% CI 0.75, 0.98) p = 0.024] in a 1253 patient trial comparing docetaxel plus ramucirumab to docetaxel plus placebo. The efficacy of ramucirumab administered in combination with docetaxel, in the subgroup of patients with EGFR T790M mutation-positive NSCLC, has not been studied.

Pemetrexed was received FDA Approval as a single agent for treatment of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy, based on a multi-center, randomized, open label, active-control study comparing pemetrexed to docetaxel in patients with NSCLC after prior chemotherapy, which demonstrated a marginally significant improvement in overall survival [HR 0.78 (95% CI: 0.61, 1.0)]. In patients with NSCLC (squamous and non-squamous histology) treated with pemetrexed after progression on platinum doublet, the ORR was 9% (95% CI: 5, 12). The ORR of pemetrexed in 158 patients with adenocarcinoma histology from this study was 13%.[xiii] The efficacy of pemetrexed in patients with EGFR T790M mutation-positive NSCLC has not been studied.

Nivolumab is a monoclonal antibody which binds and blocks ligand binding to the anti-programmed death receptor-1 (PD-1). Nivolumab was approved for the treatment of both squamous and non-squamous metastatic NSCLC based on the demonstration of superior OS compared to docetaxel in two randomized controlled trials. The ORR was 19% (95% CI: 15, 24) with a median DoR of 17.2 months in patients with non-squamous, NSCLC. The efficacy of nivolumab in the subgroup of patients with EGFR T790M mutation-positive metastatic NSCLC has not been established.

On 13 November 2015, osimertinib (TAGRISSO) received accelerated approval for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. The approval was based on ORR of 59% (95% CI 54, 64) in a pooled analysis of 411 patients in two single arm trials. The median DoR in a cohort of 63 patients with EGFR T790M mutation-positive NSCLC who received osimertinib in Phase 1 was 12.4 months. At the recommended dose of osimertinib 80 mg daily, dose reductions occurred in 4.4% of patients, and discontinuations due to adverse reactions occurred in 5.6% of patients. The most common adverse reactions (all Grades) occurring in 30% or more of patients treated with osimertinib were diarrhea (42%), rash (41%), and dry skin (31%). No Grade 3 to 4 adverse reactions occurred at a frequency of 2% or greater. Warnings and Precautions for osimertinib in the U.S. Prescribing Information include: interstitial lung disease/pneumonitis (3.3%), QTc prolongation (0.2% with increase greater than 500 msec), and cardiomyopathy (1.4%).

Table 1 summarizes the FDA-approved products for the second-line treatment of metastatic NSCLC, which are considered available therapy for the proposed indication sought by Clovis. Erlotinib, gefitinib, and afatinib are not included because the indication is limited to patients with disease progression on an EGFR TKI. Both pembrolizumab and osimertinib are not considered available therapy because they remain under accelerated approval for second-line treatment of patients with metastatic NSCLC; however data for osimertinib are included for reference.

Table 1 Approved Therapies for NSCLC in the Second-Line Setting

Date	Product Indication	Studies and Approval Endpoints
DEC- 1999	**DOCETAXEL** Single agent for locally advanced or metastatic NSCLC after platinum therapy failure	1. Docetaxel (N=55) vs. BSC (N=49) • mOS 7.5 m (5.5, 12.8) vs 4.6 m (3.7, 6.1); HR 0.56 (0.35, 0.88); p=0.01 • ORR 5.5% (1.1, 15.1) vs N/A 2. Docetaxel (N=125) vs. Vinorelbine/Ifosfamide (N=123) • mOS 5.7 m (5.1, 7.1) vs. 5.6 m (4.4, 7.9); HR 0.82 (0.63, 1.06); p=0.13 • ORR 5.7% (2.3, 11.3) vs. 0.8% (0.0, 4.5)
FEB- 2004	**PEMETREXED** Single agent for locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	Pemetrexed (N=205) vs. Docetaxel (N=194) Non Squamous population • mOS 9.3 m (7.6, 9.6) vs 8.0 (6.3, 9.3); HR 0.78 (0.61, 1.0)
DEC-2014	**RAMUCIRUMAB** In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving ramucirumab	Ramucirumab/Docetaxel (N=628) vs Placebo/Docetaxel (N=625) • mOS 10.5 m (0.95, 11.2) vs 9.1 (8.4, 10.0); HR 0.86 (0.75, 0.98) p = 0.024 • mPFS 4.5 m (4.2, 5.4) vs 3.0 m (2.8, 3.9) ; HR 0.76 (0.68, 0.86) p < 0.001 • ORR 23% (20, 26) vs. 14% (11, 17); p < 0.001
MAR-2015	**NIVOLUMAB** Metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving nivolumab	I. Nivolumab (N=135) vs. Docetaxel (N=137) Squamous NSCLC • mOS 9.2 m (7.3, 13.3) vs. 6.0 m (5.1, 7.3); HR 0.59 (0.44, 0.79) p=0.00025 • ORR 20% (14, 28) vs 9% (5, 15) II. Nivolumab (N=292) vs. Docetaxel (N=290) Non-Squamous NSCLC • mOS 12.2 m (9.7, 15.0) vs. 9.4 m (8.0, 10.7); HR 0.73 (0.60,0.89) p=0.0015 • ORR 19% (15, 24) vs 12% (9, 17)
NOV-2015	**OSIMERTINIB**[A] Treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.	Two multicenter, single-arm, open-label studies of patients with metastatic EGFR T790M mutation-positive NSCLC with pooled ORR (N=411) of 59% (95% CI 54, 64) by blinded independent central review. The median duration of response in 63 patients in Phase 1 with EGFR T790M NSCLC was 12.4 months.

[A] Accelerated approval therefore not considered available therapy per FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics, May 2014; BSC= best supportive care; mOS= median Overall Survival; ORR= objective response rate; mPFS= median Progression-free Survival

3.3 Rociletinib Regulatory History

On 24 June 2015, Clovis initiated the rolling submission for NDA 208542, rociletinib for the treatment of patients with EGFR mutation positive metastatic NSCLC who have been previously treated with and EGFR-targeted therapy and who have the EGFR T790M mutation as detected by an FDA approved test. The final component of the application was submitted on 30 July 2015.

Key pre-submission and post-submission regulatory issues and interactions between FDA and Clovis that are related to the clinical development of rociletinib are summarized in Table 2.

Table 2 Key Regulatory Activities Related to the Clinical Development of Rociletinib

Date	Discussion
12/20/2011	Clinical development program for CO-1686 (rociletinib) initiated under IND 113560 with Study CO-1686-008 (TIGER X), titled "A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)." The IND was allowed to proceed on 20 January 2012.
05/14/2013	Orphan drug designation granted for use of CO-1686 in EGFR mutation-positive NSCLC.
11/20/2013[A]	End-of Phase 1 (EOP1) meeting. Clovis sought FDA feedback on its plan to request Breakthrough Therapy Designation, the acceptability of a single-arm trial to support a NDA for accelerated approval, and on the design of a pivotal clinical study designed to confirm the clinical benefit of rociletinib.
05/19/ 2014	Breakthrough Therapy Designation granted for the treatment of patients with EGFR mutation-positive NSCLC, whose disease has progressed on prior EGFR-directed therapy due to T790M-mediated acquired drug resistance. Breakthrough was granted on the basis of investigator-assessed ORR of 54.5% according to RECIST v1.1.
07/17/ 2014	End of Phase 2 (EOP2) meeting to discuss Clovis' plans for clinical studies intended to support an NDA submission for accelerated approval based on efficacy data from patients with centrally-confirmed T790M mutation+ NSCLC in study CO-1686-008 or CO-1686-019 who received rociletinib 625 mg BID, and to seek FDA input on proposals for confirmatory clinical studies.
05/05/2015	Protocol amendment #2 submitted to IND 113560 amending Study CO-1686-020 (TIGER-3) to change the rociletinib dose from 625 mg BID to 500 mg BID. Clovis stated that data from Study CO-1686-008 (TIGER-X) suggested that patients who received rociletinib 500 mg BID and 625 mg BID experienced responses that were comparable in frequency, depth, and duration, and with an overall acceptable safety profile. Under this amendment, all patients who initiated rociletinib at 625 mg BID were permitted a dose reduction to 500 mg only if necessitated by unacceptable toxicity.

06/09/2015	Type B Pre-NDA meeting to discuss and reach agreement on the proposed content, format, and timelines for the proposed NDA submission for accelerated approval. During this meeting, Clovis provided preliminary investigator-assessed ORR by dose, pooled between studies CO-1686-008 and CO-1686-019. At the 500 mg BID and 625 mg BID dose levels, Clovis reported ORR of 50% (24/48) and 49% (73/150), respectively. Clovis informed FDA that the proposed dose for marketing would be 500 mg BID. Clovis stated that the confirmatory trial is study CO-1686-020 as the study population most similar to the patient population in the proposed NDA submission.
06/24/2015	Clovis commenced the rolling submission of NDA 208542 with submission of the non-clinical data. The final component comprising the clinical data was submitted on 30 July 2015. Clovis requested accelerated approval under 21 CFR 314 Subpart H for rociletinib 500 mg BID based on ORR of 38.2% (95% CI 25.4, 52.3) as assessed by investigator using RECIST v1.1. Draft labeling stated that the recommended dose of rociletinib is 500 mg orally twice daily until disease progression or unacceptable toxicity.
11/09/2015	During the Mid-Cycle Communication with Clovis, FDA provided an update of the status of the review and communicated significant issues arising from the review. FDA stated its disagreement with Clovis' reported efficacy results of the pooled analysis for Studies CO-1686-008 and CO-1686-019. The disagreement was based on Clovis' inclusion of patients with unconfirmed responses in the efficacy assessment. Clovis acknowledged that their efficacy analysis had included patients with unconfirmed responses. FDA requested that Clovis submit additional datasets including updated tumor measurement raw datasets. Additionally, FDA informed Clovis that the application would likely be referred to the Oncologic Drug Advisory Committee (ODAC).
11/16/2015	Clovis submitted additional data in response to FDA's request. The data submission constituted a major amendment to the NDA and extended the PDUFA goal date by 3 months.
12/15/2015	Clovis held a teleconference with FDA to discuss the magnitude of clinical benefit provided by rociletinib and the appropriate rociletinib dose to provide optimal benefit-risk in the intended population. Clovis stated their intention to amend the NDA to propose 625 mg BID for marketing based on the observation of a better point estimate for tumor response at that dose. Clovis clarified that there were no new data to support this decision. Clovis also stated that this change would result in the amendment of the ongoing confirmatory trial CO-1686-020 (TIGER-3).
01/08/2016	Clovis submitted a revised draft label to reflect the 625 mg BID dose as the proposed commercial dose for rociletinib.

02/01/2016	Clovis submitted a proposal to IND 113560 and to the NDA to amend Study CO-1686-020 to evaluate the 625 mg BID dose in a 3rd study arm. The proposed change would increase the sample size from 600 to 900 patients and Clovis stated that there would be no formal efficacy comparison of the two rociletinib arms.
02/19/2016	FDA held a teleconference with Clovis to provide a status update on the review and provide preliminary information regarding issues that may be addressed during the ODAC. FDA recommended that Clovis be prepared to discuss the benefit-risk assessment of rociletinib and to discuss the data that support the dose changes during the clinical development of rociletinib. Additionally, FDA stated that the available pharmacokinetic data submitted in the NDA did not appear to support Clovis' proposal to change the recommended dose from 500 mg BID to 625 mg BID.
03/08/2016	Clovis submitted an enrollment update for Study CO-1686-020 (TIGER-3). As of 7 March 2016, a total of 117 patients have been randomized. Clovis submitted a formal amendment to IND 113,560 to amend trial CO-1686-020 to evaluate the 625 mg BID dose in a 3rd study arm. The proposed protocol change randomizes patients 1:1:1 to receive rociletinib 500 mg, 625 mg, or chemotherapy and increases the sample size from 600 to 900 patients. Clovis stated that there would be no formal efficacy comparison of the two rociletinib arms.

