ROCILETINIB FOR THE TREATMENT OF T790M-POSITIVE MUTANT EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) NON-SMALL CELL LUNG CANCER (NSCLC)

BRIEFING DOCUMENT FOR THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

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ABBREVIATIONS

AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	the area under the curve
$AUC_{(0–24)}$	the area under the concentration versus time curve from time zero to 24 hours
$AUC_{(0–73)}$	the area under the concentration versus time curve from time zero to 72 hours
AUC_{ss}	the area under the concentration-time curve at steady-state
BID	twice daily
BMI	body mass index
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
CLcr	creatinine clearance
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration at steady state
$C_{min,ss}$	minimum observed plasma concentration
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EOP2	end of Phase 2
FB	free base
FFPE	formalin fixed paraffin embedded
GI	gastrointestinal
HBr	hydrobromide
hERG	Human ether-à-go-go-related-gene
IC_{50}	half maximal inhibitory effect
IDMC	independent data monitoring committee
IGF1R	insulin-like growth factor 1 receptor
ILD	interstitial lung disease
INSR	insulin receptor

INV	investigator
IRR	independent radiological review
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LOD	Limit of Detection
mDOR	median duration of response
mPFS	median progression-free survival
MOA	mechanism of action
MTD	maximum tolerated dose
NAT2	N-acetyl transferase 2
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-(L)1	programmed death-ligand 1
P-gp	p-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic
PopPK	population pharmacokinetics
PPI	proton pump inhibitor
PR	partial response
PROs	patient reported outcomes
PT	preferred term
RP3	randomized Phase 3
QD	once daily
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	standard deviation
SD	stable disease
SGLT2	sodium-glucose linked transporter 2
SMQ	Standardized MedDRA Queries
SOC	system organ class
$T_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	time from dosing at which C_{max} occurs
WT	wild type

1 EXECUTIVE SUMMARY

1.1 BACKGROUND

Lung cancer is the second most common serious cancer in the United States (US) and is the leading cause of cancer deaths worldwide (Herbst et al 2008). In the US, 85% of lung cancer cases are non-small cell lung cancer (NSCLC), the majority of which present as advanced/metastatic disease (stage IIIB or stage IV) at the time of diagnosis (Houston et al 2014). Approximately 15% of metastatic NSCLC patients in the US have activating epidermal growth factor receptor (EGFR) mutations. EGFR mutations are more common in patients who are female, never or light smokers, of Asian origin, and with adenocarcinoma histology (Linardou et al 2009).

Current guidelines recommend first and second generation EGFR tyrosine kinase inhibitors (TKIs) as initial treatment for patients with EGFR activating mutations (Mok 2014). Although these EGFR-directed TKIs are effective in many patients, the median progression-free survival (PFS) is only 9-14 months (Mok et al 2009, Rosell et al 2012, Sequist et al 2013). In 50 - 60% of patients, resistance to first-line EGFR inhibitor treatment is due to the emergence of a second EGFR mutation, T790M (Sequist et al 2011, Yu et al 2013).

Currently, treatment options for patients who have progressed on first-line EGFR-directed therapy are limited. Platinum doublet and single-agent chemotherapy are well-established treatment choices for recurrent NSCLC. While these agents provide some anti-tumor activity, they are associated with significant toxicity (see Section 2.1.2). The response rate to doublet chemotherapy containing platinum is less than 20% in Mutant EGFR NSCLC patients of European descent (Table 3). Importantly, only one-third of patients who progress on front-line EGFR TKIs will receive platinum-based chemotherapy. For patients deemed inappropriate for platinum-based chemotherapy, single agent cytotoxic chemotherapy is generally provided. Both docetaxel and pemetrexed are approved in this setting, providing response rates of less than 10% (Table 4). Although the immune checkpoint inhibitor nivolumab was recently approved in NSCLC, the efficacy of nivolumab in mutant EGFR patients remains unproven. In addition to fully approved agents in NSCLC, 2 novel agents received accelerated approval by the FDA (pembrolizumab and osimertinib) in 2015. Early data on treating mutant EGFR patients with PD-(L)1 inhibitors suggests that tumor responses in mutant EGFR NSCLC are lower than those observed in unselected patients. Osimertinib, a third generation EGFR TKI that specifically targets T790M mutation, was granted accelerated approval by the US Food and Drug Administration (FDA) based on single arm Phase 2 clinical data in November 2015. As neither osimertinib nor pembrolizumab have received full approval, clinical benefit with these agents has not been confirmed in randomized, controlled trials. In summary, there are limited effective treatment options for T790M-positive patients with advanced NSCLC.

Rociletinib is a novel, potent, small molecule, third generation TKI that irreversibly binds and inhibits EGFR with the common activating (L858R, Del19) and T790M resistance mutations. The proposed indication of rociletinib is for the treatment of patients with mutant EGFR NSCLC who have been previously treated with an EGFR-targeted therapy and have the T790M mutation as detected by an FDA approved test. The results from two Phase 2 studies show that rociletinib 625 mg BID treatment has a favorable benefit:risk profile in patients with recurrent T790M-positive mutant EGFR NSCLC based on clinically meaningful and durable responses and a well-established and acceptable safety profile in this patient population with terminal lung cancer.

1.2 ROCILETINIB PHARMACOLOGICAL CHARACTERISTICS

In pharmacokinetic (PK) studies, rociletinib was absorbed rapidly. The maximum concentration (C_{max}) was reached within 1.5 to 2.5 hours. Rociletinib showed little accumulation with repeated dosing, consistent with its short half life ($T_{1/2}$). The mean area under the curve (AUC) $_{(0-24)}$ accumulation ratio of rociletinib ranged from 0.75 to 1.17. The elimination half-life of rociletinib was 2.7 to 3.5 hours.

The 3 major metabolites of rociletinib in humans are M502, M544 and M460. Cytochrome P450s play only a minor role in rociletinib metabolism. At steady-state, exposure to M502 and M544 is higher than rociletinib, while the exposure to M460 is approximately half that of rociletinib. Metabolites M502 and M544 have a half-life of 20 hours, and M460 has a half-life of 51 hours. None of the rociletinib metabolites inhibits EGFR. However, rociletinib metabolites M502 and M460 showed biochemical and cellular potency against insulin-like growth factor 1 receptor (IGF1R) / insulin receptor (INSR) with M502 most likely the cause for hyperglycemia in some rociletinib-treated patients. Additionally, M460 appears to play a contributory role in the development of QT prolongation in some patients through the inhibition on the human ether-à-go-go-related-gene (hERG) channel. The polymorphic enzyme N-acetyl transferase 2 (NAT2) plays a role in the clearance of M502 and M460. Analysis of the NAT2 genotyping has determined that slow acetylator status is associated with a higher level of M460 and also a mild increase of M502 exposure.

Intensive PK data for rociletinib and its 3 major metabolites (i.e., M460, M502, and M544) was obtained from 18, 21, and 23 patients at 500 mg BID, 625 mg BID, and 750 mg BID doses, respectively. Population PK (PopPK) analyses were based on PK data from 371 patients in Study 008 and 54 patients in Study 019 (studies described in Section 1.3).

In PopPK analyses, weight, age, race, gender, and T790M status did not have a significant effect on rociletinib and metabolite exposure. Rociletinib and metabolite exposures were similar in patients with mild to moderate renal impairment and mild hepatic impairment compared to those with normal renal and hepatic function, respectively.

1.3 ROCILETINIB CLINICAL PROGRAM

To support the clinical development for rociletinib, 11 clinical studies have been initiated (Table 6). The efficacy and safety evidence to support accelerated approval of rociletinib comes from 2 ongoing, single arm, open label studies in patients with previously treated mutant EGFR NSCLC (Studies CO-1686-008 [referred to as Study 008 hereafter] and CO-1686-019 [referred to as Study 019 hereafter]):

- Study 008: A Phase 1/2, open-label, safety, PK and preliminary efficacy study of oral rociletinib in patients with previously treated mutant EGFR NSCLC
- Study 019: A Phase 2 open-label, multicenter, safety and efficacy study of oral rociletinib as second-line EGFR-directed TKI in patients with mutant EGFR NSCLC

In addition, a Phase 3 randomized confirmatory study of rociletinib (Study 020) is ongoing and described in Section 9.

Patients were selected by a tissue-based companion diagnostic (therascreen® EGFR RCQ PCR kit) to detect the T790M mutation for the studies reported here, and this companion diagnostic is currently under review by the Center for Devices and Radiological Health (CDRH).

1.3.1 Study 008

Study 008 is a Phase 1/2, 2-part, open-label study to assess efficacy, PK, and safety of rociletinib in patients with previously treated EGFR-positive NSCLC.

Phase 1

The primary objectives of Phase 1 were to evaluate safety and PK profile of rociletinib. Assessment of antitumor activity was a secondary endpoint. Patients in the Phase 1 study were required to have mutant EGFR disease based on local testing, however presence of the T790M mutation was not required. Patients were required to submit a tumor tissue biopsy during screening for retrospective central T790M evaluation. Prior treatment with EGFR directed therapy was required, and prior chemotherapy was permitted. Patients were treated continuously with oral rociletinib daily for a 21 day cycle and had assessments for safety and PK. In the initial stage of the Phase 1 part of the study, 57 patients were treated with a free base (FB) formulation of rociletinib (rociletinib FB) at doses ranging from 150 mg once a day (QD) up to 900 mg BID. Subsequently, the formulation was changed to the final rociletinib hydrobromide (HBr) tablet formulation (see Section 3.1), and an additional 54 patients were treated at doses of 500 mg, 625 mg, 750 mg, and 1000 mg BID for a total of 111 patients. A maximum tolerated dose (MTD) for rociletinib was not reached in the Phase 1 part of the study. Tumor assessments were performed every 6 weeks. The end of study evaluation was conducted 28 days after the last dose.

Phase 2

The primary objectives of the Phase 2 part of the study were to evaluate tumor response to rociletinib (objective response rate [ORR] and duration of response [DOR]) by investigator assessment in patients with a with a centrally-confirmed T790M mutation. Only rociletinib HBr was studied in the Phase 2 part. Secondary objectives included the evaluation of tumor response (ORR and DOR) by independent radiograpic review (IRR), and PFS (both IRR and investigator assessments) and the safety profile of rociletinib. Patients were treated with continuous oral rociletinib daily for each 21 day cycle, with no treatment interruption between cycles.

Patients were assigned to 1 of 3 treatment cohorts. Two of these cohorts were based on previous treatment history:

- Cohort A consisted of patients with progression of disease while on treatment with an EGFR-TKI. These patients were required to have evidence of T790M mutation in EGFR by the sponsor's central laboratory and were allowed to have multiple lines of prior EGFR-TKIs and prior chemotherapy, including intervening chemotherapy. In addition, for Cohort A, patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, and must not qualify for Cohort B. Thus Cohort A was enriched for later line patients.
- Cohort B consisted of earlier line patients with progression of disease while on treatment with only 1 prior EGFR-TKI. These patients were required to have evidence of T790M mutation in EGFR by the sponsor's central laboratory and were only allowed to have 1 prior line of chemotherapy, which must have been before the EGFR inhibitor. These patients were also required to have measurable disease by RECIST Version 1.1. Thus Cohort B was enriched for earlier line patients.
- Cohort C was added to study those patients with a positive local test who were T790M negative or unknown by central testing. Additional discussion of T790M-negative or unknown patients can be found in Section 9.1.1.

In the Phase 2 part of the study, no dose escalation beyond the starting dose was permitted. Dose reduction was allowed per investigator discretion in increments of 125 mg BID. Patients were treated continuously until disease progression or death. Tumor assessments were performed every 6 weeks. End of study evaluation was conducted 28 days after the last dose. Patients were followed every 2 months to capture subsequent therapy as well as survival data.

In Phase 2, patients were initially enrolled at 750 mg BID. However, lower doses appeared to provide better tolerability while maintaining objective response rates, and enrollment was subsequently opened at 500 mg BID and 625 mg BID to perform a comprehensive evaluation of dose, response and tolerability across multiple dose levels. No formal dose comparison analysis was performed in Study 008.

1.3.2 Study 019

Study 019 is an ongoing single arm, open-label, dual cohort, multicenter Phase 2 study designed to evaluate the safety and efficacy of rociletinib administered orally BID to patients with previously treated mutant EGFR NSCLC. The primary endpoint is ORR by independent radiological review.

Patients were treated with oral rociletinib daily for 28 day cycles, with no treatment interruption between cycles. Only rociletinib HBr was studied in Study 019. All patients in this study are earlier line patients requiring progression of disease while on treatment with only 1 prior EGFR-TKI which must have been the immediate prior therapy, discontinued within 30 days of starting rociletinib. These patients were also required to have evidence of T790M mutation in EGFR by the sponsor's central laboratory and were only allowed to have 1 prior line of chemotherapy, which could not be intervening chemotherapy, and measurable disease by RECIST Version 1.1. No dose escalation beyond the starting dose was permitted. Dose reduction was allowed per investigator discretion in increments of 125 mg BID. Patients were treated continuously until disease progression or death, and tumor assessments were performed every 8 weeks. The end of study evaluation was conducted 28 days after the last dose, and patients were followed every 2 months thereafter.

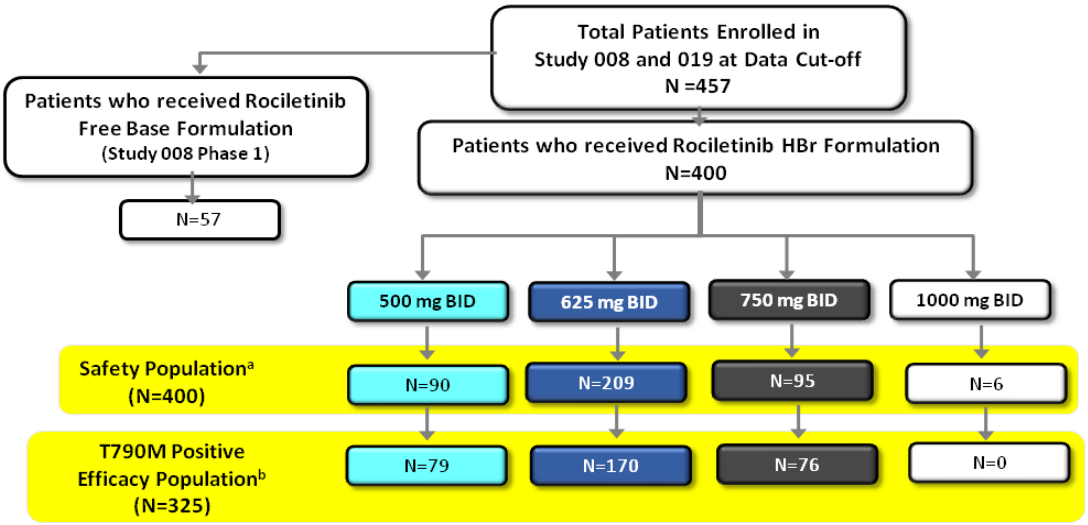
1.4 PATIENT SUMMARY AND CHARACTERISTICS

Overall, 457 patients received at least 1 dose of rociletinib FB or rociletinib HBr in Study 008 or at least 1 dose of rociletinib HBr in Study 019. Of the 457 patients, 57 patients received rociletinib FB in the Phase 1 part of Study 008 and are not included in the safety and efficacy analyses. The remaining 400 patients are the safety population, comprised of 90 (23%) patients who received rociletinib 500 mg BID, 209 (52%) patients who received rociletinib 625 mg BID, 95 (24%) patients who received rociletinib 750 mg BID, and 6 (2%) patients who received rociletinib 1000 mg BID (Figure 1).

The inclusion/exclusion criteria for patients in Study 008 and Study 019 are similar (see Section 3.6.1.4). Furthermore, patient demographics and disease characteristics are similar between the 2 studies and are consistent for patients with recurrent mutant EGFR NSCLC (see Section 3.7). Therefore, data from both studies are combined to allow for a robust assessment of safety and efficacy of rociletinib. The Safety Population included any patient who received at least 1 dose of rociletinib HBr, regardless of T790M status.

The T790M Efficacy Population contains only patients treated with the rociletinib who had evidence of the T790M mutation by the central laboratory test (T790M positive) and who had scans submitted for IRR of tumor response dosed at either 500 mg BID, 625 mg BID, or 750 mg BID.