[A]Written Response meeting

4 Clinical Studies to Support Efficacy and Safety

Two clinical studies, CO-1686-008 (TIGER-X) and CO-1686-019 (TIGER-2) were submitted to establish the antitumor activity and safety of rociletinib. These studies share similar features and are described together with key differences highlighted. FDA's review of this NDA limited the evaluation of anti-tumor activity to the subgroup of patients in both studies who received rociletinib HBr, who had centrally confirmed T790M mutation positive NSCLC, and whose radiographs were evaluated by IRR. The evaluation of safety was limited to patients who received at least one dose of rociletinib HBr at doses ranging from 500 mg to 1000 mg twice daily (BID).

4.1 Study Design

CO-1686-008 is an ongoing, first-in-human, multi-center, open-label, dose-escalation, dose-expansion study evaluating the safety, pharmacokinetics, and anti-tumor effects of rociletinib in patients with locally advanced or metastatic EGFR mutation-positive NSCLC who have progressed after prior treatment with an EGFR-tyrosine kinase inhibitor. The dose escalation component was designed to assess the safety, maximum tolerated dose (MTD), and

recommended Phase 2 dose (RP2D). The Phase 2 component was designed to assess anti-tumor effects in two cohorts of patients with the T790M mutation-positive NSCLC.

In dose-finding phase of this study, patients received rociletinib in escalating doses in a non-randomized fashion, using a 3+3 schema based on the occurrence of dose limiting toxicities. The study initiated dose escalation with the free base (FB) formulation of rociletinib capsules. Patients received doses ranging from 150 mg daily to 900 mg FB BID. Following a protocol amendment and the introduction of the hydrobromide formulation (HBr), patients received doses ranging from 500 mg to 1000 mg BID.

According to Clovis, the MTD was not reached in the Phase 1 portion of the trial. Dose expansion in Phase 2 commenced at the 750 mg BID dose; the protocol was subsequently amended to evaluate additional doses. Patients were enrolled one of three cohorts based on extent of prior treatment and T790M mutation status. Within each of the cohorts, the dose administered was modified in a non-random (i.e., sequential) fashion:

- **Cohort A:** required at least 1 previous line of EGFR-directed therapy; additional previous therapies, including cytotoxic chemotherapy, were permitted. Enrolled only patients with T790M-positive NSCLC.
- **Cohort B:** required progression on a single-line of previous EGFR-directed therapy as the most recent treatment prior to enrollment. Only 1 prior chemotherapy regimen prior to EGFR TKI was allowed. Enrolled only patients with T790M-positive NSCLC.
- **Cohort C:** under Protocol Amendment 6, this cohort was added. Patient who met the entry criteria for Cohort A or B other than the requirement for centrally confirmed T790M mutation –positive NSLC were eligible for this cohort. Specifically, if the central T790M result was unavailable or if the central T790M test was negative but a local contemporaneous T790M test was positive.

CO-1686-019 is an ongoing, multicenter, open-label, two-cohort study designed to evaluate the anti-tumor effects of rociletinib, as measured by ORR, in patients with advanced NSCLC that harbors an EGFR mutation and have had disease progression after one prior EGFR-TKI. Patients are enrolled in one of two cohorts:

- **Cohort A** comprises patients with a T790M mutation-positive NSCLC; all patients are receiving rociletinib 625 mg BID.
- **Cohort B** comprises patients with T790M mutation-negative NSCLC; all patients receiving rociletinib 500 mg BID.

There was no formal data monitoring committee for either study. There were a total of seven protocol amendments for CO-1686-008 and four amendments for CO-1686-019. The key changes in these amendments are summarized below.

The Phase 1 portion of CO-1686-008 was initiated on 27 March 2012 at sites in the US and France and completed on 13 May 2014. The Phase 2 portion of the study is currently ongoing in the US, Europe, and Australia and was initiated on 26 February 2014.
For study CO-1686-019, the first patient was enrolled on 17 June 2014 in and the study is currently ongoing with 42 enrolled patients. At the time of the data-cutoff (29 April 2015), zero patients were enrolled in cohort B.

Table 3 Summary of Key Protocol Changes

Amendment/ Date		Changes
Study CO-1686-008		
1	25 January 2012	Addition of serial ECGs at baseline, Tmax, steady state concentration, end of treatment (EOT) and as clinically indicated; in Phase 2 at baseline, cycle 1 day 15, EOT and as clinically indicated; Grade 4 rash included in DLT definition; caution in use of inducers and inhibitors of CYP2C8 and CYP2D6 added.
2	4 October 2012	Post-progression rociletinib permitted; >1 intra-patient dose escalation permitted with sponsor approval; palliative XRT permitted for non-target lesions.
3	8 July 2013	Introduction of HBr tablets; Dose escalation in Phase 1 re-started using the HBr tablets and Continual Reassessment Method (CRM) introduced; introduction of cohort designations.
4	10 December 2013	Exclusion of patients with exon 20 insertion; dosing in Phase 2 to begin at 750 mg BID; removal of limits for albumin; decrease in washout time for prior EGFR TKI from 5 days to 3 days; assessment of fasting glucose and HgBA1C added; additional guidance on management of hyperglycemia added.
5	1 April 2014	Amendment never rolled out to clinical sites; changes incorporated in Amendment #6.
6	17 April 2014	Addition of Cohort C; patients randomly assigned 1:1 to receive 500 mg BID or 625 mg BID; introduction of centralized radiologic review (IRR); Introduction of quarterly review of safety data by sponsor and coordinating investigators; change in requirement to obtain biopsy to assess EGFR mutational status from within 28 days to within 60 days prior to rociletinib initiation; implementation of fasting glucose assessments on Day 4, 8, 15 in Cycle 1; addition of language to specify that patients may have received potassium and magnesium supplementation to meet requirement for levels in normal range; addition of language specifying that prior EGFR TKI-related toxicity must have resolved to Grade $\leq$ 1 prior to initiating rociletinib; addition of link to QTC prolonging medications; removal of allowable QTc interval up to 470 ms for women and addition of resting bradycardia <55 beats/minute as exclusion. Hyperglycemia included in DLT definition.
7	7 August 2014	Additional consent required to continue treatment beyond progression; clarification that only patients with stable CNS metastases were eligible. Removal of requirement to randomize patients by dose.
Study CO-1686-019		
1	1 May 2014	Rociletinib dose switched from 750 mg BID to 625 mg BID; patients with asymptomatic CNS metastases allowed; TID dosing schedule introduced as possible regimen for dose reduction.
2	9 May 2014	Requirement for QTc assessment on day 15 cycle 1
3	27 October 2014	Added tumor assessment for patients who discontinued rociletinib prior to progression; patients with leptomeningeal carcinomatosis excluded; added requirement that patients with clinical progression have radiographic confirmation of progression.
4	16 March 2015	Addition of Cohort B (500 mg BID)

Source: Reviewer Table CSR Study CO-1686-008 and CO-1686-019 Initial submission

4.2 Patient Population

In Study CO-1686-008, patients were enrolled from study sites in the U.S., Australia, France and Poland (Phase 2 only).

In Study CO-1686-019, patients were enrolled from study sites in North America, Australia, Europe, and Asia. Patients with local or unresectable locally advanced NSCLC who had progressed during treatment with a single agent EGFR-TKI, were enrolled into one of two disease-specific cohorts (A or B).

Except where specified, inclusion and exclusion criteria below are applicable to the patients in Study CO-1686-008 and Study CO-1686-019 who are included in the efficacy analyses.

Key Inclusion Criteria:

- Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC
- Documented evidence of tumor with ≥ 1 EGFR mutations not including exon 20 insertion
- Prior EGFR directed therapy
    - Phase 1 CO-1686-008: prior treatment with EGFR-directed therapy (e.g., erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). Prior chemotherapy, including chemotherapy since last EGFR-TKI was allowed.
    - Phase 2 CO-1686-008 (Cohort A): disease progression confirmed by radiologic assessment while receiving treatment with EGFR-TKI (e.g., erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). Prior chemotherapy, including chemotherapy since last EGFR-TKI was allowed.
    - Phase 2 CO-1686-008 (Cohort B) and CO-1686-019: disease progression confirmed by radiologic assessment while receiving treatment with first EGFR-TKI (e.g., erlotinib, gefitinib, afatinib, or dacomitinib). In these patients, last EGFR TKI use was within 30 days prior to rociletinib initiation and no intervening treatment since last EGFR-TKI use was permitted. Patients were permitted to have received up to 1 prior chemotherapy regimen (excluding chemotherapy administered with curative intent).
- Central laboratory confirmation of T790M mutation following disease progression on EGFR-TKI (note: patients in CO-1686-008 Cohort C were not required to have central confirmation of T790M status)
- Presence of measurable disease according to RECIST Version 1.1 (note: Phase 1 patients in CO-1686-008 were not required to have measurable disease)
- ECOG Performance Status (PS) 0-2 (0-1 for CO-1686-019)
- Adequate bone marrow, hepatic, and renal function; electrolytes in normal range (repletion of magnesium and potassium were allowed to meet requirement)

Key Exclusion Criteria:

- Presence of EGFR exon 20 insertion activating mutation
- Known pre-existing interstitial lung disease
- Patients with leptomeningeal carcinomatosis (other CNS metastases permitted if treated, asymptomatic, and not requiring steroids)
- Patients receiving medications with potential to prolong QT who cannot switch to an alternate
- Patients with personal or family history of long QT syndrome or QTcF > 450 ms
- Clinically abnormal ECG, implantable pacemaker or cardioverter defribrillator, resting bradycardia <55 bpm

In addition to the above, addenda to the protocol (6 June 2014) in France and South Korea excluded patients with abnormal fasting glucose at baseline from participating in Study CO 1686-019.

4.3 Safety and Efficacy Measurement Assessment

The efficacy measurement assessment was conducted by computed tomography (CT) scans of the chest, abdomen, and pelvis according to RECIST version 1.1 criteria, and repeated every 8 weeks (Cycle 2, 4, 6) and every 3 cycles thereafter. Imaging of the brain was required at baseline and was repeated at follow-up tumor assessment in patients with known brain metastases. Scans were assessed by investigator and, for a subset of patients, by independent radiology review (IRR).

Safety assessments included monitoring for adverse events (graded according to NCI-CTCAE version 4.03), hematologic and clinical chemistry laboratory parameters, hemoglobin A1c, and urinalysis. Electrocardiography (ECG), physical examinations, vital signs, and ECOG performance status were also monitored. ECG was conducted at screening, Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every cycle thereafter. Fasting glucose monitoring occurred at screening, Cycle 1 Day 1, 4, 8, and 15, Cycle 2 Day 1 and 15, and Day 1 of every cycle thereafter. Serum chemistry was checked at screening, Cycle 1 Day 1 and 15, and Day 1 of every cycle thereafter.

4.4 Analysis Plan

For the purposes of FDA's review of this NDA, the assessment of anti-tumor activity and safety is limited to patients who received the hydrobromide salt (HBr) formulation of rociletinib, as this is the formulation proposed for commercial use and the free-base form of rociletinib is not bioequivalent to the HBr salt.

The efficacy analysis population includes the subgroup of the safety population with EGFR T790M mutation positive NSCLC as determined by central testing enrolled in Study CO-1686-008 and all patients enrolled in Cohort A of Study CO-1686-019.

Efficacy analyses were conducted in the following groups: patients who received rociletinib 500 mg (N=79) and a pooled population of patients who received rociletinib 500 mg, 625 mg, or 750 mg BID (N= 325). Eight patients treated with rociletinib at doses of 750 mg BID or 1000 mg BID were excluded from the efficacy analysis because Clovis stated that their scans were not referred to the IRR for assessment.

The safety analyses were conducted in a pooled group of patients who received rociletinib 500 mg, 625 mg, 750 mg, or 1000 mg BID (N = 400) as well as by dose cohort in patients who received Clovis' initial recommended dose of 500 mg BID and the newly proposed dose of 625 mg BID. .

Objective response rate (ORR) by IRR was the primary efficacy outcome measure considered by the FDA, with duration of response (DoR) and ORR by investigator as secondary outcome measures. The incidence of adverse events, deaths, dose modifications (treatment interruptions, dose reductions, dose discontinuation) was assessed as primary safety endpoints. In addition, exploratory analyses of safety including time-to-event for select adverse events and exposure-toxicity were also conducted.