Figure 1: Patient Enrollment in Study 008 and Study 019 for IRR Analysis



[a] Safety Population includes all patients who received ≥ 1 dose of rociletinib HBr
[b] T790M Positive Population includes patients with a centrally-confirmed T790M positive test who received ≥1 dose of rociletinib HBr and were eligible for IRR assessment of tumor response. Excluded are 34 patients across doses who were T790M-negative, 33 patients across doses who were T790M-unknown, and 4 T790M-positive patients each at 750mg BID and 1000mg BID doses who did not have an IRR assessment.

All patients had confirmed presence of EGFR activating mutation. The results of T790M status assessment using companion diagnostic test was similar across all dose groups. Overall, 83% of patients were confirmed as T790M-positive based on tumor tissue obtained at the time of progression but prior to entry into the study.

Rociletinib exposure, based on median number of cycles and median duration of treatment, was similar for patients who received 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID doses. As of the data cut-off date of 31 July 2015, the median duration of treatment was 157 days (5.2 months), 128 days (4.2 months), 176 days (5.8 months), and 213 days (7.0 months) in the 500 mg, 625 mg, 750 mg BID, and 1000 mg BID dose groups and 150 days (5.0 months) for all dose groups combined (Table 9).

The study population in Studies 008 and 019 was representative of the population of EGFR NSCLC patients with recurrent disease after standard EGFR TKI therapy in the US, and baseline characteristics were similar across the dosing groups (Table 10). The majority of patients were non-Asian (75% of those whose race was available) and enrolled in the US (89%). Most patients were female (70%), non-smokers (64%), and had a median age of 62 years. Overall, 99% of patients had Eastern Cooperative Oncology Group performance score (ECOG PS) 0-1, and 46% had a history of central nervous system (CNS) involvement. These characteristics indicate poor prognosis. Eleven percent of patients had a history of hyperglycemia.

Patients had recurrent disease with a median of 27 months from the time of the initial diagnosis and with the extent of the disease involving more than 2 sites in 83% of patients, with lymph node, CNS, bone, and liver being the most common sites of metastatic disease. Patients received a median of 2 prior therapies for lung cancer, including 38% of patients who received more than 1 prior EGFR TKI. The median number of days between stopping the prior EGFR TKI and starting rociletinib was 6 days.

Patient disposition, including reasons for discontinuation of therapy, was similar for patients who received 500 mg BID, 625 mg BID, 750 mg BID and all rociletinib dose groups combined. As of the data cut-off date, 39% of patients continued to receive rociletinib therapy. The main reason for treatment discontinuation was progressive disease (75%), followed by adverse events (AEs) in 14% of patients. Patient disposition was generally consistent in the Safety Population (Table 11) and T790M Positive Population (Appendix 11.1, Table 29).

Because there was no dose relationship identified based on IRR analysis (Figure 12), all doses evaluated by IRR (500 mg BID, 625 mg BID, and 750 mg BID) were combined to allow for a robust assessment of efficacy across several dose groups. Combined data are presented next to individual dose groups, where appropriate. For consistency, efficacy data by IRR is presented and discussed. Efficacy data by investigator assessment is provided in Appendix 11.3.

1.5 EFFICACY FINDINGS

Results for the primary endpoint of ORR for T790M Positive Population by IRR are shown in Table 1. Overall the ORR for the combined doses was 30.2% (95% CI 25.2 - 35.5%). The 95% confidence intervals (CI) were overlapping for the 500 mg BID, 625 mg BID, and 750 mg BID dose groups. The ORR were similar for 625 mg BID, 750 mg BID, and for all rociletinib doses combined: 32.4%, 32.9%, and 30.2%, respectively. The ORR for the 500 mg BID dose group (22.8%) was lower, and slightly below the lower boundary of 95% CI for ORR for all rociletinib doses combined (25.2%).

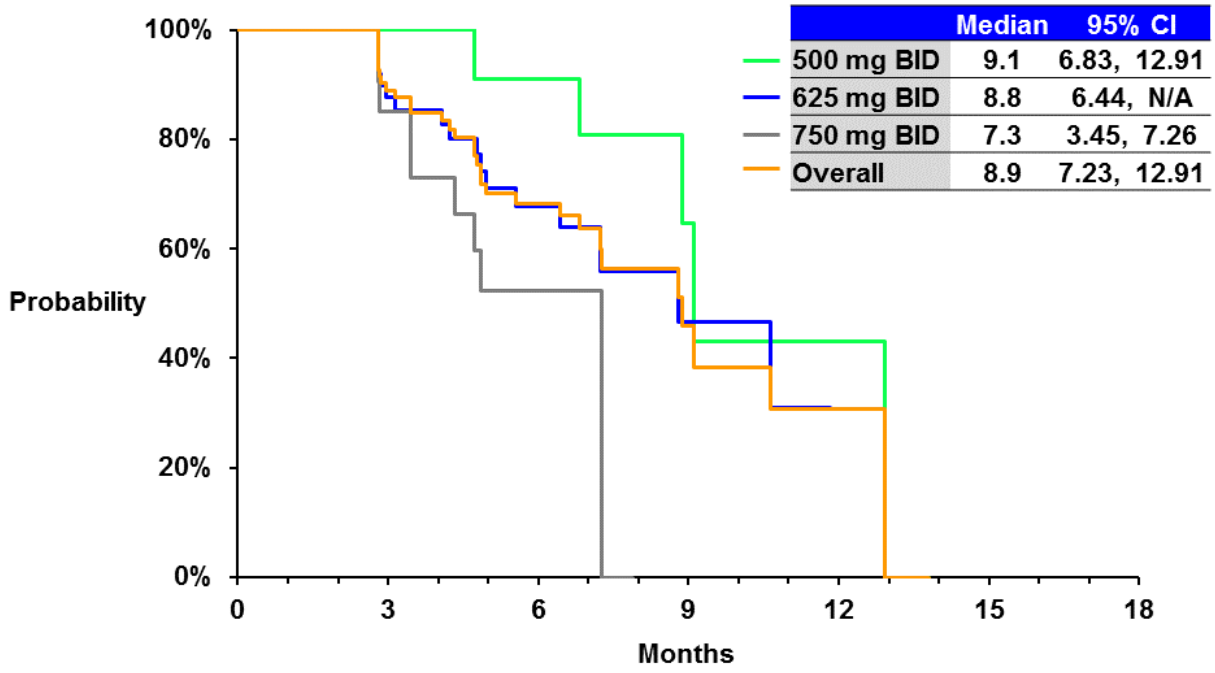
Table 1: Confirmed Objective Response Rate by IRR (T790M Positive Population)

	500 mg BID N = 79	**625 mg BID N = 170**	**750 mg BID N = 76**	**Overall N = 325**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Confirmed Response Rate	18 (22.8)	55 (32.4)	25 (32.9)	98 (30.2)
95% CI	14.1 - 33.6%	25.4 - 39.9%	22.5 - 44.6%	25.2 - 35.5%
Best Overall Confirmed Response				
CR	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
PR	18 (22.8)	54 (31.8)	25 (32.9)	97 (29.8)
SD[a]	38 (48.1)	56 (32.9)	25 (32.9)	119 (36.6)
PD	10 (12.7)	32 (18.8)	14 (18.4)	56 (17.2)
Not evaluable[b]	13 (16.5)	27 (15.9)	12 (15.8)	52 (16.0)

[a] All SD patients including SD ongoing without progressive disease.
[b] Patients without sufficient data to evaluate a tumor response due to one of the following reasons: patient died before the scan, patient discontinued before the scan, patient had no valid baseline lesions, or no data available for technical reasons. Patients s included in the denominator.

Patients who responded to rociletinib experienced significant DOR. For the rociletinib dose groups combined, the median DOR was 270 days (8.9 months) based on IRR, and for the individual dose groups, the median DOR was 277 days (9.1 months), 268 days (8.8 months), and 221 days (7.3 months) for 500 mg BID, 625 mg BID and 750 mg BID, respectively (Figure 2).

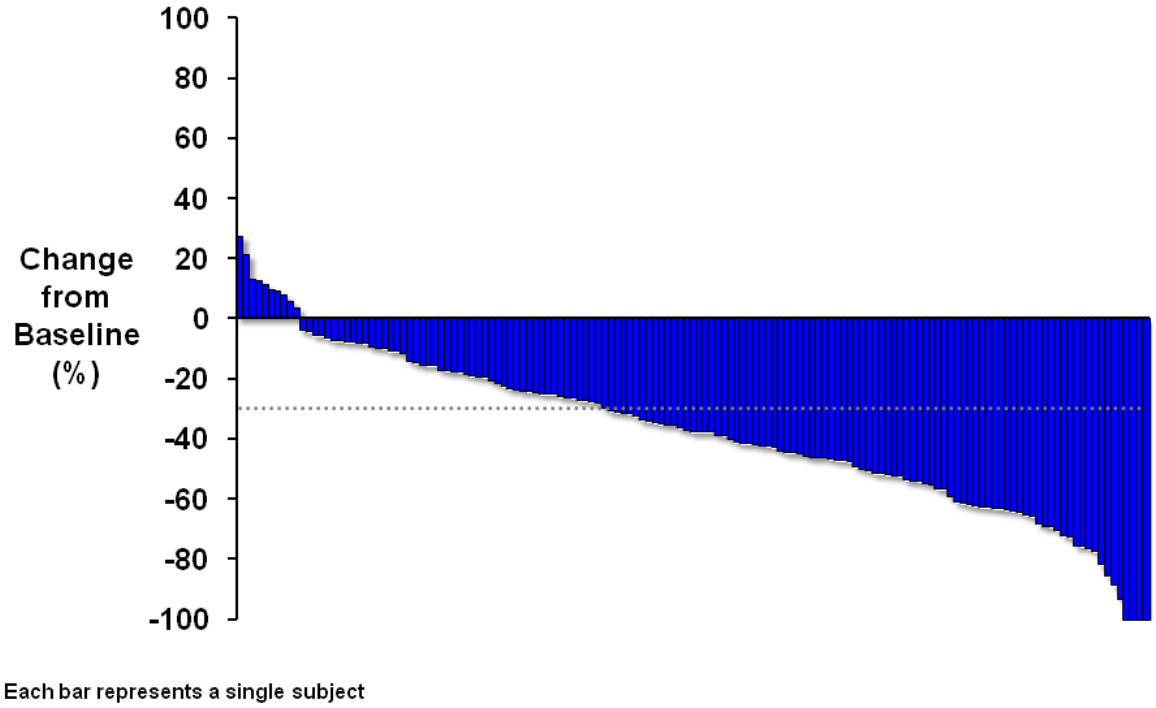
Figure 2: Duration of Confirmed Response by IRR at 500 mg BID, 625 mg BID and 750 mg BID and All Doses Combined (T790M Positive Population)



Abbreviations: BID = twice daily; CI = confidence interval.

The direct result of anti-tumor activity is a reduction of measurable disease evident by tumor target lesion reduction. In the largest dose group, 625 mg BID, 149 patients (91.5%) of the 163 patients with target lesions present at baseline experienced target lesion reduction when compared to baseline based on IRR assessments (Figure 3).

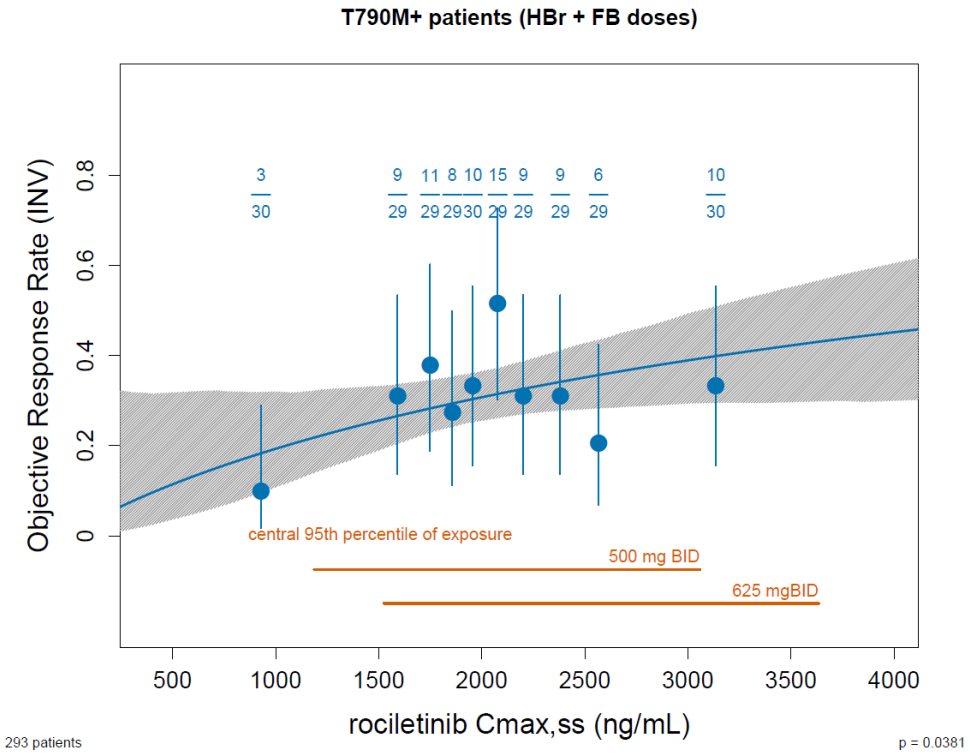
Figure 3: Best Response in Sum of Target Lesions per RECIST as Assessed by IRR Reviewer 1



Note: Patients whodid not have target lesions were excluded from this analysis. Each bar represents a single patient. Patients with zero percent change from baseline are shown as 0.5 for visual clarity.

Dose response analysis by dose in T790M-positive patients in the rociletinib HBr 500 mg BID, 625 mg BID, and 750 mg BID dose groups, showed that there is a trend of increasing ORR with dose, however it is not statistically significant. No significant relationships were identified with age, sex, weight, BMI, race, or history of hyperglycemia. However, ORR correlated significantly with rociletinib dose when all doses, including all doses that had been studied in the Phase 1 dose escalation part of the study using rociletinib FB, were included in the analysis. The PopPK-model-predicted-rociletinib exposure at steady state shows significant correlation between ORR and rociletinib $C_{max,ss}$ (Figure 4). The model also showed that at the starting dose of 500 mg HBr BID, a higher percentage of patients have lower rociletinib exposure than for the 625 mg HBr BID dose. Taken together, these data suggest that the exposures associated with the 500mg BID dose may be at the lower end of the range required for antitumor activity.

Figure 4: Exposure-response Relationship Between Confirmed ORR by Investigator Assessment and $C_{max,ss}$ in T790M-positive Patients.



Note: A univariate logistic regression relationship with the log of rociletinib $C_{max,ss}$ is shown by the solid blue line with the gray shaded area representing the 95% confidence interval, visualized on a linear x-axis. A total of 90 events are shown for 293 patients. Each solid circle represents the ORR in each of 10 equally sized bins (~30 patients each). The error bars on each point are the 95% confidence intervals calculated using the Clopper-Pearson method. The ratios at the top of the figure are the number of events (numerator) and total number of patients (denominator) in each bin of exposure.

In summary, rociletinib demonstrated clinically meaningful and durable responses in T790M-positive Mutant EGFR NSCLC patients with recurrent disease across the dose groups. Overall, the ORR was 30.2% (95% CI 25.2 – 35.5%) for rociletinib doses combined (n=325). The ORR and 95% CI were similar between the 625 mg BID dose group and the rociletinib doses combined (32.4% [95% CI 25.4 - 39.9%] and 30.2% [95% CI 25.2 - 35.5%], respectively). Similar findings were reported based on the investigator assessment of ORR. A PopPK model that assessed ORR across all doses of rociletinib administered showed a significant association between rociletinib dose and tumor response rate. In addition, the model-predicted rociletinib exposure at steady state shows significant correlation between ORR and rociletinib $C_{max,ss}$. The model also revealed that at the starting dose of 500 mg HBr BID, a higher percentage of patients have rociletinib exposure in the lower end of the range than for 625 mg HBr BID dose.

1.6 SAFETY FINDINGS

The New Drug Application (NDA)dataset contains 400 patients who had initiated treatment with rociletinib 500 mg BID (n=90), 625 mg BID (n=209), 750 mg BID (n=95), or 1000 mg BID (n=6) (Table 13). The median duration of treatment in this safety population was 149.5 days (4.9 months) and ranged from 1 day to 571 days (18.8 months) across doses. Across all doses, 40% of patients were treated with rociletinib for longer than 6 months.