4.5 Results

4.5.1 Study Conduct

Data from 358 patients enrolled in Study CO-1686-008 were included in the NDA. The first patient was enrolled on 27 March 2012. The Phase 1 component of the study was conducted in 8 sites in Australia, France, and the United States (U.S.) and was completed on 13 May 2014. The Phase 2 component is ongoing in 50 sites in Australia, France, Poland, and the U.S with an 8.8 month median duration of follow-up for the 265 patients.

Data from a total of 42 patients enrolled in Study CO-1686-019 were included in the NDA. Patients were enrolled from 23 sites in Australia, Europe (France, Germany, United Kingdom), North America (US, Canada), and Asia (Korea). The first patient was enrolled on 17 June 2014; the study is ongoing with a 5.4 month median duration of follow-up.

Enrollment and follow-up cut-off dates for both studies are listed in Table 4.

Table 4 Data Cut-off Dates by Dose Group

Dose group*	# Patients	Enrollment cut-off date	All Visits Prior to
500 mg twice daily	90	20 March 2015	31 July 2015
Central T790M +	79		
625 mg twice daily	209	31 December 2014	
Central T790M+	170		
750 mg twice daily	95	31 December 2014	31 December 2014
Central T790M+	80		
1000 mg twice daily	6		
Central T790M+	4		
Total/ Central T790M+	**400/333**		

Source: Reviewer table based on Table 2.7.3-1 Summary of Clinical Efficacy: 90-Day Efficacy Update; *All patients received rociletinib HBr tablets;

A total of 400 patients comprise the safety population while the efficacy population is comprised of 325 patients. Table 5 illustrates the efficacy and safety analysis populations by study and rociletinib dose. Overall, demographic and disease characteristics were similar across both studies with the exception of prior number of therapies and number of prior EGFR-TKIs. Patients in Cohort A of Study CO-1686-008 were more heavily pre-treated than were patients in Cohort B of Study CO-1686-008 and patients in Study CO-1686-019.

Table 5 Efficacy and Safety Analysis Populations: CO-1686-008 and CO-1686-019

Analysis Population	Rociletinib HBr Dose Cohorts					Overall
	Study 1				Study 2	
	500	625	750	1000	625	
Efficacy	79	128	76	0	42	**325**
Safety	90	167	95	6	42	**400**

Source: Reviewer Table; 60-Day Safety Update and 90-Day Efficacy Update

Patient disposition at the time of data cut-off is shown by dose group in the efficacy analysis population in Table 6. Most patients (47%) discontinued treatment due to progressive disease.

Table 6 Patient Disposition: Efficacy Analysis Population

	500 mg (N=79)	625 mg (N=170)	750 mg (N=76)	Pooled (N=325)
Discontinued	46 (58.2)	110 (64.7)	45 (59.2)	201 (61.8)
Ongoing	33 (41.8)	60 (35.3)	31 (40.8)	124 (38.2)
Reason for discontinuation				
Progressive Disease	34 (43)	80 (47.1)	38 (50)	152 (46.8)
Physician Decision	1 (1.3)	3 (1.8)		4 (1.2)
Adverse Event[A]	7 (8.9)	15 (8.8)	3 (3.9)	25 (7.7)
Protocol Deviation		1 (0.6)		1 (0.3)
Withdrawal By Subject	1 (1.3)	5 (2.9)	1 (1.3)	7 (2.2)
Lost To Follow-Up		1 (0.6)		1 (0.3)
Death	1 (1.3)			1 (0.3)
Other	1 (1.3)	5 (2.9)	2 (2.6)	8 (2.5)

Source: Reviewer Table ADSL 90-Day Efficacy Update. [A]Proportion of patients with adverse reaction leading to rociletinib discontinuation is underestimated based on the demographics dataset.

Eighty-two percent of patients in the pooled efficacy population were enrolled in North America, with greater than 99% enrolled in the U.S. Most patients were female (70%), White (63%), never smokers (63%), with ECOG performance status score of 0-1 (99%). At baseline, all patients had received a prior EGFR TKI; 64% had only received one prior EGFR-TKI. Table 7 provides an overview of the demographic and disease characteristics of the pooled efficacy analysis population and by dose cohort.

Table 7 Demographic and Disease Characteristics of the Efficacy Analysis Population

	500 mg (N=79)	625 mg (N=170)	750 mg (N=76)	Pooled^ (N=325)
Age, median (range)	62 (26-90)	63 (34-88)	61 (30-85)	62 (26-90)
<65 years, n (%)	43 (54)	94 (55)	43 (57)	180 (55)
≥ 65 years, n (%)	36 (46)	76 (45)	33 (43)	145 (45)
Sex, n (%)				
Female	59 (75)	117 (69)	50 (66)	226 (70)
Race, n (%)				
American Indian/Alaska Native		1 (1)		1 (0)
Asian	15 (19)	42 (25)	19 (25)	76 (23)
Black/African American		7 (4)	1 (1)	11 (3)

	500 mg (N=79)	625 mg (N=170)	750 mg (N=76)	Pooled^ (N=325)
Native Hawaiian/Other Pacific Islander		3 (2)		3 (1)
White	51 (65)	97 (57)	55 (72)	203 (62)
Ethnicity, n (%)				
Hispanic Or Latino	2 (3)	8 (5)	2 (3)	12 (4)
Not Hispanic Or Latino	64 (81)	142 (84)	74 (97)	280 (86)
Geographic Region, n (%)				
Asia	0	3 (2)	0	3 (1)
Australia	6 (8)	12 (7)	7 (9)	25 (8)
Eastern Europe	1 (1)	1 (1)	1 (1)	3 (1)
North America	61 (77)	139 (82)	66 (87)	266 (82)
Western Europe	11 (14)	15 (9)	2 (3)	28 (9)
ECOG performance status[a], n (%)				
0-1	78 (99)	170 (100)	76 (100)	324 (99)
Smoking Status, n (%)				
Former Smoker	29 (37)	65 (38)	22 (289)	116 (36)
Never Smoked	47 (60)	104 (61)	54 (71)	205 (63)
Prior Treatments, n (%)				
1-2	35 (44)	107 (63)	44 (58)	186 (57)
3-5	36 (46)	51 (30)	21 (28)	108 (33)
>5	8 (10)	12 (7)	11 (14)	31 (10)
Prior TKIs, n (%)				
1	49 (62)	115 (68)	45 (59)	209 (64)
≥2	30 (38)	55 (32)	31 (41)	116 (36)
Time since NSCLC diagnosis				
Median (range) months	33 (7-86)	23 (3-165)	27 (5-165)	26 (3-165)
> 6 – 12 months	6 (8)	20 (12)	8 (11)	34 (10)
>12 – 24 months	25 (32)	70 (41)	24 (32)	119 (37)
>24 months	48 (61)	79 (46)	43 (57)	170 (52)
Number of Metastatic sites				
Median (range)	2 (1-6)	3 (1-6)	3 (1-6)	3 (1-6)
Sites of metastases, n (%)				
Liver	26 (33)	55 (32)	29 (38)	110 (34)
CNS	25 (32)	58 (34)	34 (45)	117 (36)

	500 mg (N=79)	625 mg (N=170)	750 mg (N=76)	Pooled^ (N=325)
Bone	24 (30)	81 (48)	34 (45)	139 (43)
EGFR mutations, n (%)				
Exon 19 deletion	48 (61)	118 (69)	57 (75)	223 (69)
L858R	24 (30)	40 (24)	18 (24)	82 (25)

[a] *At Baseline.*
^ *Patients on 500/625/750 dose groups*
Source: Reviewer table ADSL 90-day Efficacy Update

4.5.2 Efficacy

The primary outcome measure of objective response rate (ORR) as assessed by central radiologic review (IRR) is 22.8% (95% CI 14.1, 33.6) for patients who received rociletinib 500 mg BID, as agreed-upon during the 09 June 2015, pre-NDA meeting. As an exploratory analysis, data across all dose groups were pooled to assess ORR given the observed plateau in exposure across doses ranging 500 mg BID to 1000 mg BID, and the flat exposure-response observed (See Section IV, Clinical Pharmacology). In this pooled analysis, the ORR is 30.2% (95% CI 22.5, 35.5).

The median duration of response is 9.1 months (95% CI 6.8, 12.9) for patients who received rociletinib 500 mg BID and 8.9 months (95% CI 7.2, 12.9) for patients in the pooled analysis. The results of the efficacy analyses are summarized in Table 8 and Table 9 below and depicted in Figure 1**.**

Efficacy was also evaluated as per investigator assessment. Based on this analysis, the ORR is 27.8 (95% CI 18.4, 39.1) for patients who received rociletinib 500mg BID and 31.4% (95% CI 26.4, 36.7) in the pooled analysis. The median duration of response by investigator is 8.9 months (95% CI 4.4, 9.1) for patients who received rociletinib 500mg BID and 7.2 months (95% CI 5.1, 9.1) in the pooled analysis.

Table 8 Objective Response by IRR

Analysis Value	500mg (N=79)	625mg (N=170)	750mg (N=76)	Pooled^ (N=325)
	n/N(%)	n/N(%)	n/N(%)	n/N(%)
CR	0/79 (0)	1/170 (0.6)	0/76 (0)	1/325 (0.3)
PR	18/79 (22.8)	54/170 (31.8)	25/76 (32.9)	97/325 (29.8)
SD	28/79 (35.4)	45/170 (26.5)	18/76 (23.7)	91/325 (28)
PD	10/79 (12.7)	32/170 (18.8)	14/76 (18.4)	56/325 (17.2)
NE [a]	4/79 (5.1)	10/170 (5.9)	1/76 (1.3)	15/325 (4.6)
Ongoing with unconfirmed response	1/79 (1.3)	0/170 (0)	2/76 (2.6)	3/325 (0.9)
Ongoing without a response	9/79 (11.4)	11/170 (6.5)	5/76 (6.6)	25/325 (7.7)
Missing [b]	9/79 (11.4)	17/170 (10)	11/76 (14.5)	37/325 (11.4)
Objective response rate CR+PR (ORR)	18/79 (22.8)	55/170 (32.4)	25/76 (32.9)	98/325 (30.2)
95% Confidence Interval	[14.1, 33.6]	[25.4, 39.9]	[22.5, 44.6]	[22.5, 35.5]

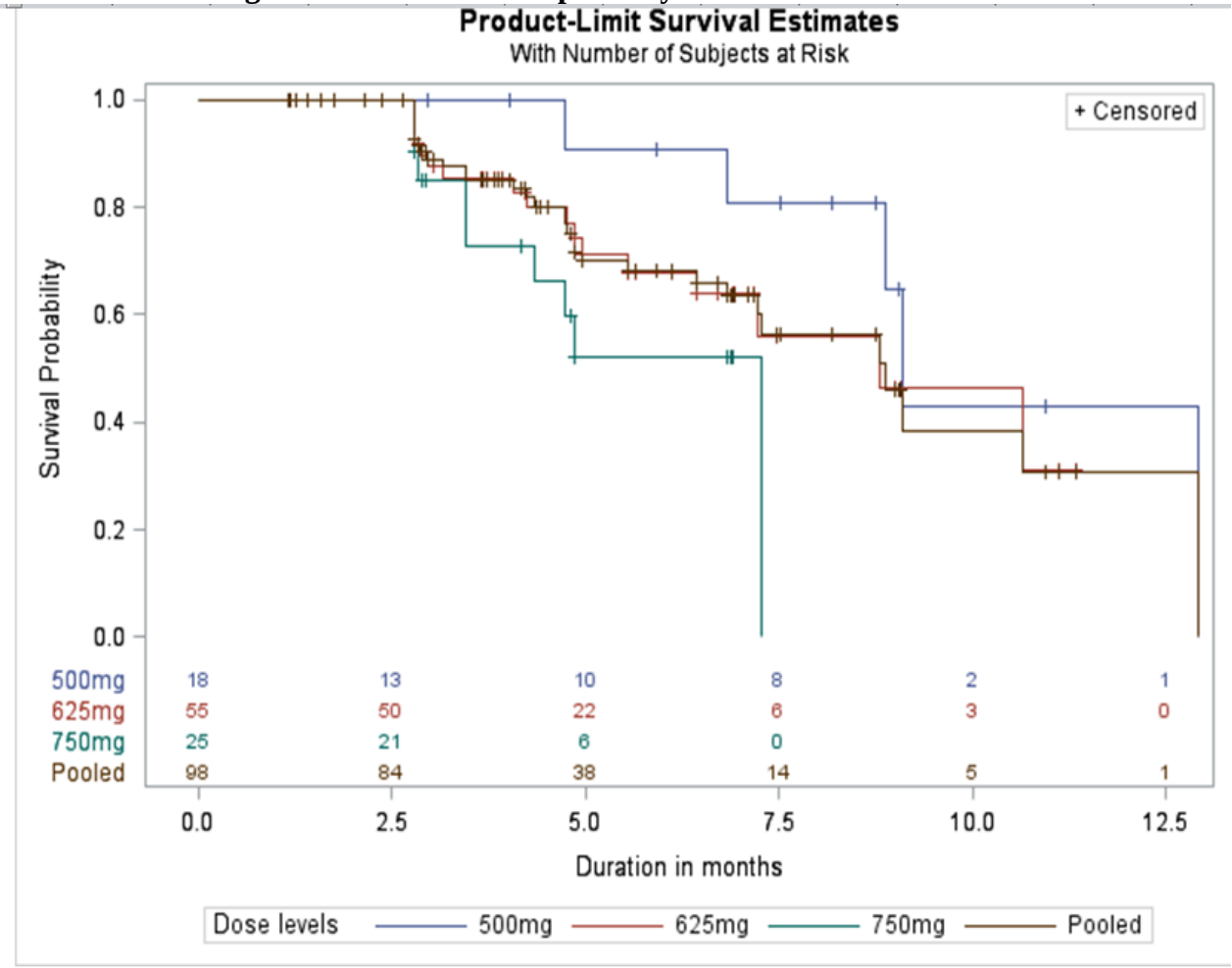
Source: Reviewer Table, ADORIRR IR39 2/25/2016 update *Abbreviations: n, N=number of patients.*
[a] *Not Evaluable tumor measure*
[b] *Missing tumor measure*
^ *Patients on 500/625/750 dose groups*