Almost all patients treated with rociletinib reported 1 or more treatment-emergent adverse events (AEs) regardless of causality. The rate of AEs leading to discontinuation was similar across all doses (21% overall) and included 38 (45%) events of disease progression across all doses. The rate of serious adverse events (SAEs) overall across doses was 47%. Thirteen percent, 17%, and 15% of patients experienced a AE with an outcome of death in the 500 mg BID, 625 mg BID, and 750 mg BID dose groups, respectively. Overall 16% of patients experienced an AE with an outcome of death; however, 86% of these reported deaths were related to disease progression (Table 13).

The most common TEAEs were diarrhea, nausea, hyperglycemia, and fatigue across all doses (Table 14). Skin effects that are seen with non-selective EGFR inhibitors, including acneiform rash, stomatitis and paronychia, were not commonly observed. This lack of effect confirms the wild type (WT) sparing profile of rociletinib. The most common TEAEs Grade 3 or higher by PT were hyperglycemia, electrocardiogram QT prolonged, fatigue, and anemia (Table 15). The majority of these events were Grade 3 and Grade 4 events were less frequent.

Overall, 51% of patients experienced TEAEs leading to dose reduction. TEAEs that led to dose reduction or interruption of treatment, regardless of causality, are presented for all dose groups in Table 16. The most common TEAEs leading to dose reduction were hyperglycemia, electrocardiogram QT prolonged, nausea, diarrhea, and fatigue.

Approximately 21% of patients discontinued rociletinib across all doses (Table 17), and about half (49%) of treatment discontinuations were due to events of disease progression. Discontinuation rates for other events, including QT prolonged and hyperglycemia were low and similar across doses (3% and 1%, respectively).

Overall, 47% of patients reported SAEs across all dose groups (Table 18). The most common SAE across all doses was progression of the underlying lung cancer (preferred term neoplasm progression), with 16% of patients experiencing the SAE overall. Aside from hyperglycemia in the 500 mg BID group (13%), all other SAEs occurred in less than 10% of patients.

Overall, 16% of patients experienced at least 1 AE with an outcome of death across dose groups (Table 19). Fifty-five of 64 (86%) of these events were related to disease progression and were judged to be unrelated to rociletinib treatment by the investigator. Additionally, 5 patients died of pneumonia, 1 of sepsis, 1 of aspiration, and 2 patients died with no cause identified. One patient where the investigator reported cause of death was disease progression had experienced a ventricular tachyarrhythmia on the day of death (see Appendix 11.5.3).

1.6.1 Adverse Events of Special Interest

1.6.1.1 QTc Prolongation

Rociletinib causes QT prolongation. With rociletinib, this effect is caused by the metabolite, M460 (Section 3.4.2.2). A comprehensive electrocardiogram (ECG) monitoring program was included in the clinical trials, and all ECGs were collected and analyzed centrally. More than 25,000 individual ECG tracings were included in the NDA. The frequency of QTcF changes based on central laboratory evaluation are summarized in Table 23. Change in QTc >60ms increased with increasing dose. For other parameters, the QTc changes at 500mg BID and 625mg BID were similar, with a higher frequency of events at 750 mg BID. QTc >500 ms was observed in 13% of patients across doses. QTc prolongation was evident by Day 15 of treatment (Figure 16) and generally did not increase further. The effect on QTc is reversible once rociletinib is stopped.

Overall 40% of patients experienced a AE of QTc prolongation across all doses, with 13% reported as Grade 3 or higher. Thirteen percent of patients had dose modifications, and 3% discontinued treatment due to TEAEs of QTc prolongation. There were 3 SAEs of ventricular tachyarrhythmia, which is an important clinical sequel of QTc prolongation. These events all occurred in the 625mg BID dose group. Two patients with ventricular tachyarrhythmia recovered, and the other patient was successfully converted to sinus tachycardia but died on the same day (see Appendix 11.5).

There were 2 unexplained deaths (1 at 625mg BID and 1 at 750mg BID). Both were judged related to rociletinib by the investigators (see Appendix 11.5).

A risk minimization strategy has been developed to address QT prolongation. The strategy contains 5 elements. First, patient selection criteria have been identified. Proposed labeling will contain clear guidance on which patients are not suitable for rociletinib based on baseline risk factors that increase the risk of QT complications. Second, ECG monitoring should be conducted during therapy. Data shows that the ECG effect is stable by Day 15, so the proposed product labeling recommends ECG monitoring at baseline, after 15 days of therapy, and periodically thereafter. Third, patients should be educated on the effect of electrolyte depletion on the risk of QT prolongation. The proposed label contains a warning that electrolytes should be checked and normalized before starting therapy and whenever clinically indicated (e.g. should the patient develop persistent or severe diarrhea). Fourth, co-administration of

drugs that cause QT prolongation should be avoided while taking rociletinib. Fifth, the proposed label contains clear guidance on when to interrupt rociletinib for prolonged QTc and how to restart. Additional information on proposed labeling and risk management is provided in Section 8, and discussions are ongoing between the sponsor and FDA regarding content of the risk minimization plan and the implementation method.

1.6.1.2 Hyperglycemia

Hyperglycemia was the most common AE associated with rociletinib, occurring in 58% of patients across the dose groups (Table 21). Grade 3 and above hyperglycemia was reported in 34% of patients across the dose groups. Most of the Grade 3 events occurred early in treatment. Twenty-four percent and 23% of patients in the 500 mg BID and 625 mg BID dose groups, respectively, required dose modification, compared to 47% and 50% in the 750 mg BID and 1000 mg BID dose groups. Across dose groups, 40% to 50% patients reported use of at least 1 glucose lowering medication while taking rociletinib (Table 22).

One percent of patients discontinued rociletinib because of hyperglycemia, and 9% of patients experienced SAEs of hyperglycemia across dose groups. These data suggest that hyperglycemia was managed effectively in most cases by following guidance that was developed once the mechanism of action (MOA) was understood.

Because most cases of Grade 3 or higher hyperglycemia occurred early in treatment, regular glucose monitoring in the initial weeks of therapy followed by periodic monitoring can effectively manage potential hyperglycemia. Hyperglycemia may be managed with hypoglycemic agents that are effective against insulin resistance, such as metformin. Rociletinib dose reductions are recommended for symptomatic or severe events.

1.6.1.3 Interstitial Lung Disease

Interstitial lung (ILD) disease is a well-characterized class effect of EGFR inhibitors and other TKIs. The incidence of ILD MedDRA standardized medical queries (SMQ) associated with rociletinib falls within the expected range, with 11 (2.8%) cases observed. Nine cases in the ILD SMQ were pneumonitis with 6 (2.9%) cases in the 625 mg BID and 3 (3.2%) in the 750 mg BID dose groups. Four of the 11 total cases resulted in discontinuation of rociletinib.

1.6.1.4 Other Adverse Events of Special Interest

Fifteen patients (4%) reported an AE of acute pancreatitis, of which 10 (2.5%) were Grade 3 or higher.

Cataract is a late effect of rociletinib treatment, as the median time to cataract was 241 days. At the time of the data cutoff for the NDA 60-day Safety Update, there were 12 patients (3%) with cataract(s) reported across all doses. As this can be a very late onset event, the NDA database was re-analyzed with a cut-off date of January 2016, and there were a total of 41 patients (10%) with cataracts. The sponsor

will propose that the labeling, including patient information labeling, will advise of the risk of cataract formation and of the potential long latency, and that patients who develop visual disturbance should be referred for ophthalmological assessment.

1.6.2 Safety Conclusions

Overall, rociletinib has a well-defined, manageable and differentiated safety profile due to its targeted MOA. Thirty-seven percent of patients had treatment duration greater than 6 months. Prescriber education will assist management of events of hyperglycemia and QTc prolongation. Awareness of these effects will enable appropriate patient selection and implementation of the recommended management strategies that reduce the risk of potentially serious sequelae.

1.7 SELECTION OF RECOMMENDED DOSE

The sponsor has selected rociletinib 625mg BID as the recommended dose based on the following rationale:

While there were no statistically significant differences in the efficacy results (ORR, DOR) based on investigator or IRR at 500 mg BID and 625 mg BID doses (Table 1, Figure 2), for IRR, the 95% CI were overlapping for the 500 mg BID and 625 mg BID dose groups. The ORR by IRR was similar for 625 mg BID and for all rociletinib doses combined: 32.4% and 30.2%, respectively (Table 1). The ORR for the 500 mg BID dose group (22.8%) was lower, and was slightly below the lower boundary of 95% CI for ORR for all rociletinib doses combined (25.2%). While efficacy was demonstrated for rociletinib at and above 500 mg BID, confirmed responses were not observed during Phase 1 in patients who received rociletinib FB below the 900 mg BID dose levels (doses equivalent to or below 396 mg BID HBr, see Section 4.4 for details) (Figure 13). This finding suggests that a threshold of exposure is needed for response, and that the threshold of exposure lies between exposure achieved with 500 mg BID and that achieved with the next lowest doses studied in Phase 1.

No significant exposure response relationship was identified based on IRR data (500 mg BID, 625 mg BID, 750 mg BID) (Figure 12). However, ORR correlated significantly with rociletinib dose when all doses, including all doses that had been studied in the Phase 1 dose escalation part of the study using rociletinib free base , were included in the analysis. The PopPK-model-predicted-rociletinib-exposure at steady state shows significant correlation between ORR and rociletinib $C_{max,ss}$ (Figure 4). The model also showed that at the starting dose of 500 mg HBr BID, a higher percentage of patients have lower rociletinib exposure than for the 625 mg HBr BID dose (see Section 4.4 for details). Taken together, these data suggest that the exposures associated with the 500mg BID dose may be at the lower end of the range required for antitumor activity (Figure 4). Consistent with these results, the point estimate for ORR is higher at 625 mg BID as compared to 500 mg BID (32.4% vs 22.8%) (Table 1). It is notable that the

lower boundary of the confidence interval at 625 mg BID is 25.4% whereas the lower boundary of the confidence interval at 500 mg BID is 14.1%.

The safety profile of rociletinib was generally similar at 500 mg BID and 625 mg BID (Table 13) and this includes the common treatment-emergent adverse events (AEs) of QT prolongation and hyperglycemia. A proposed comprehensive risk management strategy is required for all patients taking rociletinib, in order to minimize the risk of serious clinical events.

As there appears to be a threshold of exposure to rociletinib that drives tumor response, the sponsor has selected 625 mg BID as the recommended dose based on the best understanding of the optimal benefit:risk profile and in order to give each patient the greatest chance to benefit from rociletinib therapy. A recommended dose of 625 mg BID also provides dose modification flexibility without potentially compromising clinical benefit since a dose reduction to 500 mg will allow patients to continue to be treated at a dose known to be active.

Both doses of rociletinib, 500 mg BID and 625 mg BID, will be further evaluated in the Phase 3 confirmatory study.

1.8 CONFIRMATORY STUDY

Study 020 is a Phase 3, open-label, multicenter, randomized study of oral rociletinib monotherapy versus single-agent cytotoxic chemotherapy in patients with EGFR NSCLC after failure of at least 1 previous EGFR-directed TKI and platinum doublet chemotherapy. This population represents patients with the most advanced disease. Patients are to be randomized 1:1:1 to receive rociletinib at 500 mg BID or 625 mg BID or investigator choice standard of care chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel).

The primary endpoint for this study is PFS based on disease progression according to RECIST Version 1.1. Key secondary endpoints include ORR and DOR according to RECIST Version 1.1 , and overall survival (OS). The primary and key secondary endpoints will be tested among the centrally confirmed T790M-positive and all randomized patients, using an ordered step-down multiple comparisons procedure separately for the 500 mg BID and 625 mg BID dose groups as compared to the chemotherapy arm. The study is 90% powered to detect a 40% improvement in PFS (hazard ratio of 0.6) at the 0.025 significance level for either rociletinib 500 mg BID or 625 mg BID dose groups compared to chemotherapy, but is not powered for formal comparison of 500 mg BID versus 625 mg BID.

Study 020 is currently open for enrollment in the US, Europe, South Korea, Taiwan, and Australia. The first patient was enrolled in the US on 04 May 2015. As of 26 February 2016, a total of 114 patients have been randomized at 80 study sites, including 45 patients that have been randomized at 32 study sites in the US. An additional 50 study centers will be opened outside of the US to compensate for the availability of third-generation EGFR TKIs. New territories currently undergoing site selection include

Canada, China, Malaysia, Philippines, Thailand, Romania, and Russia. Study 020 is projected to complete in 2018, with the last patient visit in the second half of 2018.

1.9 BENEFIT RISK DISCUSSION

Most first-line patients achieve an initial response and receive durable clinical benefit following treatment with EGFR TKIs, however the majority of patients will develop treatment resistance due to a T790M mutation in 9-14 months (Mok et al 2009, Rosell et al 2012, Sequist et al 2013). Survival rates of patients with advanced NSCLC who progress following treatment with EGFR-TKI remain very low, with a median OS of 1 to 2 years (Yu et al 2013).

Rociletinib has been studied primarily in the US in a patient population with predominantly poor baseline prognostic factors. For example, 24% and 32% of patients treated at 625 mg BID had 4 or more prior therapies and more than 1 prior EGFR TKI, respectively. In addition, 41% had previously been treated with both platinum doublet chemotherapy and an EGFR TKI. Therefore, the majority of patients would have been candidates for single-agent cytotoxic chemotherapy as the only remaining therapeutic option.

Despite the poor prognostic factors of patients in the rociletinib studies, the ORR in patients receiving 625 mg BID rociletinib was 32% by IRR and 34% by investigator assessment. Responses were durable, with a median duration of confirmed response of 8.8 months by IRR and 7.2 months by investigator assessment.

In determining if rociletinib provides a meaningful advantage over available therapy as one of the conditions for accelerated approval, the FDA defines available therapy as those drugs with full approval, which includes platinum doublet chemotherapy, single-agent chemotherapy, and the immunotherapy nivolumab. Limited data are available regarding efficacy of platinum doublet chemotherapy in patients with recurrent disease, however, data from several front line Phase 3 randomized clinical trials are available. The ORR in these studies is generally 20-25% with a median DOR ranging from 4-6 months (Table 3). Given that these are earlier line patients than were treated in the rociletinib development program, and that some of these studies include predominantly Asian patients who have a better prognosis, the clinical benefit observed in these studies is likely to be an overestimate of the efficacy expected for patients with recurrent disease in the US. Importantly, only one-third of patients who progress on first-line EGFR TKIs will receive platinum based chemotherapy, and single-agent chemotherapy will be the choice for many patients. Single agent docetaxel and pemetrexed are commonly used in this setting, with response rates below ≤ 10% and a reported median DOR of 4.6 to 9.1 months. (Table 4). In addition, chemotherapy is associated with well described toxicities that present a burden to patients' everyday lives.

Although immunotherapies have shown great promise and are approved in many indications, early data with the PD-1 inhibitor nivolumab suggests that tumor responses in mutant EGFR NSCLC patients are less common than those observed in unselected patients (Gettinger et al 2015). While no definitive conclusions regarding the efficacy of these agents in mutant EGFR patients can be made at present, these data are consistent with the hypothesis that immunotherapy might be less active in patients with lower mutational burden such as mutant Mutant EGFRNSCL (Rizvi et al 2015).

Rociletinib has a well-defined, manageable, and differentiated safety profile. Across all doses, 36% of patients had treatment duration greater than 6 months. Based on the understanding of the underlying mechanisms, monitoring and treatment guidelines have been developed for adverse events of hyperglycemia and QT prolongation. Thus, prescribers will be provided with effective risk management strategy, as described in Section 8, which will include patient selection, dose reduction and treatment recommendations, and prescriber education. This comprehensive approach to risk management should reduce the risk of potentially serious sequelae in the intended population of patients with recurrent mutant EGFR NSCLC.

One other agent targeting T790M mutation, osimertinib, has recently been granted accelerated approval. The safety and efficacy of osimertinib were demonstrated in 2 single-arm studies which enrolled patients mostly in Asia (60%). Clinical benefit provided by osimertinib has not been demonstrated in randomized, controlled trials, and continued approval for this indication may be contingent upon further confirmatory studies (AstraZeneca Pharmaceuticals LP November 2015). The response rate in the subgroup (n=108) enrolled in North America was 52%. While osimertinib is associated with significant rates of skin rash (41%), stomatitis (12%) and nail toxicity (25%), (AstraZeneca Pharmaceuticals LP November 2015), these events are uncommon with rociletinib. Some patients may be unable or unwilling to endure additional skin toxicity while others may have a cardiac exclusion that makes osimertinib inappropriate. For these patients, rociletinib is an important treatment alternative that can deliver meaningful clinical benefit. Thus the safety profiles of osimertinib and rociletinib are clearly unique. In addition to unique toxicities, emerging data suggest that the patterns of acquired resistance differ between the 2 agents (Section 2.1.4). The importance of these resistance mechanisms and their implications for treatment decisions are currently under study.