Table 9 Duration of Response by IRR Assessment

	500mg (N=18)	625mg (N=55)	750mg (N=25)	Pooled^ (N=98)
Disease Progression, n	5	17	9	31
Median duration of response (months) 95% CI	9.1[6.8,12.9]	8.8[6.4, not reached]	7.3[3.4,7.3]	8.9[7.2,12.9]

Source: Reviewer table, ADEFIRR Efficacy 90-Day update
^ *Patients on 500/625/750 dose groups*

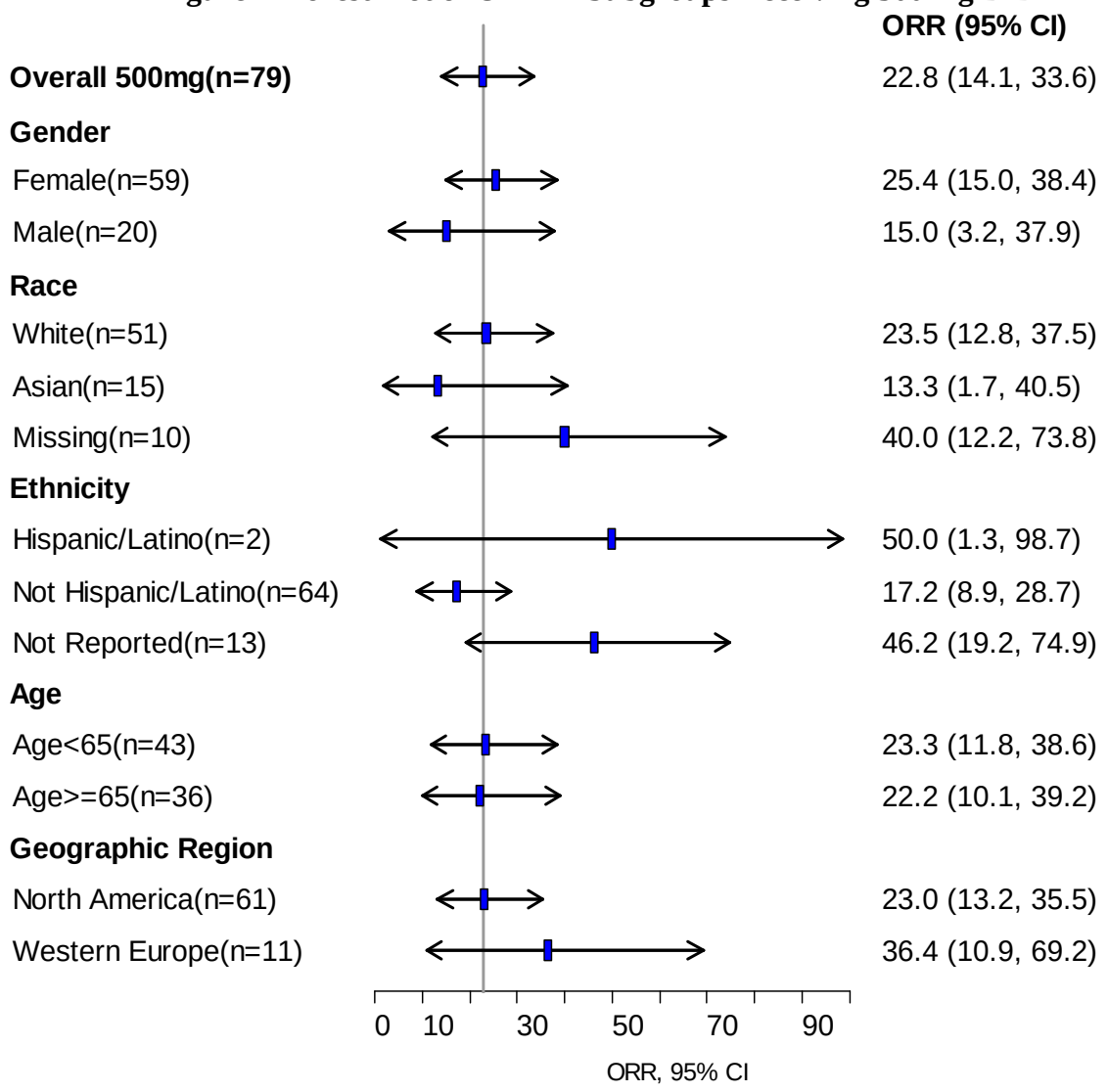
Figure 1 Duration of Response by Rociletinib Dose Cohort



Source: Reviewer Table, ADEFIRR Efficacy 90-Day update

Exploratory analyses of ORR were also conducted as a function of demographic and disease characteristics. The results of these analyses are depicted in the Forest plot (Figure 2).

Figure 2 Forest Plot of ORR in Subgroups Receiving 500 mg BID



Source: Reviewer Table, ADORIRR IR39 update

4.5.3 Safety

4.5.3.1 Safety Population

The safety analysis population consists of a total of 400 patients. Almost all patients (99.5%) had one or more adverse event. The overview of adverse events by severity and dose cohort is provided below in Table 10.

Table 10 Overview of Adverse Events Safety Analysis Population 019 (n= 400)

	500 N= 90 n (%)	625 N = 209 n (%)	750 N = 95 n(%)	1000 N = 6 n (%)	Total N= 400 n (%)
≥ 1 TEAE	90 (100)	207 (99)	90 (100)	6 (100)	398 (100)
≥ 1 SAE	40 (44)	97 (46)	45(47)	5 (83)	189 (47)
Fatal SAE (all)	12 (13)	35 (17)	14 (15)	3 (50)	64 (16)
Fatal SAE (non-progression)	3 (3)	2 (1)	2 (2)	2 (33)	9 (2)

Source: Reviewer table; ADAE 60-day Safety Update

Incidence of overall AEs and Grade ≥ 3AE

In the pooled analysis, the most common adverse events (by preferred term) included diarrhea (55%), nausea (52%), hyperglycemia (58%), and fatigue (44%). Refer to Table 11 for adverse events that occurred in 10% or more of patients in the safety analysis population. The incidence of adverse reactions commonly associated with EGFR targeted therapies is shown in Table 18.

Table 11 Common Adverse Events by SOC and Preferred Term (All Grades ≥10%)

	All Doses N= 400		500 BID N=90		625 BID N= 209	
SOC, Preferred Term	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Blood/ lymphatic system disorders						
Anemia	19	4	16	3	22	5
Thrombocytopenia	11	1	9	1	8	0
Gastrointestinal disorders						
Diarrhea	55	3	56	0	55	4
Nausea	52	4	50	3	52	3
Vomiting	30	4	29	7	32	2
Constipation	27	1	21	1	30	0
Abdominal pain	13	2	9	1	14	2
Dry mouth	10	0	12	0	8	0
Gastroesophageal reflux disease	9	0	12	0	8	0
General disorders						
Fatigue	44	5	47	4	41	5
Edema peripheral	13	0	16	0	12	0
Asthenia	12	3	13	2	11	2
Pyrexia	7	0	9	0	8	0
Infections and infestations						
Upper respiratory tract infection	**7**	0	12	0	6	0
Investigations						
Electrocardiogram QT prolonged	33	11	33	8	33	10
Weight decreased	26	2	27	0	19	1
AST increased	9	2	8	2	9	2
Platelet count decreased	6	<1%	10	0	5	<1%
Metabolism and nutrition disorders						
Hyperglycemia (SMQ/Narrow)	58	34	54	31	55	32

	All Doses N= 400		500 BID N=90		625 BID N= 209	
SOC, Preferred Term	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Decreased appetite	36	1	32	0	34	1
Hypokalemia	15	3	14	0	16	4
Hypomagnesemia	9	0	10	0	8	0
Dehydration	10	2	6	1	10	3
Musculoskeletal disorders						
Muscle spasms[B]	24	1	28	0	22	0
Back pain	12	1	9	0	14	1
Arthralgia	10	0	9	0	11	0
Nervous system disorders						
Headache	22	1	27	2	22	0
Dizziness	15	1	13	0	16	1
Respiratory disorders						
Dyspnea	19	2	19	2	18	3
Cough	19	0	22	0	20	0
Psychiatric disorders						
Insomnia	10	0	8	0	11	0

Source: Reviewer Table; ADAE 60-day Safety Update. [A]Patients with missing NCI CTAE Grade are excluded.
[B]There were no laboratory data to assess the incidence of rhabdomyolysis.

4.5.3.2 Serious Adverse Events

Serious adverse events were reported in 44% of patients who received rociletinib 500 mg BID; non-fatal serious adverse events were reported in 39% of patients. The incidence of serious adverse events, excluding malignant neoplasm progression and occurring in 2% or more of patients is outlined in Table 12. For patients who received rociletinib 500 mg BID, these events (by preferred term) are hyperglycemia (12%), vomiting (6%), pancreatitis (4%), and nausea (3%).

Table 12 Incidence of Non-Fatal SAEs by Dose (≥2%)

Preferred Term	All Doses N= 400	500 BID N= 90	625 BID N= 209
Hyperglycemia	8%	12%	6%
Pneumonia	4%	2%	3%
Pancreatitis	2%	4%	2%
Abdominal pain	1%	0	2%
Diarrhea	2%	2%	2%
Nausea	2%	3%	2%

Source: Reviewer table; ADAE 60-Day Safety Update

Less frequent serious adverse events in patients who received rociletinib 500 mg or 625 mg include Torsades the pointes, cataracts, diabetic ketoacidosis, QT prolongation, pulmonary

embolism, supraventricular tachycardia, cardiac arrest, cerebrovascular accident, transient ischemic attack, ventricular fibrillation, syncope, and sepsis.

4.5.3.3 Dose Modifications

The evaluation of dose modifications (reductions, dose delays, discontinuations) due to adverse reactions was based on data submitted in the safety datasets. Additional analyses of dose reductions were conducted based on data submitted to the NDA in response to information requests (IRs). Analysis using these data suggests that the incidence of dose reductions may have been under-represented in the safety datasets. In general, the findings reported here are based on the safety datasets except with regards to the analysis of dose reductions. Table 13 provides an overview of dose modifications based on the safety datasets.