1.10 CONCLUSION

In conclusion, rociletinib 625 mg BID has a favorable benefit:risk profile in patients with recurrent T790M-positive mutant EGFR NSCLC based on clinically meaningful and durable responses and well established and acceptable safety profile in this patient population with terminal lung cancer.

2 PRODUCT DEVELOPMENT RATIONALE

2.1 CURRENT TREATMENT OF METASTATIC NSCLC

Lung cancer is the second most common serious cancer is the US, with over 200,000 new cases each year (NCI 2015), and is the leading cause of cancer deaths worldwide (Herbst et al 2008). In the US, 85% of lung cancer cases are NSCLC, the majority of which present as advanced/metastatic disease (stage IIIB or stage IV) at the time of diagnosis (Houston et al 2014).

Approximately 15% of metastatic NSCLC patients in the US have activating EGFR mutations. EGFR mutations are more common in patients who are female, never or light smokers, of Asian origin, and with adenocarcinoma histology (Linardou et al 2009). Current guidelines recommend EGFR TKIs as first-line treatment for patients with EGFR activating mutations (Mok 2014). FDA approved EGFR TKIs for first-line use are erlotinib (Tarceva), gefitinib (Iressa), and afatinib (Gilotrif). The ORR of EGFR TKIs is approximately 50-70% and a median PFS of approximately 9 to 14 months (Mok et al 2009, Rosell et al 2012, Sequist et al 2013).

While currently approved EGFR TKIs have shown dramatic responses for patients with mutant EGFR NSCLC, non-Asian patients have worse efficacy outcomes compared to Asian patients, and majority of patients experience toxicities resulting from WT EGFR inhibition in skin and gastrointestinal (GI) tract. These toxicities are generally mild, but can be problematic and adversely affect activities of daily living in some patients (Lynch et al 2007). Many patients need treatment for these toxicities, and some require dose reductions, interruptions ,or rarely, discontinuation.

2.1.1 Treatment of recurrent mutant EGFR NSCLC

All patients treated with approved first-line EGFR TKIs will experience disease progression (Mok et al 2009, Rosell et al 2012, Sequist et al 2013). In 50 - 60% of patients, failure of first-line EGFR inhibitor treatment is due to development of a second EGFR mutation, T790M (Sequist et al 2011, Yu et al 2013).

FDA approved therapies for patients with recurrent NSCLC (excluding NSCLC associated with anaplastic lymphoma kinase [ALK] mutations) are summarized in Table 2. Platinum doublet chemotherapy and/or single agent chemotherapy remain the well-established treatments of choice for recurrent NSCLC. Chemotherapies have no efficacy advantage in EGFR mutation driven NSCLC and provide moderate benefit while associated with well described toxicities (Table 3 and Table 4).

Agents that received recent accelerated approval from FDA (pembrolizumab, osimertinib) are not the appropriate comparators for a new drug as their efficacy has yet to be demonstrated randomized controlled studies. While 2 immune checkpoint inhibitors were approved in 2015, their benefit in mutant EGFR NSCLC patients is based on small subgroup analyses and remains unclear. Osimertinib, a third generation EGFR TKI, received accelerated approval for T790M-positive mutant EGFR NSCLC based on single arm Phase 2 clinical trial experience in November 2015. A confirmatory Phase 3 study against cytotoxic chemotherapy is still ongoing.

Table 2: FDA Approved Therapies for Patients with Recurrent NSCLC (excluding ALK-positive NSCLC)

Drug	Date of Approval	Indication	Primary Efficacy Endpoint
Full Approvals			
docetaxel	1999	Recurrent NSCLC	Overall Survival
pemetrexed	2004	Recurrent nonsquamous NSCLC	Overall survival
erlotinib	2004	Recurrent NSCLC	Overall Survival
ramucirumab (+docetaxel)	2014	Recurrent NSCLC	Overall Survival
nivolumab	2015	Recurrent NSCLC	Overall Survival
Accelerated Approvals			
pembrolizumab	2015	Recurrent NSCLC (PD-L1+)	Objective Response Rate
osimertinib	2015	Recurrent NSCLC (T790M+)	Objective Response Rate

2.1.2 Platinum-doublet chemotherapy

Chemotherapy remains the treatment of choice for mutant EGFR NSCLC patients with progression following EGFR TKI therapy. For patients who are well enough to tolerate such therapy, platinum doublet chemotherapy provides the most anti-tumor activity (Carnio et al 2014). However, only 32% of patients who progressed on a front-line EGFR TKI in the EURTAC study were able to receive subsequent therapy with platinum doublet chemotherapy (Rosell et al 2012). Such therapy provides limited clinical benefit and is often associated with debilitating toxicities such as fatigue, vomiting, myelosuppression, and neurotoxicity (Bristol-Myers Squibb Company) that affect activities of daily living. Limited data are available regarding efficacy of platinum doublet chemotherapy in patients with recurrent disease. Thus, the best available data from front line randomized clinical trials (Table 3) are likely to overestimate efficacy of platinum doublet chemotherapy in patients with recurrent disease. In addition, since chemotherapy treatment outcomes differ for Asian versus non-Asian patients, EURTAC study, which was conducted in Western Europe, is likely to give the best estimate of efficacy in the US-based population.

Table 3: Activity of Platinum Based Doublet Chemotherapy in Newly Diagnosed NSCLC

	Randomized Phase 3 Clinical Trials in Frontline NSCLC			
	EURTAC[a]	**LUX-lung 3[b]**	**LUX-Lung 6[c]**	**IPASS[d]**
Regimen	Platinum + Docetaxel or Gemcitabine	Cisplatin + Pemetrexed	Cisplatin + Gemcitabine	Carboplatin + Paclitaxel
Patients	Treatment naïve, EGFR mutation positive	Treatment naïve, EGFR mutation positive	Treatment naïve, EGFR mutation positive	Treatment naïve, nonsmokers
East Asia patients	0%	72%	100%	100%
ORR	16%	23%	23%	47%
mDOR	3.7 months	5.5 months	4.3 months	5.5 months
mPFS	5.2 months	6.9 months	5.6 months	7.4 months
Grade ≥3 AEs	67%	48%	60%	61%

ORR = objective response rate; mDOR = median duration of response; mPFS = median progression free survival; AEs = adverse events
[a] (Soo et al 2011)
[b] (Sequist et al 2013)
[c] (Wu et al 2014)
[d] (Mok et al 2009)

2.1.3 Single-agent chemotherapy

For patients who are not eligible to receive platinum doublet chemotherapy, or who progress after platinum doublet therapy, single agent chemotherapy is the standard of care. Single agent chemotherapy in an unselected patient population provides response rates of 5-9% and DOR of 4.6 – 9.1 months (Table 4) (Carnio et al 2014). Recently, docetaxel plus ramucirumab was approved for patients with progressive disease after front line therapy with an ORR of approximately 23%, however, 79% of patients reported Grade 3 or higher toxicities (Garon et al 2014).

Table 4: Activity of Single Agent Chemotherapy and Docetaxel plus Ramucirumab Combination in Recurrent NSCLC

	Clinical Study			
	Single agent docetaxel[a]	**Single agent docetaxel[b]**	**Single agent pemetrexed[b]**	**Docetaxel + ramucirumab[c]**
Study design	Randomized Phase 3 (RP3)	RP3		RP3
Patients	Unselected patients with PD after platinum-containing therapy	Unselected patients with PD after platinum-containing therapy		Unselected patients with PD after platinum-containing therapy
Territories	US	Global		Global
ORR	6.7%	8.8%	9.1%	23%
mDOR	9.1 months	5.3 months	4.6 months	Not reported
mPFS	Not reported	2.9 months	2.9 months	4.5 months
Grade ≥3 AEs	Not reported (54% Grade 4 neutropenia)	Not reported (40% Grade 3-4 neutropenia)	Not reported	79% (49% Grade 3-4 neutropenia)

ORR = objective response rate; mDOR = median duration of response; mPFS = median progression-free survival; AEs = adverse events
[a] (Fossella et al 2000)
[b] (Hanna et al 2004)
[c] (Garon et al 2014)

2.1.4 Immunotherapy and 3rd Generation EGFR TKIs

The anti-PD-1 targeted antibody nivolumab was recently approved by the FDA for the treatment of metastatic non-squamous NSCLC with progression on or after platinum-based chemotherapy (Bristol-Myers Squibb Company March 2015). Pembrolizumab, another immune checkpoint targeting agent, has received accelerated approval and is indicated for patients whose tumors express PD-(L)1 as determined by an FDA-approved test (Merck & Co. Inc December 2015). Efficacy of these agents in mutant EGFR NSCLC remains unclear, and patients with EGFR genomic tumor aberrations should have disease progression on FDA-approved therapy for EGFR aberrations prior to receiving these agents. For nivolumab, the ORR was 17% in a small subgroup of mutant EGFR patients (Gettinger et al 2015). For pembrolizumab, the response rate was 18% in unselected previously treated patients (Garon E.B. et al 2015). A small subgroup analysis in a randomized clinical study demonstrated no PFS benefit for mutant EGFR patients (hazard ratio 1.78) (Herbst et al 2015). Although the small number of mutant EGFR patients included in these studies does not allow for definitive conclusions on efficacy in this subgroup, these results are consistent with exploratory studies suggesting that activity of immunotherapy might be less in patients with lower mutational burden such as mutant EGFR patients (Rizvi et al 2015).

While osimertinib (Tagrisso) was granted an accelerated approval by the FDA for patients with T790M mutations in November 2015, clinical experience with this agent is limited and a confirmatory randomized Phase 3 study is ongoing. The safety and efficacy of osimertinib were demonstrated in 2 single-arm studies involving a total of 411 patients with recurrent EGFR T790M mutation who were mostly enrolled in Asia (60%). In these 2 studies, 57% of patients in the first study and 61% of patients in

the second study experienced a tumor response. The response rate in the subgroup (n=108) enrolled in North America was lower (52%). The most common side effects of osimertinib are diarrhea (42%), rash (41%), dry skin (31%), stomatitis (12%) and nail toxicity (25%). Osimertinib may cause serious side effects, including inflammatory lung disease and cardiomyopathy. Continued approval for this indication may be contingent upon further confirmatory studies (AstraZeneca Pharmaceuticals LP November 2015).

In addition, emerging data suggest that the patterns of acquired resistance differ between rociletinib and osimertinib. For example, all irreversible inhibitors bind to the C797 residue in EGFR, and a C797S mutation dramatically reduces the potency of all irreversible EGFR TKIs (Niederst et al 2015). One of the most common mechanisms of resistance to osimertinib is an acquired C797S EGFR mutation which has been identified in approximately 22% of T790M-positive patients, however a lower frequency (2.5%) of this mutation has been observed in T790M-positive patients treated with rociletinib (Table 5).

Table 5: Frequency of C797S in Samples from Patients who Received Osimertinib or Rociletinib

Compound	Sample Profiled	Evaluable Patients	C797S Frequency
Osimertinib [a]	Plasma	67	22%
Rociletinib [b]	Tissue	9	0%
Rociletinib [c]	Plasma	40	2.5%

[a] (Oxnard et al 2015)
[b] (Piotrowska et al 2015)
[c] (Chabon et al)

2.2 MEDICAL NEED FOR ACCLERATED APPROVAL OF ROCILETINIB

Accelerated approval is granted to drugs that treat serious conditions, generally provide a meaningful advantage over available therapies, and demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. According to recent FDA guidance (Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014), FDA recognizes that it is preferable to have more than 1 treatment approved under the accelerated approval provisions because of the possibility that clinical benefit may not be verified in post-approval confirmatory trials. FDA will consider products as addressing an unmet medical need if the only approved treatments were granted accelerated approval based on a surrogate endpoint and clinical benefit has not been verified by post-approval studies. In addition, it was previously recognized by the Oncologic Drugs Advisory Committee (January 2005) that approval of 1 therapy under the accelerated approval regulations should not preclude approval under those regulations of additional therapies for the same indication. Therefore, in determining if rociletinib provides a meaningful advantage over available therapy as one of the conditions for accelerated approval osimertinib, which was granted accelerated approval based on the surrogate endpoint of objective response rate, will not be considered as available therapy for patients with T790M-positive mutant EGFR NSCLC.

Although EGFR inhibitors are effective initial treatments for patients with advanced EGFR mutated NSCLC, most patients' progress within a year of starting EGFR therapy. Ultimately, the disease is fatal. The current standard of care for patients who have progressed beyond their initial EGFR TKI is cytotoxic chemotherapy. The response rate to platinum containing doublet chemotherapy, which is associated with significant toxicities, is less than 20% in mutant EGFR NSCLC patients of European descent (Table 3). Importantly, only one-third of patients who progress on front-line EGFR TKIs will receive platinum-based chemotherapy. For patients deemed inappropriate for platinum-based chemotherapy, single-agent cytotoxic chemotherapy is generally provided. Both docetaxel and pemetrexed are approved in this setting, providing response rates of less than 10% (Table 4). Additionally, combination of ramucirumab and docetaxel has demonstrated responses in unselected patients. The combination, however, is associated with significant toxicity and is not appropriate for all NSCLC patients.

The wide acceptance of single agent chemotherapy as the standard of care for recurrent NSCLC is further supported by the choice of docetaxel as a comparator in recent randomized Phase 3 studies of immune checkpoint inhibitors (Gettinger et al 2015, Herbst et al 2015). Unfortunately, early data on treating mutant EGFR patients with PD-(L)1 inhibitors suggests that tumor responses in mutant EGFR NSCLC are lower than those observed in unselected patients..

Overall, chemotherapy remains the choice of therapy for vast majority of mutant EGFR NSCLC patients with recurrent disease after therapy with approved EGFR TKIs. Osimertinib, a third generation EGFR TKI

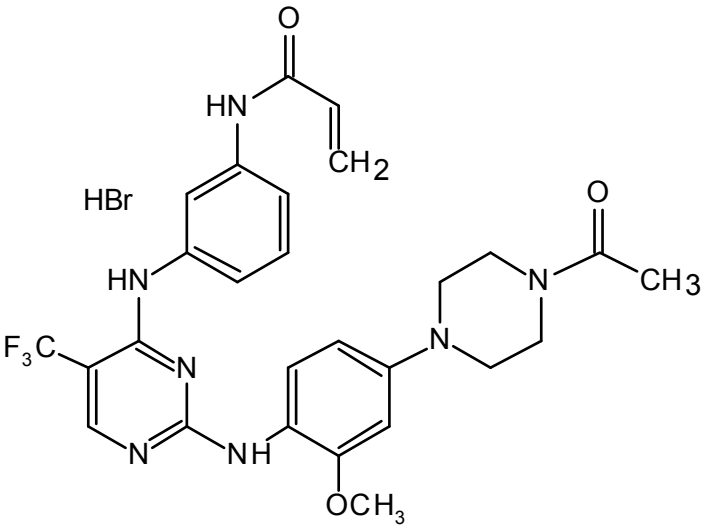
that specifically targets T790M mutation, was granted accelerated approval by the FDA based on single arm Phase 2 clinical data in November 2015. It is important to recognize that there are clear differences between rociletinib and osimertinib with regards to their structure, metabolism, clinical activity, safety profile and potential mechanism of resistance, which support the existing high unmet medical need for rociletinib in T790M-positive mutant EGFR NSCLC. The availability of both agents will allow for the broadest patient population to be eligible for treatment with a T790M targeted agent based on an individual patient's medical history including treatment sequencing, or ability to combine with other agents to provide the greatest clinical benefit to patients with advanced mutant EGFR NSCLC. For example, although treatment with a prior T790M targeted agent was not allowed prior to participation in rociletinib studies, a recent report in a small number of patients suggests that sequencing osimertinib after rociletinib may be active (Sequist et al 2015). This theoretically has the potential to allow patients to remain on an EGFR TKI longer and delay the emergence of C797S mediated resistance. Studies to further elucidate the mechanisms of response and resistance to these agents, as well as combination studies, are ongoing.

3 OVERVIEW OF THE ROCILETINIB DEVELOPMENT PROGRAM

3.1 ROCILETINIB DESCRIPTION

Rociletinib is a TKI for oral use that contains rociletinib as its hydrobromide salt. The molecular formula for rociletinib HBr is $C_{27}H_{28}F_3N_7O_3$, and the chemical structure is (N-{3-[(2-{[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]amino}-5-(trifluoromethyl)pyrimidin-4-yl)amino]phenyl}prop-2-enamide hydrobromide) (Figure 5).

Figure 5: Chemical Structure of Rociletinib



Rociletinib is a new chemical entity that was originally developed as a FB capsule formulation that was used in the initial stages of Phase 1 part of Study 008. During that study, the free base formulation was superceded by the hydrobromide salt formulation of rociletinib (rociletinib HBr tablet) which has improved PK properties. Rociletinib HBr has been evaluated in nonclinical pharmacology, PK, toxicology, and clinical studies. All patients in the safety and efficacy populations described in Section 3.6.1.7, as well as the Clinical Pharmacology studies described in Table 6 received rociletinib HBr tablets. If approved, rociletinib HBr will be commericially available in 125 mg and 250 mg tablet strengths. Where appropriate throughout this document, rociletinib HBr will be referred to as rociletinib and the free base formulation will be referred to as rociletinib FB.

3.2 REGULATORY HISTORY

Rociletinib has been in clinical development as an investigational drug for mutant EGFR NSCLC since January 2012. Rociletinib received Orphan Drug Designation for the treatment of mutant EGFR NSCLC in May 2013. In May 2014, rociletinib received Breakthrough Therapy Designation for the treatment of patients with mutant EGFR NSCLC whose disease has progressed on prior EGFR-directed therapy due to T790M-mediated acquired drug resistance. The NDA for rociletinib was submitted by Clovis Oncology, Inc. (the sponsor) on July 30, 2015. The sponsor is seeking accelerated approval of rociletinib under 21 Code of Federal Regulations (CFR) Subpart H, Section 314 for the treatment of patients with mutant EGFR NSCLC who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation as detected by an FDA-approved test based on the established surrogate endpoint of ORR and supported by DOR.

In the end of Phase 2 (EOP2) meeting in 2014, FDA agreed to the use of ORR as the primary endpoint and DOR as a secondary endpoint for Study 008 and Study 019. In the pre-NDA meeting on 09 June 2015, FDA generally agreed with the proposed efficacy datasets including combined investigator ORR and durability data from Study 008 and 019 for patients who received 500 mg BID and 625 mg BID, supported by IRR assessed ORR and durability data, could potentially serve as the basis of a substantive NDA review for accelerated approval. FDA asked the sponsor to submit a 90-day update on the durability of response assessed by investigator and IRR for all patients who were determined to have a complete response (CR) or partial response (PR) in the original NDA submission. In the pre-NDA meeting, FDA generally agreed that Study 020 can be used as the confirmatory study, and the study design has been amended to incorporate FDA comments

In a mid-cycle communication dated 09 November 2015, the sponsor received feedback from FDA that the efficacy population in Studies 008 and 019 should include all T790M-positive patients, including patients who may have been enrolled in the absence of measureable disease, and that ORR and DOR must be based on the fraction of patients who have a confirmed PR or CR as per RECIST Version 1.1. FDA requested data in the form of a major amendment, which resulted in extension of the PDUFA date to 28 June 2016.

3.3 SUMMARY OF PRECLINICAL FINDINGS

3.3.1 Mechanism of Action

Rociletinib is a novel, potent, small molecule, third generation TKI that irreversibly binds and inhibits EGFR with the common activating (L858R, Del19) and T790M resistance mutations, and has minimal activity towards WT EGFR. Rociletinib binding results in sustained EGFR pathway blockade in tumor cells. In human cancer cell lines expressing mutant and WT EGFR, rociletinib potently inhibits *in vitro* proliferation of cells expressing mutant EGFR, while minimally affecting the proliferation of WT EGFR dependent cells. Rociletinib is at least 10-fold more potent in mutant EGFR as compared to WT EGFR cell lines. Rociletinib administration was well tolerated and resulted in tumor regressions as a single agent in subcutaneous, patient-derived, and transgenic lung cancer models driven by mutant EGFR.

3.3.2 Toxicology

In nonclinical repeat-dose studies of rociletinib in rats and dogs, common findings included diarrhea, dermal lesions, and glandular atrophy in toxicology species. Other organs identified as targets in nonclinical species treated with rociletinib were the gastrointestinal tract and hematopoietic systems. In dogs, gastrointestinal tract lesions involved the hard palate, buccal mucosa, and esophagus. In rats, body weight loss and inappetence caused mortality. The findings in the hematopoietic system were primarily seen in moribund rats and predominantly involved the erythroid lineage. Most of the toxicity findings completely reversed at the end of a 1-month recovery period. Rociletinib was not genotoxic when evaluated in 2 *in vitro* assays and 1 *in vivo* assay.

Rociletinib was not a selective developmental toxicant and was not teratogenic in the rat or rabbit. The teratogenic potential of rociletinib was studied in 2 embryofetal development studies in rats (70-300 mg/kg or 0.5 to 2.3 times the recommended human dose on a mg/m^2 basis) and rabbits (5-40 mg/kg or 0.1 to 0.6 times the recommended human dose on a mg/m^2 basis). A decrease in fetal body weights was noted at the dose of 300 mg/kg in rats, which correlated with a decrease in maternal body weight and was a maternal toxic dose. No decrease in fetal weights were noted at 40 mg/kg in rabbits. In a dose-range finding embryofetal development study in rabbits (10-200 mg/kg or 0.2 to 3.1 times the recommended human dose on a mg/m^2 basis), decreases in fetal weights were noted at 80 mg/kg or 1.6 times the recommended human dose on a mg/m^2 basis, which were also correlated with decreases in maternal body weights and was a maternal toxic dose.

The cardiac safety of rociletinib was evaluated in *in vitro* assays for Human ether-à-go-go-related-gene (hERG) activity and hERG trafficking and *in vivo* safety pharmacology studies using conscious telemetry-instrumented dogs and monitoring of ECGs in the 28- and 91-day repeat-dose study in dog. No significant nonclinical cardiac safety results were observed.

Additional studies were performed or are planned with the 3 major human metabolites of rociletinib (M502, M544, and M460, Section 3.4.2). The pharmacology of these metabolites is discussed in in the context of clinical pharmacology in Section 3.4. The 3 metabolites were not positive in an *in vitro* bacterial mutation assay, however they were all positive in an *in vitro* micronucleus assay in human peripheral blood lymphocytes. Exposures of M502 and M460 in the rat and dog were lower than the exposures observed in patients, thus 28-day GLP repeat dose studies with these metabolites are planned.

3.4 CLINICAL PHARMACOLOGICAL CHARACTERISTICS OF ROCILETINIB

The development program studied doses across the dose range of 500-1000 mg BID. Importantly there were a substantial number of patients treated at multiple doses: 90 patients at 500 mg BID, 209 patients at 625 mg BID, and 95 patients at 750 mg BID, with intensive PK data for rociletinib and its 3 major metabolites, M460, M502, and M544, obtained from 18, 21, and 23 patients, respectively. PopPK analyses were based on PK data from 371 patients in Study 008 and 54 patients in Study 019 The details of the PK profile are provided below, but in summary:

- There are 3 main metabolites: primary metabolite M502, and its further metabolism to form secondary metabolites M460 and M544 (Figure 6).
- The parent molecule is responsible for efficacy, as the metabolites show limited potency against WT and mutant EGFR. The steady state exposure is similar across all rociletinib HBr doses.
- Studies of these metabolites have determined that M502 is likely responsible for the observed hyperglycemia, through the reversible inhibition on the IGF1R/INSR receptors
- M460 is likely responsible for the effect on QTc, through the inhibition on the hERG channel.
- In addition, analysis of the NAT2 status has determined that slow acetylator status influences the levels of the metabolites. N-acetylation by a polymorphic enzyme NAT2 likely mediates the metabolic pathway of M502 to M544 and might also play a role in the elimination of M460. Therefore, slow acetylator status is associated with a higher level of M460 with a mild increase of M502 exposure. The changed balance of the metabolites may affect the adverse event profile (Section 5.9.7).

3.4.1 Rociletinib HBr Pharmacokinetics

Phase 1 and 2 studies have evaluated the safety of rociletinib at doses up to 1000 mg BID. No MTD) was established in these studies. Pharmacokinetic analyses showed that Day 1 exposure to rociletinib increased with rociletinib HBr dose in the range studied, 500 mg to 1000 mg BID, but this effect was blunted by Day 15 (Appendix 11.1, Figure 18).

In PK studies, rociletinib was absorbed rapidly. The C_{max} was reached within 1.5 to 2.5 hours. Rociletinib showed little accumulation with repeated dosing, consistent with its short $T_{1/2}$ of 2.7 to 3.5 hours. The mean $AUC_{(0-24)}$ accumulation ratio of rociletinib ranged from 0.75 to 1.17. Rociletinib is mainly excreted via feces (85%), with a small amount in the urine (4.4%).

The steady-state C_{max} and $AUC_{(0-24)}$ of the 3 metabolites were variable and no clear trend with dose was observed. M502 was the major metabolite in plasma with the steady-state exposure approximately 3.5-fold of that for rociletinib. M544 and M460 were detected at lower levels with steady-state exposures approximately 1.5-fold and half of that for rociletinib, respectively.

In healthy volunteers, food increased absorption of rociletinib as compared with fasting administration. Results indicated that a high-fat meal increased AUC by 54% and C_{max} by 21%. Therefore, patients in rociletinib clinical trials took rociletinib with food or within 30 minutes after a meal.

While no formal studies were conducted in renal impairment, renal function does not appear to affect PK. In the PopPK analyses of combined data from Study 008 and Study 019, most patients had normal renal function (48%). However, 31% and 12% had mild and moderate renal function impairment, respectively, as classified by creatinine clearance (CR_{cl}) cut-off values calculated using the Cockcroft-Gault equation. Results of PopPK analyses concluded that rociletinib and metabolites exposures in patients with mild and moderate renal impairment were similar to patients with normal renal function.

Similarly, no formal studies were conducted in hepatic impairment, but liver function does not appear to affect PK. In the PopPK analyses, most patients had normal hepatic function (76%). However, 15% and 1.2% of patients had mild and moderate hepatic impairment, respectively, based on the NCI Organ Dysfunction Working Group criteria. PopPK analyses concluded that rociletinib and metabolites exposures in patients with mild hepatic impairment were similar to patients with normal hepatic function.

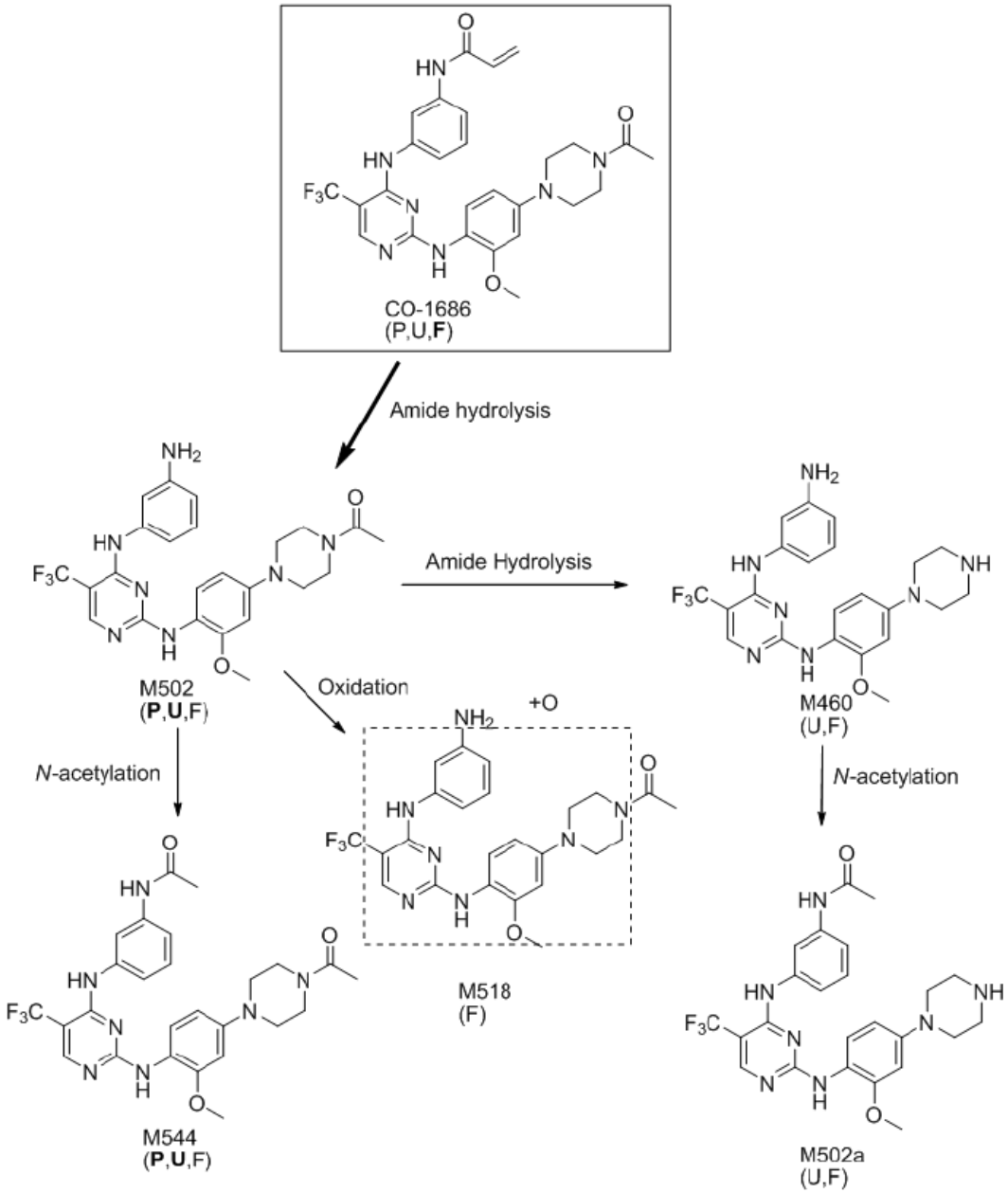
In addition, weight, age, gender, race, and T790M status do not have a significant effect on rociletinib and metabolite exposure.

3.4.2 Metabolites

In vitro, cytochrome P450s (CYPs) played a minor role in rociletinib metabolism. Moreover, CYPs did not play a significant role in the formation of M502 or M460. *In vivo*, rociletinib is extensively metabolized

by amide hydrolysis forming M502. The biotransformation pathway of rociletinib in the human following a single oral dose of [^{14}C]-rociletinib is shown in Figure 6.

Figure 6: Biotransformation Pathway of Rociletinib in Human Following a Single Oral Dose Administration



CO-1686 = rociletinib
Bold font: major component in the matrix
Bold arrow: major metabolic pathway
P=plasma; U=urine, F=feces
[1] The dotted box for M518 represents the broad region in the molecule where the oxidation may take place.
[2] In humans following rociletinib single dose administration, M460 was not readily detectable in the plasma by radioactivity detector, despite detectable levels of M460 was reported in the plasma by the LC-MS/MS method in 4 out of 6 subjects in the study.

Following a single rociletinib dose of 625 mg, metabolite M502, and to a lesser extent M544, were the major components of plasma total radioactivity detected in plasma (69.1% and 22.7% of plasma total radioactivity $AUC_{(0-72)}$, respectively, compared to 13.7% for rociletinib). Rociletinib is more rapidly eliminated than its metabolites M502, M544, and M460 (mean $T_{1/2}$ of 2.7, 20, 20, and 51 hours, respectively). Following BID dosing, the accumulation ratio was similar between M502 and M544, but much higher for M460 (2.23 to 3.04, 1.93 to 3.11, and 14.6 to 17.4, respectively).

None of the rociletinib 3 main metabolites (M502, M460, and M544) inhibit WT or mutant EGFR. M502 and M460 are bioactive and were investigated preclinically in more detail.

Although hyperglycemia and prolonged QTc were observed in patients (see Sections 5.9.1 and 5.9.2, respectively), these safety findings were not observed in toxicology studies likely due to lower levels of M502 and M460 in nonclinical species.

3.4.2.1 M502

Rociletinib metabolites M502 and M460 show biochemical and cellular potency against IGF1R/ INSR. M502 and M460 have comparable *in vitro* potency toward IGF1R and INSR. M460 and M502 were directly tested in an oral glucose tolerance test in the rat at plasma exposures comparable to those observed in patients. Dosing of M502 resulted in significant elevations in postprandial glucose and insulin levels, while M460 caused a non-significant increase in postprandial glucose and insulin levels.