Table 13 Dose Modifications for Adverse Events: Safety Analysis Population

	Interruptions	Reductions	Discontinuation
Number of patients (%)	226/400 (57%)	204/400 (51%)	85/400 (21%)
Median time to 1st event (days)	22 (1-504)	22 (1-427)	55 (1-538)
Within 14 days (+/- 3) of drug	99 (25%)	85 (21%)	17 (4%)

Source: Reviewer Table; ADTTE 60-Day Safety Update

4.5.3.4 Dose Interruptions

Dose interruptions were reported in 57% of patients. The most common adverse reactions leading to dose interruption in 5% or more patients are hyperglycemia (22%), QT interval prolongation (41%), nausea (10%), fatigue (8%), diarrhea (7%), vomiting (6%). Median time to rociletinib interruption was 22 days (range 1-504).

Table 14 Dose Interruptions (≥ 5%) by Preferred Term and Dose: Safety Analysis Population

Preferred Term	All Doses N= 400 n, (%)	500 mg N= 90 n, (%)	625 mg N= 209 n, (%)	750 mg N= 95 n, (%)	1000 mg N= 6 n, (%)
Hyperglycemia	87 (22%)	18 (20%)	39 (19%)	27 (28%)	3 (50%)
QT prolonged	41 (10%)	8 (9%)	23 (11%)	10 (11%)	0
Nausea	40 (10%)	6 (7%)	22 (11%)	11 (12%)	1 (17%)
Fatigue	30 (8%)	3 (3%)	15 (7%)	11 (12%)	1 (17%)
Diarrhea	28 (7%)	2 (2%)	20 (10%)	5 (5%)	1 (17%)
Vomiting	25 (6%)	6 (7%)	13 6%)	6 (6%)	0

Source: Reviewer Table: ADAE 60-Day Safety Update

4.5.3.5 Dose Reductions

In the safety analysis population, 51% of patients had one or more dose reductions due to adverse events. In these patients, the median time to first dose reduction was 22 days (range 1 to 427 days). At the 500 mg dose, 40% of patients had one or more dose reductions and the median time to first dose reduction was 21 days (range 3 to 308 days).

Additional analyses of dose reductions were conducted based on datasets submitted at FDA's request (IR-19 and IR-39). These analyses indicated that 218 (55%) of patients had one or more dose reductions, as shown in Table 15. Most patients (80%) had 1-2 dose reductions. Overall, 202/204 identified in the safety datasets as having dose reductions due to adverse events matched the patients in the additional dataset (i.e., 202/218 or93%) submitted per FDA's request. Among these 202 patients, the incidence of dose reductions by dose cohort is shown in Table 15.

Table 15 Incidence of Dose Reductions by Dose Cohort (Safety Population N= 400)

	Number of Dose Reductions n (%)					
Dose Cohort	**1**	**2**	**3**	**4**	**5**	**Total**
500 mg BID	21 (23%)	12 (13%)	3 (3%)	0	0	36(40%)
625 mg BID	54 (26%)	32 (15%)	11 (5%)	2 (1%)	0	99 (53%)
750 mg BID	22(24%)	18 (19%)	17 (18%)	5 (5%)	1 (1%)	63 (66%)
1000 mg BID	1 (17%)	0	3 (50%)	0	0	4 (67%)

Source: Reviewer Table REDDEL08 IR-39,EXRED019 IR-19, ADTTE 60-Day Safety Update

An analysis was conducted to determine whether the rate of dose reductions differed between the phases in which patients were enrolled (e.g., Phase 1 versus Phase 2). Among patients in both studies, a greater proportion (65%) of patients in Phase 1 of CO-1686-008 had dose reductions compared to patients in Phase 2 of CO-1686-008 and CO-1686-019 (53%).

Investigators did not apply a consistent and uniform approach to dose modification. An analysis of the dose modifications employed across the safety population is summarized in Table 16. Of note, 6% of patients with dose reductions also had dose escalation, defined as an increase in the total daily dose from dose prior to dose change.

Table 16 Characteristics of Dose Reductions

	Patients with Dose Reductions N= 218
Dose Reduction Category	**n (%)**
Decrement 125 mg BID[A]	154 (71%)
Decrements ≥250 mg BID	23 (11%)
Decrease to once daily dosing schedule, maintain same dose at each administration	30 (14%)
Decrease both schedule and dose administered	8 (4%)
More than 3 dose reductions	8 (4%)

Source: Reviewer Table REDDEL08 IR-39,EXRED019 IR-19.
[A]These patients excluded from other categories

The most common adverse events leading to dose reductions in 5% or more of patients in the safety analysis population are outlined in the table below.

Table 17 Incidence (≥ 5%) of Dose Reductions by Preferred Term and Dose

Preferred Term	All Doses N= 400 (%)	500 mg N= 90 (%)	625 mg N= 209 (%)	750 mg N= 95 (%)	1000 mg N= 6 (%)
Hyperglycemia	22	19	17	33	50
QT prolonged	11	9	11	13	0
Fatigue	9	2	9	16	17
Diarrhea	7	2	7	8	17
Nausea	6	3	5	11	17
Decreased appetite	6	2	6	8	17

Source: Reviewer Table; ADAE 60-Day Safety Update

4.5.3.6 Dose Discontinuations

Discontinuation of rociletinib due to adverse reaction occurred in 11% of patients. The most common adverse reactions that led to discontinuation of rociletinib in 1% or more of patients are QT prolongation (2%), pneumonia (2%), fatigue (1%), pneumonitis (1%), hyperglycemia (1%), and nausea (1%). Rociletinib was also discontinued in one patient each for sepsis, Torsade de pointes, ventricular tachyarrhythmia, cerebrovascular accident, and pulmonary embolism.

4.5.3.7 AEs Known to be Related to EGFR-TKIs

Adverse events known to occur among patients who are treated with EGFR-TKIs were assessed as events of special interest in the safety analysis population. The incidence of diarrhea was reported in 55% of patients, with serious or life-threatening (Grade ≥ 3) diarrhea occurring in 3% of patients. Composite terms which were based on aggregation of data from multiple MedDRA preferred terms were used to assess the incidence of the pulmonary, cutaneous, gastrointestinal, and ocular effects of rociletinib. The results of these analyses are below in Table 18.

Table 18 AEs Known to be Associated with Anti-EGFR Class of Drugs

	All Doses		500 mg		625 mg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
ILD/Pneumonitis	3%	1%	1%	1%	3%	1%
Rash	10%	<1%	9%	0	10%	<1%
Nail effects	1%	0	2%	0	<1%	0
Stomatitis/mucositis	4%	0	5%	0	4%	0
Diarrhea	55%	3%	56%	0	55%	4%
Cataracts	3%	1%	3%	0	2%	1%

Source: Reviewer table ADAE 60-Day Safety Update; ILD/pneumonitis (Acute respiratory distress syndrome, ILD, pneumonitis, radiation pneumonitis); Rash (Dermatitis acneiform, folliculitis, rash, rash macular, rash maculo-papular); Nail effects (Nail dystrophy, onychoclasis, onychalgia); Stomatitis/mucositis (Aphthous stomatitis, mucosal inflammation, stomatitis,); Cataracts (Cataract, posterior capsule opacification)

In addition, based on the toxicities observed during the rociletinib clinical development program, Clovis identified the following adverse reactions of particular interest in the evaluation of safety: QT interval (QTc) prolongation/Torsades de Pointes, cardiac arrhythmia (including ventricular arrhythmia), hyperglycemia, and acute pancreatitis.

4.5.3.8 QTc Prolongation

In the analysis of adverse reactions by MedDRA preferred term, QT prolongation was reported in 33% patients in the safety analysis population. Grade 3-4 QTc prolongation was reported in 11% of patients. There was one case of Torsade de pointes.

In the analysis of ECG data among the 400 patients in the safety analysis population, the mean baseline QTcF was 408 (Std Dev 19). After initiating rociletinib, 66 (17%) had QTc greater than 500 msec. Six patients had QTcF ≥ 580 (500 mg n= 1; 625 n= 2; 750 n= 3) including 2 patients who had QTcF >600. Table 19 provides an overview of QTc prolongation.

Table 19 Incidence of QT Prolongation: Safety Analysis Population

	500mg N= 90	**625mg N= 209**	**750mg N= 95**	**1000mg N= 6**	**Total N= 400**
Mean post-baseline QTcF, msec (Std D)	468 (43)	467 (44)	482 (45)	465 (28)	469 (39)
QTcF ≥ 481 msec, n (%)	17 (19%)	33 (16%)	35 (37%)	2 (33%)	87 (22%)
QTcF ≥501 msec, n (%)	13 (14%)	29 (14%)	24 (25%)	0	66 (17%)
Change from baseline >30 msec, n (%)	77 (86%)	167 (80%)	86 (91%)	6 (100%)	336 (84%)
Change from baseline >60 msec, n (%)	36 (40%)	79 (38%)	47 (49%)	3 (50%)	165 (41%)

Source: Reviewer table ADEG 60-Day Safety Update.

4.5.3.9 Cardiac Arrhythmia

In the safety analysis population, there were some cases of life-threatening arrhythmias as shown in Table 20.

Table 20 Cardiac Arrhythmias

Preferred Term	All Grades n (%)		Grade 3-4 n (%)	
Palpitations	9	(2%)	0	0
Syncope	7	(2%)	3	(1%)
Bradycardia	6	(2%)	1	0
Atrial fibrillation	5	(1%)	1	0
Sinus tachycardia	5	(1%)	0	0
Supraventricular tachycardia	3	(1%)	2	(1%)
Tachycardia	3	(1%)	0	0
Heart rate increased	2	(1%)	0	0
Sinus bradycardia	2	(1%)	0	0
Sudden death	2	(1%)	0	0
Arrhythmia supraventricular	1	0	0	0
Cardiac arrest	1	0	1	0
Torsade de pointes	1	0	1	0
Ventricular extra systoles	1	0	0	0
Ventricular fibrillation	1	0	1	0
Ventricular tachyarrhythmia	1	0	1	0
Ventricular tachycardia	1	0	0	0

Source: Reviewer Table ADAE 60-Day Safety Update

4.5.3.10 Hyperglycemia

The most common laboratory abnormality observed among patients receiving rociletinib is hyperglycemia. This finding is consistent with the observation of hyperglycemia in the analysis of adverse reactions reported by the investigator as a MedDRA preferred term. Patients with hyperglycemia up to Grade 3 were allowed to enroll in Studies CO-1686-008 and CO-1686-019.

To better assess the effect of rociletinib on glucose level, the evaluation of hyperglycemia was limited to patients with normal fasting glucose levels at screening and on the first day of treatment. Patients were not excluded if they were on anti-hyperglycemia medications such as metformin prior to initiating rociletinib.

A total of 217 patients (54%) had normal grade glucose at screening and at baseline. Among patients with normal glucose at screening and on Day 1 of Cycle 1, the incidence of hyperglycemia among the 214 patients who had baseline and follow-up evaluations while on treatment is shown in Table 21 below.

Table 21 Incidence of Hyperglycemia in Patients with Normal[A] Glucose at Baseline

	Shift During treatment (N= 214) n (%)					
	WNL	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total***
Baseline						
WNL	23 (11%)	82 (38%)	52 (24%)	56 (26%)	1 (<1%)	214

Source: Reviewer ADAE Table; 60-Day Safety Update; WNL- within normal limits. [A]Normal baseline defined as glucose at screening and cycle 1 day 1. *Analysis does not exclude patients who may have been receiving anti-hyperglycemics at baseline

Among patients with normal fasting glucose at baseline, 89% had one or more events of hyperglycemia during the course of treatment with rociletinib. The incidence of Grade 3-4 hyperglycemia among these patients is 27%. The incidence appears to be similar across rociletinib dose cohorts as shown in Table 22.

Table 22 Glucose Change from Baseline in Patients with NormalA Baseline Glucose

	Shift During Treatment n (%)				
Dose Cohort	**WNL**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
500 mg BID (N=48)	7 (15%)	15 (31%)	14 (29%)	11 (23%)	1 (2%)
625 mg BID (N=113)	10 (9%)	49 (43%)	25 (22%)	29 (26%)	0
750 mg BID (N=52)	6 (12%)	17 (33%)	13 (25%)	16 (31%)	0
1000 mg BID (N=1)	0	1(100%)	0	0	0

Source: Reviewer ADAE Table; 60-Day Safety Update; WNL- within normal limits;. [A]Normal baseline defined as normal glucose level at screening and in cycle 1 day 1. *Analysis does not exclude patients who may have been receiving anti-hyperglycemics at baseline

Overall, 195 patients (49%) in the safety analysis population were prescribed an anti-hyperglycemia medication following initiation of rociletinib. The first anti-hyperglycemia medication used following initiation of rociletinib was an oral agent in 94% of patients; metformin was the agent used in 87% of cases.

In an analysis of concomitant medications, concomitant use of an anti-hyperglycemia agent was reported in 215 patients (54%). Insulin was used in the management of hyperglycemia in 49 of the 215 patients (23%). Clovis noted that 35 of these 215 patients (16%) had a history of hyperglycemia prior to initiating rociletinib, as ascertained from the medical history.

There were 3 cases of diabetic ketoacidosis in the safety analysis population. These cases occurred in patients who received rociletinib 500 mg (n=1) and 625 mg (n=2). In two of the cases (Grade 4), rociletinib was discontinued. One patient was reported to have a history of hyperglycemia prior to study entry.

4.5.3.11 Pancreatitis

A composite definition incorporating several MedDRA preferred terms was used to assess the incidence of the pancreatitis. Overall, pancreatitis was reported in 15 patients (4%) as shown in **Table 23.** The majority (67%) had Grade 3-4 events that resolved with treatment interruption.

Table 23 Incidence of Pancreatitis

Dose Cohort	All Grades n(%)	Grades 3-4 n(%)
500 BID	5 (6%)	4 (4%)
625 BID	9 (4%)	6 (3%)
750 BID	1 (1%)	0

Source: Reviewer Table; 60-Day Safety Update

4.5.3.12 Deaths

The incidence of death occurring during or within 30 days of last administration of rociletinib was analyzed. Death due to an adverse reaction as the primary cause of death was reported in 9 patients. Five deaths were attributed to pneumonia, and one death each to sepsis and acute respiratory distress syndrome. There were two sudden deaths. Brief summaries of the clinical course of the patients who died suddenly are provided in Table 24.

Table 24 Narratives of On-Study Sudden Deaths

USUBID Dose	AE-Preferred Term	Study Day	Clinical Summary
008-116602 **625 mg**	Sudden death	4	57-year-old male. On study Day 1, tachycardia to 125 beats per minute (bpm) was noted. Pre- and post-dose ECG revealed sinus tachycardia with occasional ventricular premature complexes and non-specific T-wave abnormalities with no QTc prolongation. The patient's physical exam revealed ECOG PS 1, a tense abdomen, and weakness. The patient died at home 3 days after 1st dose of rociletinib. No autopsy was performed.
008-117705[A] **750 mg**	Sudden death	13	66-year-old female with a history of hypertension, lung, breast, and bone radiation ≥4 years prior to trial. On screening physical, ECOG PS 1, heart rate 44 bpm, blood pressure (BP) 134/63. On study Day 1, heart rate 87 bpm, Grade 3 hypertension (BP 172/86 mmHg), and ECG normal pre- and post-rociletinib. Patient was found dead at home on study Day 12. Per Clovis, probable date of death was the previous day. No autopsy was performed.

Source: Reviewer Table; ADAE 60-Day Safety Update

[A]Narrative provided study safety meeting 27 May 2014, patient's QTc at screening was 460 ms though cycle 1 day 1 pre-dose was 430-440ms. Protocol subsequently amended to exclude pts with QTc >=450 ms at baseline and HR <=55.

4.5.4 Summary of Draft Labeling Recommendations

FDA recommends the inclusion of a Boxed Warning for the risk of QTc prolongation leading to Torsades de pointes. FDA also recommends that labeling describe ECG monitoring of QTc interval at baseline and periodically while receiving treatment with rociletinib. FDA also recommends inclusion in labeling of Warning and Precautions subsections for QTc prolongation, hyperglycemia, interstitial ling disease/pneumonitis, pancreatitis, and cataracts.

4.5.5 Risk Mitigation

The incidence of QTc prolongation in the 400 patients who received rociletinib in studies CO-1686-008 and CO-1686- sudden death and Torsades de pointes have been reported. Given these findings, FDA has considered whether a Risk Evaluation and Mitigation Strategy (REMS) should be required to mitigate the risk of QTc leading to Torsades de pointes and to ensure that the benefits of rociletinib outweigh its risks, or whether prescribers can be sufficiently informed of the risk in product labeling alone and are capable of monitoring patients for QTc prolongation. If a REMS is required, this may consist of a communication plan to educate healthcare professionals on the safe use of rociletinib or could include other measures, such as mandatory prescriber certification. FDA has requested that Clovis submit a proposal for risk mitigation.

5 Clinical Pharmacology

The pharmacokinetics (PK) of rociletinib are characterized by a short half-life (3.7 hours), large variability (coefficient of variation up to 79% for AUC in patients), and saturated absorption at doses of 500 mg BID and higher. A standard high-fat meal increased rociletinib AUC by 54% and C_{max} by 21%. The aqueous solubility of rociletinib (1 mg/mL) decreases to less than 0.1 mg/mL at pH > 2; concomitant use of omeprazole decreases the systemic exposure by 70%.

There are two major clinical pharmacology issues: 1) dose selection; and 2) rociletinib metabolism and NAT2 genetic polymorphisms.

5.1 Dose Selection

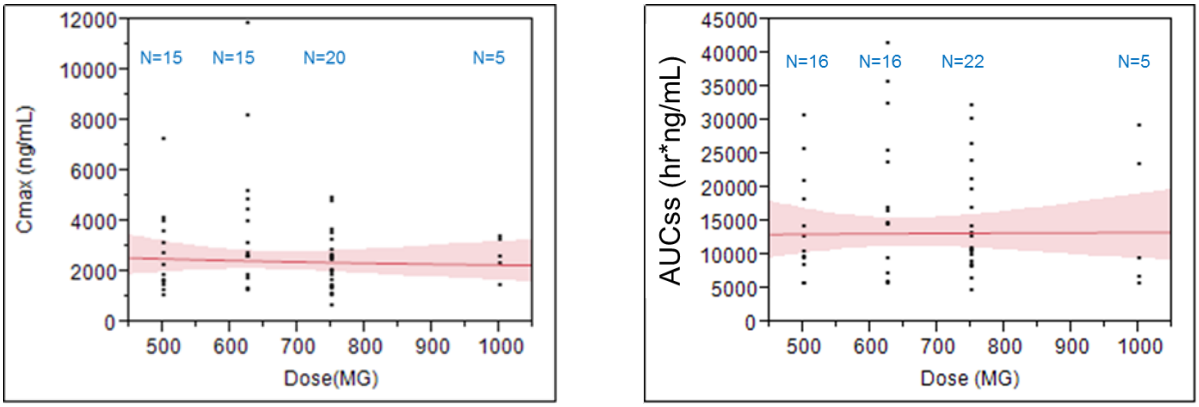
In the NDA and the proposed product labeling, Clovis initially proposed a recommended dose of rociletinib of 500 mg orally BID with food. Clovis subsequently proposed a change in the recommended dose to 625 mg BID with food after the Mid-Cycle Communication. This change is based on Clovis' interpretation of the IRR-confirmed ORR, which is higher at the 625 mg dose.

Based on the pharmacokinetic data and the exposure-response analyses for safety and efficacy, FDA proposes 500 mg orally BID with a meal as the recommended dose. The dose of 500 mg BID is recommended because of the similar systemic exposures of rociletinib across the dose range of 500 mg to 1000 mg BID. Furthermore, the exposure-response and exposure-toxicity analyses of the 500 and 625 mg doses indicate a similar ORR with overlapping confidence intervals for efficacy, and no major differences in safety.

5.1.1 Dose Proportionality of Rociletinib

Intensive PK data were collected at 500 mg, 625 mg, 750 mg, and 1000 mg BID on Day 15 of Cycle 1 from a subgroup of patients in Study CO-1686-008. A power model was applied to test dose proportionality (Figure 3) using $C_{max,ss}$ (N=58) and AUC_{ss} data (N=54) derived from a non-compartmental analysis. Based on this intensive PK data, FDA has concluded that there was no apparent relationship between dose and systemic exposure. Specifically, both $C_{max,ss}$ and AUC_{ss} remained unchanged as the dose increased from 500 to 1000 mg BID. The results of these analyses are summarized in Figure 3, below.

Figure 3 Dose Proportionality of Rociletinib

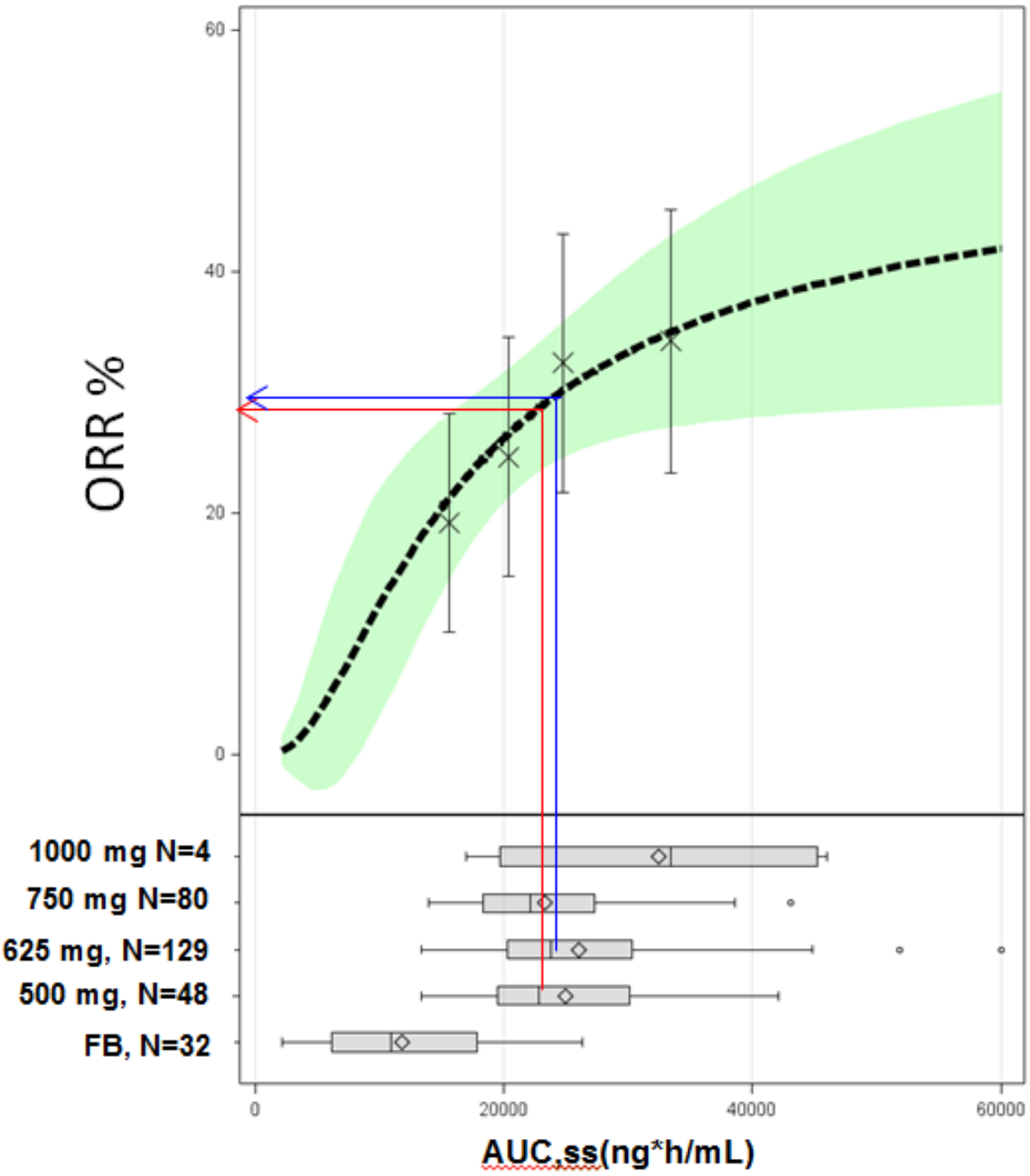


Note: Rociletinib C_{max} (left) and AUC (right) at steady-state following twice daily oral doses of rociletinib. $C_{max,ss}$ has a slope of -0.15 [-0.74, 0.45] (nominal p=0.69) and AUC_{ss} (nominal p=0.94) has a slope of 0.028 [-0.59, 0.65] from 500 to 1000 mg BID.