Exposure to circulating M502 is approximately 8-fold higher than M460 in humans and therefore, M502 likely plays a causal role in the hyperglycemia observed in some patients.

Exposure-response analysis evaluated the relationship between steady-state exposure metrics of rociletinib and its major metabolites with Grade 3 or 4 hyperglycemia using data from Study 008 and Study 019. Logistic regression analyses identified M502 AUC_{ss} as the best predictor of the probability of a Grade 3 or 4 event. No statistically significant relationships with age, body mass index (BMI), gender, race, weight, or history of hyperglycemia were identified.

3.4.2.2 M460

Based on the higher level of metabolites in humans and the absence of a significant nonclinical cardiac safety signal with rociletinib, hERG assays were conducted on the metabolites. The half maximal inhibitory effect (IC_{50}) of M460 on hERG potassium currents was 0.05 µM, which is 0.6-fold of the unbound plasma M460 C_{max} (81 nM) observed in patients at 500 mg BID. These data suggest that M460 plays a contributory role in the development of QT prolongation in humans.

Exposure-response analysis also evaluated the relationship between the plasma concentration of rociletinib and metabolites and changes in QTc using data from Study 008 and Study 019. QTc prolongation increased with total daily dose levels. In general, peak QTc prolongation was observed on

Day 15 before leveling off or declining slowly with continued treatment of rociletinib. A multivariate analysis of the influence of time-matched observed concentrations of rociletinib and its major metabolites on baseline-adjusted QTc revealed M460 concentration as the primary predictor of prolonged QTc following rociletinib treatment.

3.4.3 NAT2

The polymorphic enzyme NAT2 likely mediates the N-acetylation of M502 to form M544 and also might play a role in the elimination of M460. The population PK model for M460 suggested that slow acetylators are likely to have higher M460 concentrations.

NAT2 genotype polymorphism was assessed for the group of patients who received rociletinib at 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID and who gave additional informed consent for genomic testing. The NAT2 genotype polymorphism testing was performed by Genelex Corporation (Seattle, WA) using an assay based on polymerase chain reaction (PCR) followed by mass spectrometry to identify single nucleotide polymorphism allele. Based on NAT2 genotype results, patients were classified as having “low”, “intermediate”, and “rapid” acetylator phenotype (McDonagh et al 2014). Acetylator status is available for 303 patients, including 67 patients treated at 500 mg BID and 147 patients treated at 625 mg BID (Section 5.9.7). PK exposure stratified by NAT2 genotyping showed that slow acetylator status is associated with a higher level of M460 and also a mild increase of M502 exposure.

3.4.4 Drug-drug Interactions

Two drug interaction studies (Studies CO-1686-027 [referred to as Study 027 hereafter] and CO-1686-030 [referred to as Study 030 hereafter]) have been completed. In Study 027, rociletinib C_{max} and AUC were reduced by only approximately 15% and 26%, respectively, when rociletinib was co-administered with paroxetine. These findings, as well as the lack of effect on time from dosing at which C_{max} occurs (T_{max}) and $T_{1/2}$, suggests a limited role of CYP2D6 in rociletinib metabolism.

The C_{max} and $AUC_{(0-24)}$ of rociletinib, M502, and M544 were reduced by 69% to 72% when co-administered with the proton pump inhibitor (PPI) omeprazole. These reductions indicate that gastric pH has an effect on rociletinib exposure, with increased gastric pH causing a reduction in exposure. To examine the relevance of this finding in patients, the association between PPI use and exposure to rociletinib was examined in Study 008 and Study 019. This analysis showed that concomitant PPI did not affect exposure to rociletinib in patients.

Study 030 demonstrated that rociletinib is a weak CYP2C8 inhibitor when co-administered with rosiglitazone, may be a weak CYP2C9 inducer when co-administered with celecoxib, and is a weak CYP3A4 inducer when co-administered with midazolam. Both Study 027 and Study 030 demonstrated

that rociletinib is a weak CYP2C19 inhibitor when co-administered with omeprazole and a weak P-gp inhibitor when co-administered with digoxin.

Based on findings from the drug interaction studies, the proposed rociletinib label includes instructions to monitor digoxin concentration prior to initiation of rociletinib and throughout co-administration. Additionally, the effectiveness of steroidal contraceptives (e.g., ethinyl estradiol) may be reduced when used with rociletinib due to GYP3A4 induction, so alternative or concomitant methods of contraception are recommended.

3.5 DEVELOPMENT OF COMPANION DIAGNOSTIC TEST FOR T790M

A tissue-based companion diagnostic (therascreen® EGFR RCQ PCR kit, hereafter referred to as the *therascreen*® test) will be available to identify patients for treatment with rociletinib based on the presence of the T790M resistance mutation in contemporaneous formalin fixed paraffin embedded (FFPE) tissue specimens from patients with acquired resistance to prior TKIs. Clovis is collaborating with QIAGEN on the development and commercialization of this companion diagnostic test. The diagnostic test is being developed in parallel with rociletinib, with the goal of regulatory approval concurrent with rociletinib approval.

QIAGEN conducted a complete set of design verification studies to support the registration of the *therascreen*® test. These studies tested a range of assay performance parameters including verification of assay cut-offs, linearity, precision, reproducibility at the Limit of Detection (LOD), LOD verification, cross contamination, interfering substances, and comparison with a reference method. For some mutations where limited FFPE clinical samples were available, an FFPE cell line was used so that sufficient material could be generated to complete all studies with the required replicates. A comparison of FFPE cell lines and FFPE clinical material was additionally conducted to show that DNA derived from the cell lines performed equivalently to DNA derived from FFPE clinical samples and could be used as a surrogate in verification studies where a large amount of mutated DNA was required. This approach was used to support verification studies for 19 mutations in *EGFR*, including 8 mutations (L858R and 7 deletion 19 mutations) for which the *therascreen*® test is now approved to select patients for treatment with afatinib. FFPE clinical samples and FFPE cell lines were also used for T790M to generate sufficient design verification data to support an analytical claim for this mutation. Therefore, the analytical validation of the *therascreen*® test for detection of the T790M mutation has been completed and approved by FDA.

The *therascreen*® test was used to determine T790M status for patients enrolled in Studies 008 and 019 in order to provide clinical validation of the test. As the presence of the T790M mutation was required for enrollment in the Studies 008 (Phase 2) and 019, the rate of T790M-positive results in the enrolled population is artificially high compared to the overall patient population. To obtain a better estimate of

the rate of detection of the T790M mutation in the overall eligible patient population, an analysis of central laboratory test results from a subset of patients screened for enrollment in Studies 008 (Phase 2) and 019 was conducted. A total of 618 EGFR screening test results were reported by the central laboratory for patients screened prior to 31 December 2014. Of these, 541 results were valid and 77 results were either invalid (n = 51) or were deemed unevaluable for analysis (n= 26) due to the absence of tumor cells in the biopsy sample. Among all valid results, 63.6% (344/541) were T790M-positive and 36.6% (197/541) were T790M-negative. These data are consistent with the 50-68% T790M-positive rate reported for NSCLC patients with acquired resistance to EGFR-TKIs (Arcila et al 2011, Yu et al 2013). These data and the efficacy results obtained in T790M-positive patients, as determined by the *therascreen*® test, indicate that the *therascreen*® test is suitable to identify T790M-positive patients for treatment with rociletinib.

3.6 OVERVIEW OF CLINICAL DEVELOPMENT

A total of 11 clinical studies have been initiated to evaluated rociletinib (Table 6). Five ongoing studies, including the 2 studies supporting the NDA (Study 008 and Study 019, detailed in Section 3.6.1) and the confirmatory study (Study 020, detailed in Section 9), are being conducted in the proposed indication: the treatment of patients with mutant EGFR NSCLC who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation. Five clinical pharmacology studies have been conducted to support the NDA. In addition to the studies presented in the table, 2 studies have been initiated to evaluate rociletinib combination therapy.

Table 6: Overview of Rociletinib Clinical Studies

Study Number	Study Description and Key Design Features	Status
Clinical Efficacy Studies in Indication		
CO-1686-008 (Study 008)	Phase 1/2, open-label, safety, PK, and preliminary efficacy study in patients with advanced NSCLC; Phase 1 T790M-positive or negative; Phase 2 expansion cohorts at 500 mg, 625 mg, 750 mg BID in T790M-postive mutant EGFR NSCLC, ≥ second line; expansion cohort in T790M-negative and T790M-unknown	Enrollment complete; study ongoing
CO-1686-019 (Study 019)	Phase 2, single arm, open-label, safety and efficacy study of rociletinib as second line EGFR-directed TKI for patients with T790M-positive mutant EGFR NSCLC	Enrollment complete; study ongoing
CO-1686-020 (Study 020) Ongoing Confirmatory Study	Phase 3, randomized, open-label, study comparing rociletinib and single-agent cytotoxic chemotherapy in patients with EGFR NSCLC after at least 1 previous EGFR-directed TKI and platinum-doublet chemotherapy	Enrollment ongoing
CO-1686-031	Expanded access protocol of rociletinib as EGFR-directed therapy for patients with mutant EGFR NSCLC with the T790M resistance mutation	Study ongoing
Clinical Pharmacology Studies in Support of NDA		
CO-1686-027	Single dose rociletinib drug interactions in healthy adults to compare the effect of 1) CYP2D6 inhibition, and 2) gastric pH on rociletinib PK	Completed
CO-1686-028	^{14}C-rociletinib excretion mass balance in healthy adult males to characterize the mass balance, absorption, metabolism, and elimination pathways of rociletinib	Completed
CO-1686-029	Food effect of rociletinib in healthy adults to compare the effect of a high fat breakfast on the single dose PK of 625 mg rociletinib	Completed
CO-1686-030	Multiple dose rociletinib on PK of rosiglitazone, celecoxib, and midazolam in healthy adult males to examine the effect of 10-day BID rociletinib administration on PK of a CYP2C8, CYP2C9, and CYP3A4 substrate	Completed
CO-1686-016	3-Part study to assess the pharmacokinetics of single and multiple doses of oral CO-1686 HBr salt in healthy subjects	Completed
Other Monotherapy Studies		
CO-1686-022 (TIGER-1)*	Phase 2, randomized, open-label, study comparing rociletinib and erlotinib as 1st line treatment of patients with EGFR-mutant advanced NSCLC	Enrollment stopped early*, study ongoing
CO-1686-018 (TIGER-J)	Phase 1, open-label, safety, PK, and preliminary efficacy study in Japanese patients withT790M-positive mutant EGFR NSCLC, ≥ 2nd line (study conducted in Japan only)	Enrollment completed, study ongoing

* Study CO-1686-022 enrollment was stopped early due to clinical development re-prioritization and focus on combination therapy studies.

3.6.1 Efficacy and Safety Studies 008 and 019 to Support Accelerated Approval

The efficacy and safety evidence to support accelerated approval of rociletinib comes from 2 ongoing, single arm, open label studies in patients with previously treated mutant EGFR NSCLC:

- Study 008: A Phase 1/2, open-label, safety, PK and preliminary efficacy study of oral rociletinib in patients with previously treated mutant EGFR NSCLC.
- Study 019: A Phase 2 open-label, multicenter, safety and efficacy study of oral rociletinib as second-line EGFR-directed TKI in patients with mutant EGFR NSCLC.

3.6.1.1 Study 008 Design

Study 008 is a Phase 1/2, open-label, safety, PK, and efficacy study of oral rociletinib administered daily in previously treated patients with mutant EGFR NSCLC. In both phases of the study, patients had to have an activating EGFR mutation and have progressed on treatment with an EGFR inhibitor such as erlotinib, gefitinib or afatinib. Patients were aged ≥ 18 years, with histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC. Additionally, patients had to have a life expectancy of at least 3 months, an ECOG performance status of 0 or 1, and adequate hematological and biological function.

Phase 1

The primary objectives of the Phase 1 part of the study were to evaluate the toxicity profile of escalating doses of rociletinib to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose and to characterize the PK profile. Secondary objectives included characterization of the PK profile after a high fat breakfast compared to a fasted state, and evaluation of the effects of study drug on the QT interval/corrected QT interval (QTc) and to evaluate tumor response (ORR and DOR). This part of the study utilized a dose escalation design with no randomization.

Patients in the Phase 1 study were not required to be T790M-positive, however they were required to submit a tumor tissue biopsy for T790M evaluation during the screening period, to be subsequently assessed with a central test. Prior treatment with EGFR directed therapy was required, and prior chemotherapy, including intervening chemotherapy, was permitted.

Patients were treated continuously with oral rociletinib daily for a 21 day cycle and had assessments for safety and PK. In the initial stage of the Phase 1 part of the study, 57 patients were treated with rociletinib FB at doses ranging from 150 mg once a day (QD) up to 900 mg BID. Subsequently, the formulation was changed to the final rociletinib HBr tablet formulation (see Section 3.1), and an additional 54 patients were treated at doses of 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID for a total of 111 patients. An MTD for rociletinib was not reached in the Phase 1 part of the study.

Tumor assessments were performed every 6 weeks and patients were treated continuously until disease progression or death. The end of study evaluation was conducted 28 days after the last dose.

Phase 2

The primary objectives of the Phase 2 part of the study were to evaluate tumor response to rociletinib (ORR and DOR) by investigator assessment in patients with a with a centrally-confirmed T790M mutation. Only rociletinib HBr was studied in the Phase 2 part. Secondary objectives included the evaluation of tumor response (ORR and DOR) by IRR, and PFS (both IRR and investigator assessments) and the safety profile of rociletinib. Additional secondary objectives included evaluation of OS and disease control rate (DCR). The PK profile of rociletinib using PopPK methods to explore correlations between PK, exposure, response and/or safety findings, characterization of lung cancer and treatment related symptoms, and the effects of rociletinib on the QT/QTc interval were also explored. In addition, secondary objectives include characterization of the change in the quality of life from baseline in patient reported outcomes.

Patients were treated continuously with oral rociletinib daily for each 21 day cycle, with no treatment interruption between cycles. Patients were assigned to 1 of 3 treatment cohorts. Two of these cohorts were based on previous treatment history:

Cohort A consisted of patients with progression of disease while on treatment with an EGFR-TKI. These patients were required to have evidence of T790M mutation in EGFR by the sponsor's central laboratory and were allowed to have multiple lines of prior EGFR-TKIs and prior chemotherapy, including intervening chemotherapy. In addition, for Cohort A, patients were required to have measurable disease by RECIST Version 1.1, and must not qualify for Cohort B. Thus Cohort A was enriched for later line patients.

Cohort B consisted of patients with progression of disease while on treatment with only 1 prior EGFR-TKI. These patients were required to have evidence of T790M mutation in EGFR by the sponsor's central laboratory and were only allowed to have 1 prior line of chemotherapy, which must have been before the EGFR inhibitor. These patients were also required to have measurable disease by RECIST Version 1.1. Thus Cohort B was enriched for earlier line patients.

Cohort C was added to include patients who had a positive local test but were T790M-negative or unknown (e.g. insufficient tumor tissue) by central testing. Additional discussion of T790M-negative or unknown patients can be found in Section 9.1.1.

The Phase 2 cohorts were enrolled under several protocol versions. Under Protocol Amendment 4, patients were allocated to Cohort A or Cohort B based on previous treatment history and received rociletinib 750 mg BID. Under Protocol Amendment 6 (Protocol Amendment 5 was not implemented), patients continued to be allocated to Cohort A or B based on previous treatment history; however, within each cohort patients were randomized 1:1 to receive rociletinib 500 mg BID or 625 mg BID. Additionally, Amendment 6 allowed for patients with only local T790M-positive biopsies to enroll in cohort C if all other criteria were met. Under Protocol Amendment 7, the requirement to randomize

Cohort A and B patients to 500 mg BID versus 625 mg BID was removed; patients received rociletinib 625 mg BID until the cohort was filled, then the 500 mg BID cohort was filled sequentially.

In the Phase 2 part of the study, no dose escalation beyond the starting dose was permitted. Dose reduction was allowed per investigator discretion in increments of 125 mg BID.

Patients were treated continuously until disease progression or death. Tumor assessments were performed every 6 weeks. End of study evaluation was conducted 28 days after the last dose. Patients were followed every 2 months to capture subsequent therapy as well as survival data.

3.6.1.2 Dose Selection

Phase 1 of Study 008 enrolled T790M-positive and T790M-negative patients who were treated with rociletinib FB capsules at doses from 150 mg QD to 900 mg BID and then rociletinib 500 mg BID, 625 mg BID, 750 mg BID and 1000 mg BID to determine the MTD.

Since an MTD was not reached in Phase 1, and responses were seen across multiple dose levels, 3 dose levels of 500 mg BID, 625 mg BID and 750 mg BID were further studied in Phase 2.

In Phase 2, patients were initially enrolled at 750 mg BID dose (Amendment 4). However, lower doses appeared to provide better tolerability while maintaining objective response rates, and enrollment was subsequently open at 500 mg BID and 625 mg BID to perform a comprehensive evaluation of dose, response and tolerability across multiple dose levels (Amendment 6). No formal dose comparison analysis was performed in Study 008.

3.6.1.3 Study 019 Design

Study 019 is an ongoing single arm, open-label, dual cohort, multicenter Phase 2 study designed to evaluate the safety and efficacy of rociletinib administered orally BID to patients with previously treated mutant EGFR NSCLC. The primary endpoint is ORR by independent radiological review. Only rociletinib HBr was studied in Study 019. Patients were treated continuously with oral rociletinib daily for each 28 day cycle, with no treatment interruption between cycles. All patients in this study are earlier line patients requiring progression of disease while on treatment with only 1 prior EGFR-TKI which must have been the immediate prior therapy, discontinued within 30 days of starting rociletinib. These patients were required to have measurable disease by RECIST Version 1.1. and to have evidence of T790M mutation in EGFR by sponsor's central laboratory. Patients on Study 019 were only allowed to have 1 prior line of chemotherapy, which had to have been before the initial EGRF inhibitor. While an additional cohort was eventually added to Study 019 after the cutoff for the NDA, 42 patients as described above were enrolled and only these patients are included in the NDA.

No dose escalation beyond the starting dose was permitted. Dose reduction were allowed per investigator discretion in steps of 125 mg BID, with a required dose reduction for Grade 3 QTc events.

Patients were treated continuously until disease progression or death, and tumor assessments were performed every 8 weeks. The end of study evaluation was conducted 28 days after the last dose, and patients were followed every 2 months thereafter.

3.6.1.4 Enrollment Criteria

Study 008 allowed enrollment of mutant EGFR NSCLC patients who had progressive disease while on treatment with the first EGFR-TKI (Cohort B), as well patients who received multiple prior lines of therapy including EGFR TKI(s) (Cohort A). Study 019 focused on T790M-positive mutant EGFR NSCLC patients who had progressive disease while receiving treatment with the first single-agent EGFR-TKI. Otherwise, major inclusion/exclusion criteria were in common for both studies and are typical of those applied to studies in patients with mutant EGFR advanced/metastatic NSCLC:

- Patients must have had histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC with documented evidence of a tumor with 1 or more EGFR mutations excluding exon 20 insertion
- Male or female with a life expectancy of ≥ 3 months, and aged 18 years and older.
- An ECOG PS of 0 to 1 was required.
- Patients who had a history of ILD were excluded from the studies.
- The CNS is a common metastatic site in the population under study, and therefore patients with CNS metastases were included in Studies 008 and 019.
    - However, CNS metastatic disease, if present, was required to be treated, asymptomatic, and stable (defined as not requiring steroids for at least 4 weeks prior to start of study treatment- added in Amendment 7 language for Study 008, included in Study 019 original protocol).
- Patients with leptomeningeal carcinomatosis were excluded from both studies.
- Patients were also excluded from the studies if they were currently receiving treatment with any medication that had the potential to prolong QT interval, who had QTc prolongation at baseline, or who were at increased risk of developing QTc prolongation.
- Finally, the studies required hematologic and selected clinical chemistry serum parameters to be within predefined ranges, to avoid exposing patients who might be at increased risk of AEs.
    - Patients with pre-existing diabetes/impaired glucose tolerance were not excluded from studies of rociletinib.

3.6.1.5 Primary Endpoint

The primary efficacy endpoint for Study 008 was ORR and DOR and for Study 019, the primary efficacy endpoint was ORR. In Study 008, the primary endpoint was determined by investigator assessment. In Study 019, ORR was assessed by IRR of tumor scans.

The choice of ORR as a surrogate endpoint in NSCLC is based on knowledge that a tumor response can be directly attributed to the therapy and, in the absence of treatment, spontaneous tumor regression is extremely rare. In addition, recent meta-analysis by the FDA demonstrated an association between ORR and PFS using study-level and patient-level data in advanced NSCLC (Blumenthal et al 2015). This is relevant for targeted therapy in particular where intermediate end points such as ORR and PFS may be indicated to characterize the benefit-risk profile and establish safety and efficacy while demonstration of OS improvement is challenging in a clinical study setting due to cross over effect and availability of subsequent therapies.

ORR is defined as the number of responding patients (i.e. having a CR or PR) divided by the number of eligible patients, using RECIST Version 1.1. While early reports of rociletinib activity contained mostly Phase 1 patients and included best overall response assessment, only confirmed response data, which required confirmation of a response on a subsequent scan, is used for the purposes of this NDA.

3.6.1.6 Secondary Endpoints

For Study 008 secondary endpoints included:

- ORR, DOR and PFS per RECIST Version 1.1 by IRR
- Incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
- OS, DCR and PFS per RECIST Version 1.1
- Plasma PK parameters
- Change from baseline in patient reported outcomes (PROs)
- Change from baseline in QT/QTc interval

For Study 019 secondary endpoints included:

- DOR, DCR and PFS per RECIST Version 1.1 by IRR
- ORR, DOR, DCR and PFS according to RECIST Version 1.1 as determined by investigator assessment
- OS
- Change from baseline in PROs
- Incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
- Plasma PK parameters

3.6.1.7 Definition of Analysis Populations

The inclusion/exclusion criteria for patients in Study 008 and Study 019 are similar (see Section 3.6.1.4). Furthermore, patient demographics and disease characteristics are similar between the 2 studies and are consistent for patients with recurrent mutant EGFR NSCLC (see Section 3.7). Therefore, data from both studies are combined to allow for a robust assessment of safety and efficacy of rociletinib.

The Safety Population includes any patient who received at least 1 dose of rociletinib HBr, regardless of T790M status. The T790M Positive Population includes patients who received at least 1 dose of rociletinib and were confirmed as positive for T790M mutation by central laboratory. Of note, 4 patients treated at 750mg BID and 4 patients treated at 1000mg BID in the Phase 1 portion of Study 008 did not IRR assessment. Following discussion with FDA during the NDA review, these patients were excluded from the efficacy population.

3.6.1.8 Comparison of Key Study Design Elements of Phase 2 Studies 008 and 019

The key similarities and differences in the design of Studies 008 and 019 are shown in Table 7.

Table 7: Comparison of Key Study Design Elements of Study 008 and Study 019

	008 Phase 2 ***Cohorts A/B***	**019 Phase 2** ***Cohort A***
Study Design	Phase 1/2 study, non-randomized, multiple cohorts	Phase 2, non-randomized, single arm
Patient Type	***Cohort A*:** 1. Disease progression confirmed by radiologic assessment while on treatment with EGFR-TKI (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). Prior chemotherapy, including intervening chemotherapy before planned initiation of CO-1686, is allowed. ***Cohort B:*** 1. Disease progression confirmed by radiologic assessment while receiving treatment with first single agent EGFR TKI (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). a. EGFR TKI treatment discontinued ≤ 30 days prior to planned initiation of rociletinib b. No intervening treatment between cessation of single agent EGFR TKI and planned initiation of rociletinib c. Previous treatment with ≤1 prior chemotherapy (excluding prior neo-adjuvant or adjuvant chemotherapy or chemoradiotherapy with curative intent)	No equivalent population 1. Disease progression confirmed by radiologic assessment while receiving treatment with first single agent EGFR TKI (e.g. erlotinib, gefitinib, afatinib, or dacomitinib) a. EGFR TKI treatment discontinued ≤ 30 days prior to planned initiation of rociletinib b. No intervening treatment between cessation of single agent EGFR TKI and planned initiation of rociletinib c. Previous treatment with ≤1 prior chemotherapy (excluding prior neo-adjuvant or adjuvant chemotherapy or chemoradiotherapy with curative intent)
Mutation Status	EGFR mutation-positive, T790M testing by sponsor's central laboratory	EGFR mutation-positive T790M-postive by sponsor's central laboratory
Primary Endpoint	ORR and DOR by investigator assessment	ORR by IRR
Secondary Endpoints	ORR and DOR by IRR DCR by investigator and IRR assessment PFS, OS	ORR, DOR, DCR by investigator assessment DOR, DCR by investigator and IRR assessment PFS, OS
Radiological Assessments	Every 6 weeks	Every 8 weeks

3.7 PATIENT ENROLLMENT AND CHARACTERISTICS

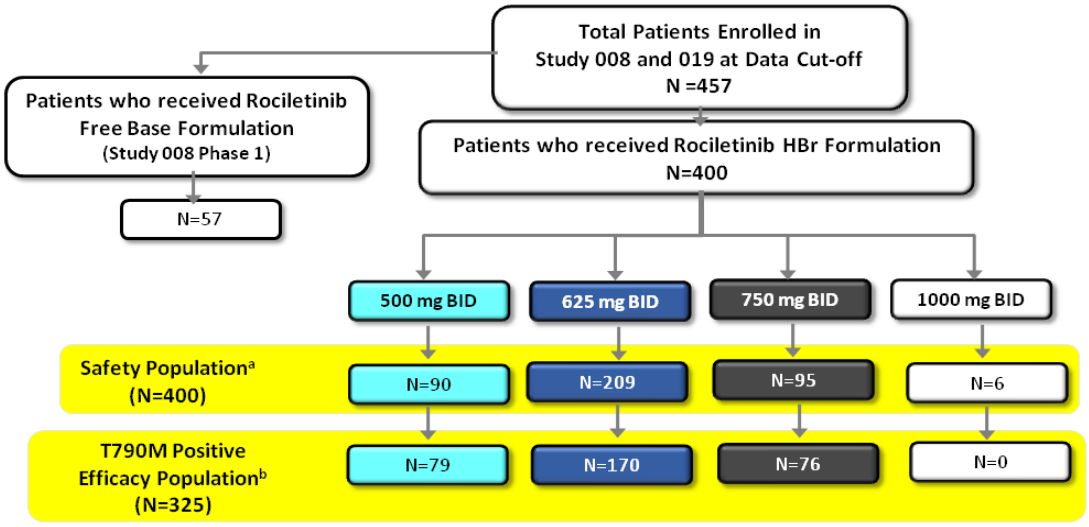
3.7.1 Patient Enrollment

Overall, 457 patients received at least 1 dose of rociletinib FB or rociletinib HBr in Study 008 and at least 1 dose of rociletinib HBr in Study 019. Of the 457 patients, 57 patients received rociletinib FB in the Phase 1 part of Study 008 and are not included in the safety and efficacy analyses. The remaining 400 patients are the safety population, comprised of 90 (23%) patients who received rociletinib 500 mg BID, 209 (52%) patients who received rociletinib 625 mg BID, 95 (24%) patients who received rociletinib 750 mg BID, and 6 (2%) patients who received rociletinib 1000 mg BID (Figure 7).

The primary efficacy population for this NDA contains only patients treated with the rociletinib HBr who have a confirmed 790M mutation by the central laboratory test (T790M-positive; T790M Positve Population) and who were submitted for independent radiographic review (IRR) of tumor response. As such, patients with negative or unknown central T790M tests and all patients at 1000 mg BID are not included in the T790M Positive Population. Overall, 325 patients were T790M-positive by central test and had tumor scans submitted for IRR, including 79 patients treated at 500 mg BID, 170 patients treated at 625 mg BID and 76 patients treated at 750 mg BID.

Primary efficacy analysis of ORR and secondary efficacy analyses of DOR and PFS are presented for the T790M Positive Population according to IRR and investigator assessment where appropriate. The cut-off dates used for patients in the NDA are provided in Table 8.

Figure 7: Patient Enrollment in Study 008 and Study 019 for IRR Analysis



[a] Safety Population includes all patients who received ≥ 1 dose of rociletinib HBr

[b] T790M Positive Population includes patients with a centrally-confirmed T790M positive test who received ≥1 dose of rociletinib HBr and were eligible for IRR assessment of tumor response. Excluded are 34 patients across doses who were T790M-negative, 33 patients across doses who were T790M-unknown, and 4 T790M-positive patients each at 750mg BID and 1000mg BID doses who did not have an IRR assessment.

Table 8: Patient Enrollment and Data Cut-off Dates

Dose Group	N	Enrollment Cut-off Date	Includes All Visits Prior to:
500 mg BID			
All	90	20 March 2015	
T790M-positive patients	79		31 July 2015
625 mg BID			
All	209	31 December 2014	
T790M-positive patients	170		
750 mg BID			
All	95	31 December 2014	31 December 2014
T790M-positive patients	76		
All other doses and patients	63	31 December 2014	31 December 2014

[a]Total calculations in tables with data from all doses include updated data for patients initially treated at 500 mg BID or 625 mg BID but also include data from the initial NDA submission cut-off of 31 December 2014 for patients initially treated at doses of 750 mg BID or 1000 mg BID.

3.7.2 Rociletinib Exposure

Overall, rociletinib exposure based on median number of cycles and median duration of treatment was similar for patients who received 500 mg BID, 625 mg BID, and 750 mg BID doses. As of the data cut-off date of 31 July 2015, the median duration of treatment was 157 days (5.2 months), 128 days (4.2 months), 176 days (5.8 months), 213 days (7.0 months) in the 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID dose groups and 150 days (5.0 months) for all dose groups combined (Table 9).

Table 9: Rociletinib Exposure in Patients Treated with 500-1000 mg BID

	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID (N=6)	Overall (N=400)
Number of Cycles Initiated					
Mean (SD)	8.9 (5.63)	7.5 (5.42)	8.6 (4.83)	10.8 (7.47)	8.1 (5.40)
Median	8.0	7.0	9.0	10.0	7.5
Min, Max	1, 22	1, 28	1, 22	2, 20	1, 28
Duration of Treatment (days)					
Mean (SD)	181.9 (117.44)	151.8 (114.73)	171.2 (98.50)	223.5 (158.89)	164.2 (112.95)
Median	157.0	128.0	176.0	212.5	149.5
Min, Max	8, 459	1, 571	12, 443	42, 409	1, 571
Duration of Treatment (months)					
<6 months	57 (63.3%)	131 (62.7%)	50 (52.6%)	2 (33.3%)	240 (60.0%)
6-12 months	28 (31.1%)	71 (34.0%)	41 (43.2%)	2 (33.3%)	142 (35.5%)

	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID (N=6)	Overall (N=400)
>12 months	5 (5.6%)	7 (3.3%)	4 (4.2%)	2 (33.3%)	18 (4.5%)
Dose Intensity [a]					
Mean (SD)	0.88 (0.168)	0.87 (0.160)	0.77 (0.195)	0.83 (0.210)	0.85 (0.176)
Median	0.93	0.91	0.79	0.93	0.90
Min, Max	0.3, 1.3	0.1, 1.0	0.4, 1.0	0.5, 1.0	0.1, 1.3

Abbreviations: BID = twice daily; NDA = New Drug Application; SD = standard deviation.
[a] Defined as the actual dose received divided by the first dose.

3.7.3 Patient Demographics and Disease Characteristics

The study population in Studies 008 and 019 was representative of the population of EGFR NSCLC patients with recurrent disease after standard EGFR TKI therapy in the US. Baseline characteristics were similar across the dosing groups (Table 10). The majority of patients were non-Asian (75% of those whose race was available) and enrolled in the UK (89%). Most patients were female (70%), non-smokers (64%) with a median age of 62 years. Overall, 99% of patients had ECOG PS 0-1, and 46% had a history of CNS involvement. These characteristics indicate poor prognosis. Eleven percent of patients had a history of hyperglycemia.

All patients had confirmed presence of EGFR activating mutation with 59% of patients carrying Exon 19 Deletion and 23% of patients positive for L858R. The results of T790M status assessment using companion diagnostic test was similar across all dose groups. Overall, 83% of patients were confirmed as T790M-positive based on tumor tissue obtained at the time of progression but prior to entry into the study.