5.1.2 Dose/Exposure-Response Relationship for Efficacy

The relationship between ORR by IRR and drug exposure was characterized by a saturable (E_{max}) model (Figure 4). Based on this model, ORR was predicted at the population median AUC_{ss} for patients at each dose. The model predicts comparable efficacy at 500 mg and 625 mg. Using this modeling, the predicted ORRs (95% CI) for the 500 mg and 625 mg dose cohorts are 28.7% (23.4 to 34.0%) and 29.5% (24.0 to 34.9%), respectively. FDA has concluded that the observed differences in ORR by dose level are likely to be due to chance findings and/or differences in patients enrolled over time as doses were modified.

Figure 4 Exposure-Efficacy Relationship of Rociletinib between AUCss and ORR (IRR)

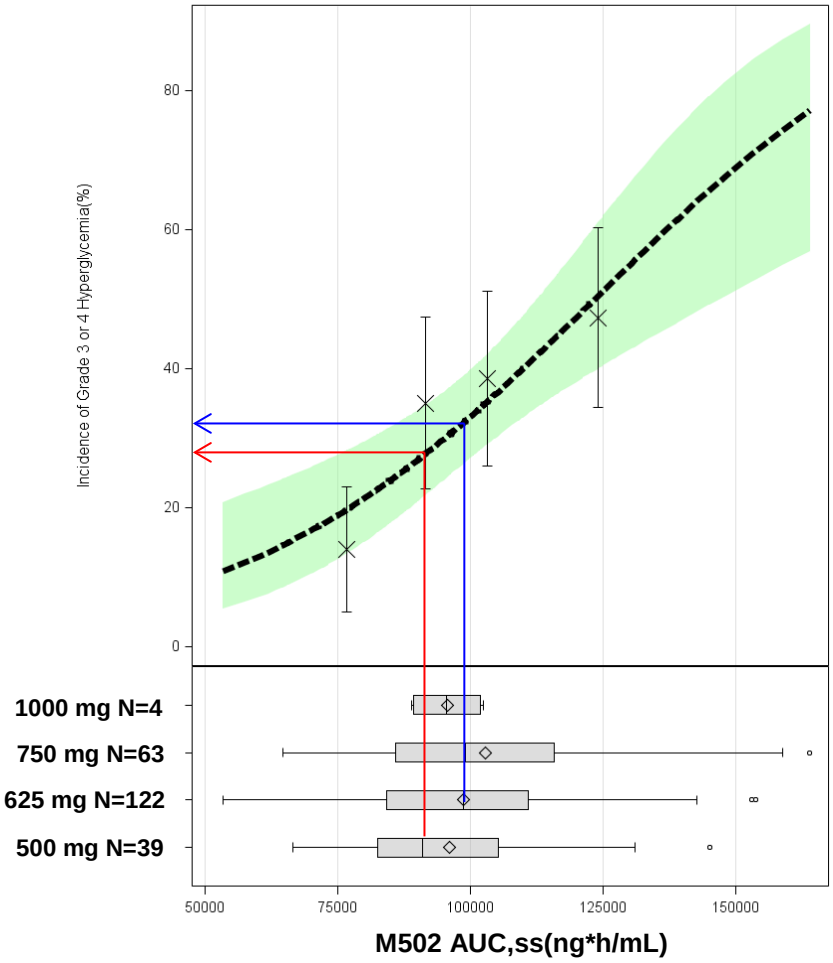


Note: The logistic E_{max} model shows the probability of ORR responder as a function of rociletinib AUC_{ss}. The median and 95% CI of the observed response rate versus rociletinib AUC_{ss} are represented by the black bars while the dashed black line and the green band represent the model predicted median and 95% interval ORR by IRR. The box plots at the bottom represent the distribution of rociletinib $AUC_{ss,}$ at each dose group (500, 625, 750, 1000 mg BID HBr formulation; and FB formulation).

5.1.3 Exposure-Response Relationship for Safety: Hyperglycemia and QTc Prolongation

Hyperglycemia and QTc prolongation were identified as clinically important adverse reactions of rociletinib. Two rociletinib metabolites, M502 and M460, have been identified as responsible for the adverse reactions of hyperglycemia and QTc prolongation, respectively. While the metabolites have limited activity against EGFR, M460 inhibits human ether-à-go-go-related gene (hERG; KCNH2) leading to QTc prolongation which is observed clinically. M502 inhibits both insulin-like growth factor 1 receptor 1 (IGF1R) and insulin receptor (INSR), and thus is considered responsible for the hyperglycemia observed clinically. There appeared to be a correlation between increasing M502 exposure ($AUC_{ss,}$ $C_{max,ss}$) and the incidence of Grade 3 or 4 hyperglycemia. At the population medians of the M502 AUC_{ss}, the predicted incidence (95% CI) for the 500 mg and 625 mg BID dose cohorts are 27.6% (21.5 to 34.6%) and 32.5% (26.5 to 39.2%) respectively (Figure 5).

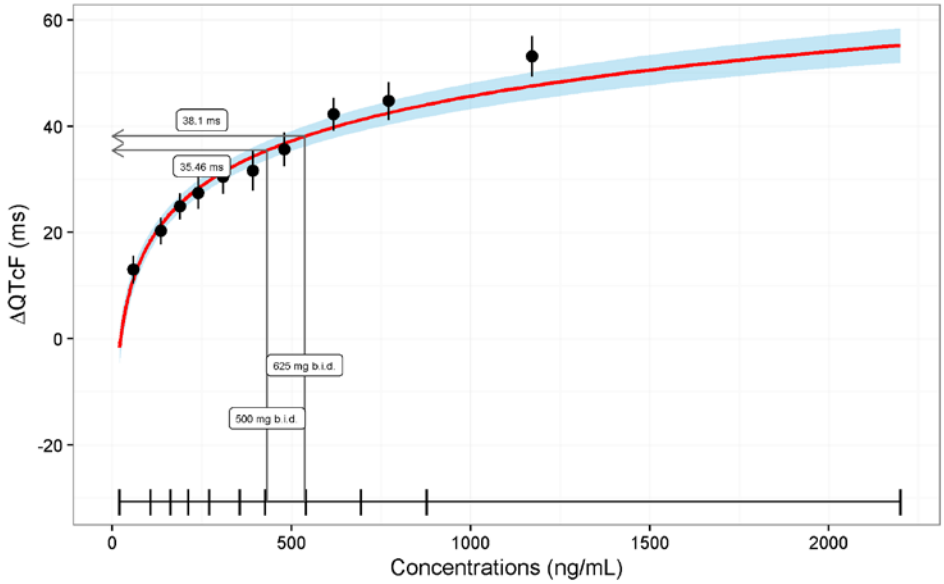
Figure 5 Exposure-Safety Relationship of M502 between $AUC_{ss,}$ $C_{max,ss}$ and Incidence of Grade 3 or 4 Hyperglycemia.



Note: The median and 95% CI of the observed response rate versus M502 exposures are represented by the black bars while the dashed black line and the green band represent the model predicted median and 95% interval of incidence of Grade 3 or 4 Hyperglycemia. The box plots at the bottom represent the distribution of M502 $AUC_{ss,}$ or $C_{max,ss}$ at each dose group.

Analyses of change in the QTcF interval based on electrocardiograms obtained in patients enrolled in Studies CO-1686-008 and CO-1686-019 indicate that prolongation in the QTc interval increases with dose (Figure 6). At the steady state C_{max} of M460, the QTcF prolongation was predicted to be a mean of 35 ms (90% CI: 34; 37) and 38 ms (90% CI: 36, 40) higher than baseline at 500 mg and 625 mg BID, respectively.

Figure 6 QTc Interval Prolongation



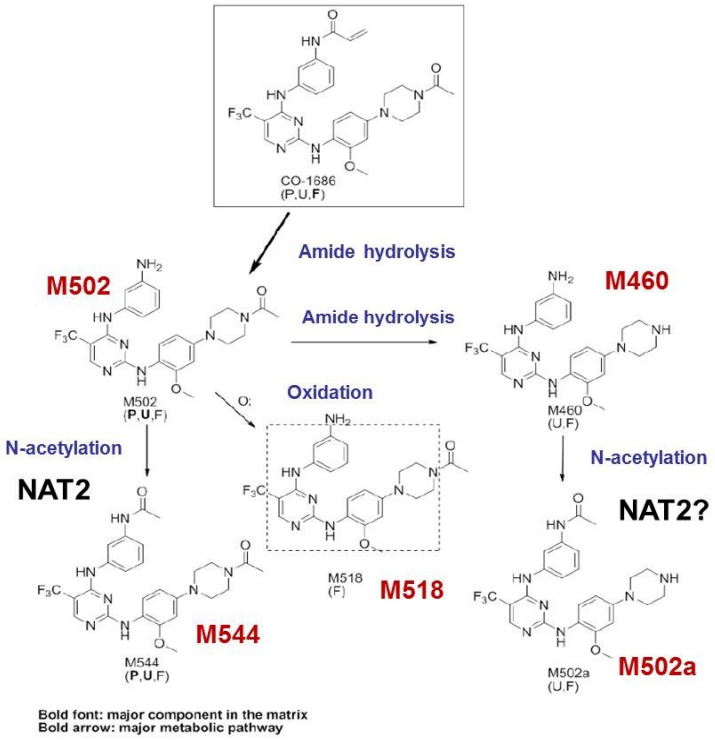
Note: The solid red line and blue band represent the predicted mean and 95% interval of change from baseline in QTcF. The arrows illustrate the steady state mean C_{max} following 625 or 500 mg BID and the corresponding increase in QTcF over baseline. The black dots and bars represent the median and 95% CI of the observed response rate in each quantile of the rociletinib AUCss.

5.2 Rociletinib Metabolism and NAT2 Genetic Polymorphisms

Rociletinib is eliminated mainly via fecal excretion, with 85.2% (65.2% unchanged) recovered in feces and 4.4% (0.4% unchanged) in urine. Metabolites M502, M544, and M460 account for 69%, 23%, and 3% respectively, of the total radioactivity in plasma, compared to 14% of rociletinib. Rociletinib has an elimination half-life of 3.7 hours, whereas the major rociletinib metabolites, M502 (which induces hyperglycemia) and M460 (which likely induces QTc prolongation), have half-lives of 20 hours and 51 hours, respectively. Compared to no apparent accumulation of rociletinib at steady state, M502 and M460 accumulated up to 5-fold and 58-fold, respectively, across doses ranging from 500 mg to 1000 mg BID with a meal.

Cytochrome P450 (CYP) isoforms play a minor role in the metabolism of rociletinib. Rociletinib undergoes extensive amide hydrolysis to metabolite M502 which is then converted to M460 via amide hydrolysis, or to M544 via N-acetylation (Figure 7). M460 is also further metabolized by N-acetylation. The acetylation of both M502 and M460 may be mediated by N-acetyltransferase (NAT2).

Figure 7 Proposed Biotransformation Pathway of Rociletinib in Humans



Source: Modified from IR-33 (date: 01/25/2016).

The NAT2 polymorphisms are known to result in variable levels of acetylation activity (e.g., slow vs. intermediate vs. rapid acetylators) within and across different racial and ethnic populations. About 40-60% of US Whites, African-Americans and Hispanics are slow acetylators Table 25.

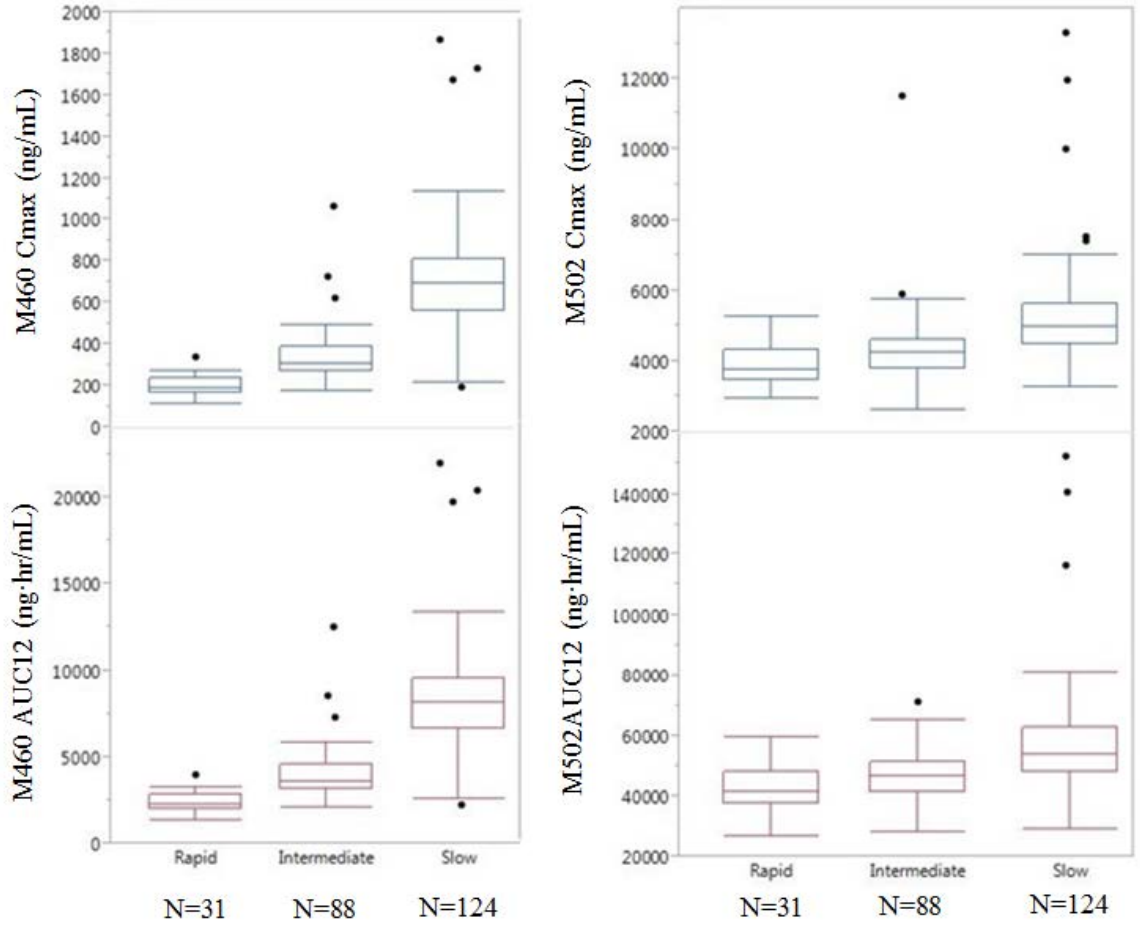
Table 25 Frequency of NAT2 Phenotypes across Racial and Ethnic Populations

NAT2 phenotype frequency %	Rapid acetylator	Intermediate acetylator	Slow acetylator
White	6-7	35-40	55-57
Black/African American	14-19	44-46	37-40
Japanese	44-45	45-49	7-10
Chinese [A]	23-30 [A]	21-45 [A]	25 [A]-52
U.S. Hispanic	14	32	54

Source: Modified from J Toxicol Environ Health B Crit Rev. 2009;12(5-6):440-7. Rapid = homozygous or heterozygous for NAT2*4 (wildtype), *12, or *13; Slow = homozygous or heterozygous for NAT2*5, *6, *7, or *14; Intermediate = heterozygous with one rapid and one slow NAT2 allele; [A] Source: Pharmacogenetics. 1997 Dec;7(6):503-14.

The NAT2 genotype and the inferred acetylator status (slow, intermediate or rapid) data was available for a subset of patients in Studies CO-1686-008 and CO-1686-019 (N=303/400). NAT2 slow acetylators had higher M502 and M460 exposures compared to intermediate or rapid acetylators (Figure 8). The higher exposures of M502 and M460 presumably lead to higher frequencies of hyperglycemia and QTc prolongation (Table 26). Similarly, dose modifications (reductions or interruptions) and dose discontinuations attributed to QTc prolongation were higher in slow acetylators compared to intermediate or rapid acetylators Table 26.

Figure 8 Summary of PK Parameters (C_{max}, AUC) for Metabolites M502 and M460 in Patients Treated with Rociletinib [500 to 1000 mg BID doses combined]



Source: Reviewer analysis of IR-38 (date: 02/19/2016) of population PK data of 243 patients with NAT2 acetylator status and corresponding PK values.

Table 26 Summary of Select Adverse Events, Laboratory Values, and Dose Modifications by NAT2 Acetylator Status [500 to 1000 mg BID Doses Combined]

	Rapid (N=35)	Intermediate (N=111)	Slow (N=157)
	n (%)		
Any AE Grade >=3	19 (54.3)	81 (73.0)	127 (80.9)
SMQ Cardiac Arrhythmia			
Overall	10 (28.6)	36 (32.4)	71 (45.2)
QTc AE [a]	9 (25.7)	29 (26.1)	64 (40.8)
Sinus bradycardia/Bradycardia	1 (2.9)	1 (0.9)	3 (1.9)
Cardiac arrest	0	0	1 (0.6)
Torsade de pointes	0	0	1 (0.6)
Ventricular extrasystoles	0	0	1 (0.6)
Ventricular fibrillation	0	0	1 (0.6)
QTcF by Central Lab ECG Assessment			
QTcF Post Baseline			
≥481ms	5 (14.3)	17 (15.3)	54 (34.4)
≥501ms	1 (2.9)	10 (9.0)	33 (21.0)
Two or more within 3 days ≥501ms	0	5 (4.5)	12 (7.6)
QTcF Change from Baseline			
>60ms	8 (22.9)	26 (23.4)	80 (51.0)
SMQ Hyperglycemia			
Hyperglycemia [b]	12 (34.3)	65 (58.6)	106 (67.5)
Glucose Values (Laboratory Testing)			
Any post baseline glucose >13.875 mmol/L (>250 mg/dL)	5 (14.3)	30 (27.0)	63 (40.1)
Any post baseline glucose >27.75 mmol/L (>500mg/dL)	0	1 (0.9)	5 (3.2)
AEs Leading To Dose Modifications (Reductions or Interruptions)			
Overall	16 (45.7)	66 (59.5)	119 (75.8)
QTc Prolongation [c]	1 (2.9)	9 (8.1)	28 (17.8)
AEs Leading To Dose Discontinuations			
Overall [d]	4 (11.4)	25 (22.5)	33 (21.0)
QTc Prolongation [c]	0	1 (0.9)	6 (3.8)

Source: Applicant's response to IR-34 (date: 02/04/2016) and IR-37 (date: 02/11/2016) including 303 patients treated at 500 to 1000 mg BID dose groups from Studies CO-1686-008 and CO-1686-019 with available NAT2 genotyping results; AEs = adverse events; SMQ = standardized MedDRA query; QTcF = QT interval corrected using Fridericia's method; [a] = incidences of sinus bradycardia/bradycardia, cardiac arrest, torsade de pointes, ventricular extrasystoles, and ventricular fibrillation are all included in the combined terms of QTc AE; [b] = incidences of blood glucose increased, glycosylated hemoglobin increased, glucose tolerance impaired, glucose urine present, hyperglycemia, and diabetic ketoacidosis are all included in combined terms of hyperglycemia; [c] = combined terms; [d] = includes AEs of disease progression.

NAT2 slow acetylators have increased M460 and M502 exposures and higher cardiovascular and metabolic adverse events. Because of these findings, additional investigation on the increased risk associated with NAT2 acetylator status and how this risk impacts the benefit risk profile of rociletinib, is ongoing.

6 Summary

In two, open-label, multi-dose, non-randomized studies (CO-1686-008 and CO-1686-019), patients with EGFR T790M mutation positive metastatic NSCLC who progressed on at least one EGFR-TKI were treated with rociletinib at doses ranging from 500 mg BID to 1000 mg BID. In patients who received 500 mg BID, the ORR is 23% (95% CI 14, 34) with a median DoR of 9.1 months. In patients who received 625 mg BID, the ORR is ORR is 32% (95% CI 25, 40) with a median DoR of 8.8 months. Although these are numerically different, based on the pharmacokinetic data, any differences in point estimates may be due to chance and differences in patient factors in these sequentially-enrolled cohorts. Overall, the exposure to rocelitinib is similar at doses of 500 mg BID and above. FDA also notes that the confidence intervals around the point estimates for ORR are wide and overlapping. Since there appears to be similar pharmacokinetics across the dose range of 500 to 1000 mg BID, pooling of the data observed in patients who received rociletinib 500 mg, 625 mg, or 750 mg BID; N=325) to achieve a better estimate of the treatment effect is considered appropriate. In the pooled analysis population, the ORR is 30% (95% CI 23, 36) with a median DoR of 8.9 months.

The toxicity profile was similar across the dose range (500 to1000 mg BID) studied. The proportion of patients requiring 3 or 4 dose reductions was higher for patients given 625 mg BID or higher. The number of dose reductions per patient was higher with increasing doses of rociletinib, likely because a dose reduction to 500 mg BID does not lead to decreased exposure to rociletinib or its major metabolites.

Common adverse reactions included diarrhea, hyperglycemia, fatigue, nausea, decreased appetite, QT prolongation, and vomiting. The most common Grade 3-4 adverse reactions were hyperglycemia and QTc prolongation. These adverse reactions frequently led to dose interruptions and dose reductions. The management of toxicity in Studies CO-1686-008 and CO-1686-019 was inconsistent. In particular, the approach to dose reductions varied significantly in Study CO-1686-008. Serious adverse reactions occurred in 47% of patients, most commonly due to malignant neoplasm progression (16%), hyperglycemia (8%) and pneumonia (4%). Seventeen percent of patients had QTc greater than 500 msec on at least one occasion. There were two sudden deaths (on Day 4 and Day 13) and one patient experienced Torsades de pointes.

Pharmacokinetic analyses revealed high variability of systemic exposure of rociletinib and its major metabolites. Rociletinib demonstrated non-linear pharmacokinetics, as systemic exposures did not increase when the dose increased from 500 mg to 1000 mg. Similar systemic exposure in terms of $C_{max,ss}$ and area under the curve at steady state (AUC_{ss}) was observed across doses ranging from 500 mg to 1000 mg, likely due to the low solubility of rociletinib. Rociletinib has an elimination half-life of 3.7 hours, whereas the major rociletinib metabolites, M502 (which induces hyperglycemia) and M460 (which induces QTc prolongation), have half-

lives of 20 hours and 51 hours, respectively. Compared to no apparent accumulation of rociletinib at steady state, M502 and M460 accumulated up to 5 fold and 58 fold, respectively, across doses ranging from 500 mg to 1000 mg BID with a meal. Exposure-response analyses indicate a plateau in response at exposures obtained with the 500 mg BID dose and above. Exposure-safety analyses suggest incidences of Grade 3 to 4 hyperglycemia and QTc prolongation increase with increased exposure. Additionally, as the acetylation of both M502 and M460 may be mediated by N-acetyltransferase (NAT2), patients who are classified as NAT2 slow acetylators based on NAT2 genotype have higher M502 and M460 exposures, and are at increased risk for QTc prolongation and hyperglycemia, although these risks also exist in patients who are classified as intermediate or fast NAT2 acetylators.

The key issues for this application are whether Clovis' proposed recommended dose of 625 mg BID is supported by the clinical and clinical pharmacology data, whether the antitumor activity of rociletinib as reflected by the ORR and DoR are reasonably likely to predict clinical benefit and are superior to available therapy, whether the risks (particularly with respect to QTc prolongation leading to Torsades de pointes) are acceptable in the intended population, and whether a REMS or other strategies may be necessary mitigate the risks of rociletinib and ensure safe use.

7 Issues for the Advisory Committee

The Division of Oncology Products 2 seeks the advice of the ODAC regarding the pending NDA for rociletinib on the following issues:

Efficacy: Is the observed ORR and DoR for patients treated with rociletinib better than available therapy for the proposed patient population, and are they likely to predict clinical benefit?

Safety: Are the risks of rociletinib, particularly QTc prolongation leading to Torsades de pointes and other serious ventricular arrhythmias, acceptable?

Overall Benefit-Risk Assessment: Is the benefit-risk profile favorable for the proposed patient population?

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