Patients had recurrent disease with a median of 27 months from the time of the initial diagnosis and with the extent of the disease involving more than 2 sites in 83% of patients, with lymph node, CNS, bone, and liver being the most common sites of metastatic disease. Patients received a median of 2 prior therapies for lung cancer, including 38% of patients who received more than 1 prior EGFR TKI. The median number of days between stopping the prior EGFR TKI and starting rociletinib was 6 days.

Baseline demographics were generally consistent in Safety Population and T790M Positive Population (Appendix 11.2, Table 28).

Table 10: Baseline Demographics in the Safety Population

	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID (N=6)	Overall (N=400)
Age (yr)					
Mean (SD)	60.7 (10.95)	62.1 (11.47)	61.5 (11.82)	65.2 (5.53)	61.7 (11.36)
Median	61.0	63.0	62.0	64.5	62.0
Age Group					
≤50	13 (14.4%)	38 (18.2%)	13 (13.7%)	0	64 (16.0%)
51-64	39 (43.3%)	76 (36.4%)	41 (43.2%)	3 (50.0%)	159 (39.8%)
65-80	35 (38.9%)	85 (40.7%)	36 (37.9%)	3 (50.0%)	159 (39.8%)
≥81	3 (3.3%)	10 (4.8%)	5 (5.3%)	0	18 (4.5%)
Gender					
Female	66 (73.3%)	144 (68.9%)	63 (66.3%)	5 (83.3%)	278 (69.5%)
Race					
White	60 (66.7%)	123 (58.9%)	66 (69.5%)	5 (83.3%)	254 (63.5%)
Black	3 (3.3%)	7 (3.3%)	2 (2.1%)	0	12 (3.0%)
Asian	16 (17.8%)	48 (23.0%)	24 (25.3%)	1 (16.7%)	89 (22.3%)
Other	11 (12.2%)	31 (14.8%)	3 (3.2%)	0	45 (11.3%)
Geographic Region					
North America	69 (76.7%)	172 (82.3%)	82 (86.3%)	6 (100.0%)	329 (82.3%)
Europe	15 (16.7%)	20 (9.6%)	5 (5.3%)	0	40 (10.0%)
Other	6 (6.7%)	17 (8.1%)	8 (8.4%)	0	31 (7.8%)
ECOG at Baseline					
0	21 (23.3%)	56 (26.8%)	31 (32.6%)	3 (50.0%)	111 (27.8%)
1	68 (75.6%)	152 (72.7%)	64 (67.4%)	3 (50.0%)	287 (71.8%)
≥2	1 (1.1%)	1 (0.5%)	0	0	2 (0.5%)
Time Since Diagnosis of NSCLC (months)					
n	90	209	95	6	400
Mean (SD)	35.3 (20.58)	33.1 (29.10)	37.6 (29.97)	47.4 (27.03)	34.9 (27.62)
Median	31.8	23.5	27.1	41.3	26.7
Time Since Diagnosis of NSCLC Group (months)					
≤3	0	2 (1.0%)	0	0	2 (0.5%)
>3-6	0	0	1 (1.1%)	0	1 (0.3%)
>6-12	6 (6.7%)	24 (11.5%)	9 (9.5%)	0	39 (9.8%)
>12-24	31 (34.4%)	82 (39.2%)	29 (30.5%)	1 (16.7%)	143 (35.8%)
>24	53 (58.9%)	101 (48.3%)	56 (58.9%)	5 (83.3%)	215 (53.8%)
History of CNS Metastases					
Yes	42 (46.7%)	96 (45.9%)	43 (45.3%)	3 (50.0%)	184 (46.0%)
Metastatic Disease Site *					

	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID (N=6)	Overall (N=400)
Lung	83 (92.2%)	197 (94.3%)	91 (95.8%)	6 (100.0%)	377 (94.3%)
Lymph Node	41 (45.6%)	98 (46.9%)	44 (46.3%)	4 (66.7%)	187 (46.8%)
Liver	27 (30.0%)	64 (30.6%)	33 (34.7%)	2 (33.3%)	126 (31.5%)
Bone	32 (35.6%)	75 (35.9%)	41 (43.2%)	3 (50.0%)	151 (37.8%)
CNS	30 (33.3%)	94 (45.0%)	44 (46.3%)	3 (50.0%)	171 (42.8%)
Other	17 (18.9%)	47 (22.5%)	20 (21.1%)	1 (16.7%)	85 (21.3%)
Number of Metastatic Disease Sites					
1	14 (15.6%)	39 (18.7%)	16 (16.8%)	1 (16.7%)	70 (17.5%)
≥2	76 (84.4%)	170 (81.3%)	79 (83.2%)	5 (83.3%)	330 (82.5%)
Number of Previous Therapies					
Mean (SD)	3.0 (1.71)	2.6 (1.91)	2.9 (2.11)	3.8 (2.04)	2.8 (1.92)
Median	3.0	2.0	2.0	3.5	2.0
Min, Max	1.0, 8.0	1.0, 13.0	1.0, 9.0	1.0, 7.0	1.0, 13.0
Number of Previous Therapies Group					
1	22 (24.4%)	78 (37.3%)	38 (40.0%)	1 (16.7%)	139 (34.8%)
≥2	68 (75.6%)	131 (62.7%)	57 (60.0%)	5 (83.3%)	261 (65.2%)
Number of Previous EGFR TKI Therapies					
Mean (SD)	1.5 (0.78)	1.5 (0.76)	1.6 (0.86)	1.8 (0.75)	1.5 (0.79)
Median	1.0	1.0	1.0	2.0	1.0
Number of Previous EGFR TKI Therapies Group					
0	0	0	0	0	0
1	55 (61.1%)	135 (64.6%)	55 (57.9%)	2 (33.3%)	247 (61.8%)
≥2	35 (38.9%)	74 (35.4%)	40 (42.1%)	4 (66.7%)	153 (38.3%)
Time Between Last Dose of a TKI and First Dose of Study Drug (days)					
Mean (SD)	73.3 (133.96)	46.8 (113.05)	37.5 (95.21)	112.2 (152.26)	51.5 (115.38)
Median	7.0	6.0	5.0	27.5	6.0
EGFR Activating Mutations					
Ex 19 Del	51 (56.7%)	125 (59.8%)	59 (62.1%)	0	235 (58.8%)
L858R	25 (27.8%)	48 (23.0%)	18 (18.9%)	0	91 (22.8%)
Other	3 (3.3%)	6 (2.9%)	1 (1.1%)	0	10 (2.5%)
T790M Status (Central Laboratory)					
Negative	5 (5.6%)	20 (9.6%)	9 (9.5%)	0	34 (8.5%)
Positive	79 (87.8%)	170 (81.3%)	80 (84.2%)	4 (66.7%)	333 (83.3%)
Unknown	4 (4.4%)	1 (0.5%)	1 (1.1%)	2 (33.3%)	8 (2.0%)
Missing	2 (2.2%)	18 (8.6%)	5 (5.3%)	0	25 (6.3%)
History of Hyperglycemia					
Yes	9 (10.0%)	28 (13.4%)	6 (6.3%)	0	43 (10.8%)

3.7.4 Patient Disposition

Overall, patient disposition including reasons for discontinuation of therapy was similar for patients who received 500 mg BID, 625 mg BID, 750 mg BID, and all rociletinib dose groups combined. Overall, 39% of patients continued to receive rociletinib therapy. The main reason for treatment discontinuation was progressive disease (75%), followed by AEs in 14% of patients. Patient disposition was generally consistent in the Safety Population (Table 11) and T790M Positive Population (Appendix 11.1, Table 29).

Table 11: Patient Disposition in the Safety Population

	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID (N=6)	Overall (N=400)
	n (%)	n (%)	n (%)	n (%)	n (%)
End-of-Treatment Status					
Ongoing	37 (41.1)	81 (38.8)	37 (38.9)	2 (33.3)	157 (39.3)
Discontinued	53 (58.9)	128 (61.2)	58 (61.1)	4 (66.7)	243 (60.8)
Primary Reason for Discontinuation of Rociletinib[a]					
Progressive disease	41 (77.4)	93 (72.7)	45 (77.6)	2 (50.0)	181 (74.5)
Adverse event	8 (15.1)	18 (14.1)	6 (10.3)	2 (50.0)	34 (14.0)
Withdrawal by patient	1 (1.9)	5 (3.9)	3 (5.2)	0	9 (3.7)
Other	1 (1.9)	5 (3.9)	2 (3.4)	0	8 (3.3)
Physician decision	1 (1.9)	3 (2.3)	0	0	4 (1.6)
Lost to follow-up	0	1 (0.8)	0	0	1 (0.4)
Protocol deviation	0	1 (0.8)	0	0	1 (0.4)
Missing	1 (1.9)	2 (1.6)	2 (3.4)	0	5 (2.1)

Abbreviations: BID = twice daily.
[a] Percentages based on the number of patients who discontinued rociletinib at each dose.

4 EFFICACY FINDINGS IN STUDY 008 AND STUDY 019

Efficacy analyses were performed based on T790M Positive Population (N = 325), which includes all T790M-positive patients who received at least 1 dose of rociletinib (see Figure 7) and had IRR analyses. Of note, 4 patients treated at 750mg BID and 4 patients treated at 1000mg BID in the Phase 1 portion of Study 008 did not IRR assessment. Following discussion with FDA during the NDA review, these patients were excluded from the efficacy population. Tumor response data (ORR, DOR) is provided for the 500 mg BID, 625 mg BID, and 750 mg BID dose groups. Additionally, because there was no relationship established between dose or exposure and ORR (Section 4.4), these dose groups were combined to provide a reliable estimate of rociletinib activity. Efficacy data for 500 mg BID, 625 mg BID, and 750 mg BID dose groups combined (overall) are presented where appropriate.

Because of the similarity of inclusion and exclusion criteria and the patient demographics and disease characteristics, clinical data from Study 008 and Study 019 are combined (see Section 3.6.1). For the combined analyses, the efficacy analysis of interest is ORR by IRR. Although IRR analysis may be associated with less observer bias, data from the individual studies show similar results between the 2 assessment methods (investigator assessment and independent assessment), suggesting that observer bias has not influenced the investigator assessed results in these studies. Confirmed ORR was defined as CR or PR as determined by the IRR or investigator, with response and/or progression evaluated using the RECIST Version 1.1. According to RECIST Version 1.1 criteria, confirmation of a response on a subsequent scan at least 1 month after the response was first observed, is required for confirmed ORR. The frequency and percentages of patients with a best objective response of CR, PR, stable disease (SD), or progressive disease (PD) are summarized.

As described in Section 3.6.1.5, the primary efficacy analysis of ORR was based on investigator assessment in Study 008, whereas in Study 019, ORR was based on assessment by IRR.

Nearly all scheduled tumor scans for patients on study were collected as 92% of patients had a complete set of tumor scans and only 6% and 1% of patients were missing 1 and 2 scans, respectively. In addition, the independent reviewers were able to read all the scans for 85% of the patients with 11% of patients missing 1 scan and 4% missing 2 or more scans.

4.1 PRIMARY EFFICACY ANALYSIS: ORR

Results for the primary endpoint of ORR for T790M Positive Population by IRR are shown in Table 12. Overall the ORR for the combined doses was 30.2% (95% CI 25.2 - 35.5%). The upper boundary of the 95% CI were overlapping for the 500 mg BID, 625 mg BID, and 750 mg BID dose groups. Median estimates of ORR were similar for 625 mg BID, 750 mg BID, and for all rociletinib doses combined: 32.4%, 32.9%, and 30.2%, respectively. The median estimate of ORR for the 500 mg BID dose group (22.8%) was slightly below the lower boundary of 95% CI for ORR for all rociletinib doses combined (25.2%).

Table 12: Confirmed Objective Response Rate by IRR (T790M Positive Population)

	500 BID N = 79	**625 BID N = 170**	**750 BID N = 76**	**Overall N = 325**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Confirmed Response Rate	18 (22.8)	55 (32.4)	25 (32.9)	98 (30.2)
95% CI	14.1 - 33.6%	25.4 - 39.9%	22.5 - 44.6%	25.2 - 35.5%
Best Overall Confirmed Response				
CR	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
PR	18 (22.8)	54 (31.8)	25 (32.9)	97 (29.8)
SD[a]	38 (48.1)	56 (32.9)	25 (32.9)	119 (36.6)
PD	10 (12.7)	32 (18.8)	14 (18.4)	56 (17.2)
Not evaluable[b]	13 (16.5)	27 (15.9)	12 (15.8)	52 (16.0)

[a] All SD patients including SD ongoing without progressive disease.
[b] Patients without sufficient data to evaluate a tumor response due to one of the following reasons: patient died before the scan, patient discontinued before the scan, patient had no valid baseline lesions, or no data available for technical reasons.

Results for the ORR for T790M Positive Population by investigator assessment are shown in Table 30. Overall, results by investigator assessment were consistent with IRR analysis with 31.4% (95% CI 26.4 - 36.7%) ORR for all rociletinib doses combined. The ORR for 500 mg BID, 625 mg BID, 750 mg BID dose groups were 27.8%, 33.5%, and 30.3%, respectively.

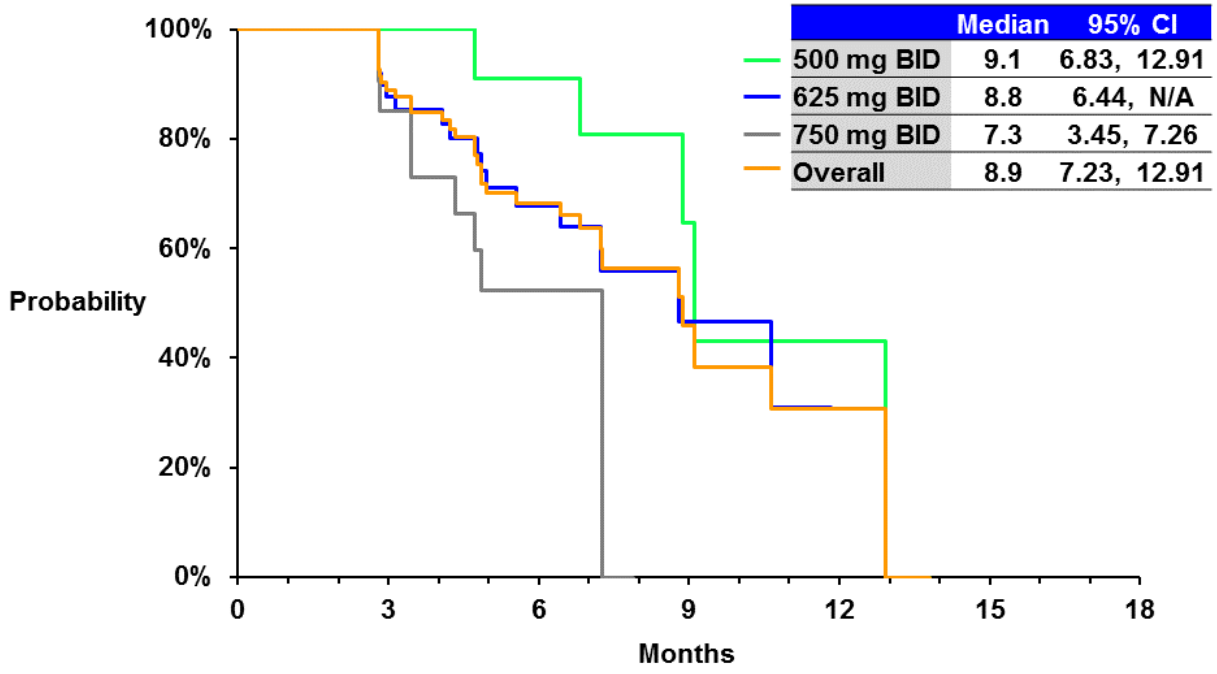
The frequency of SD varied across doses; at least 32.9% of patients experienced SD as assessed by IRR and investigator.

4.2 SECONDARY ANALYSES

4.2.1 Duration of Response

Patients who responded to rociletinib experienced significant DOR. For the rociletinib dose groups combined, the median DOR was 270 days (8.9 months) based on IRR, and for the individual dose groups, the duration of response was 277 days (9.1 months), 268 days (8.8 months), and 221 days (7.3 months) for 500 mg BID, 625 mg BID and 750 mg BID, respectively (Figure 8). Responses occurred rapidly, with approximately 75% of patients with a response exhibiting the response at their first tumor assessment. Data for the DOR based on investigator assessment can be found in Appendix 11.3, Figure 19.

Figure 8: Duration of Confirmed Response by IRR Assessment for 500 mg BID, 625 mg BID and 750 mg BID and All Doses Combined (T790M Positive Population)

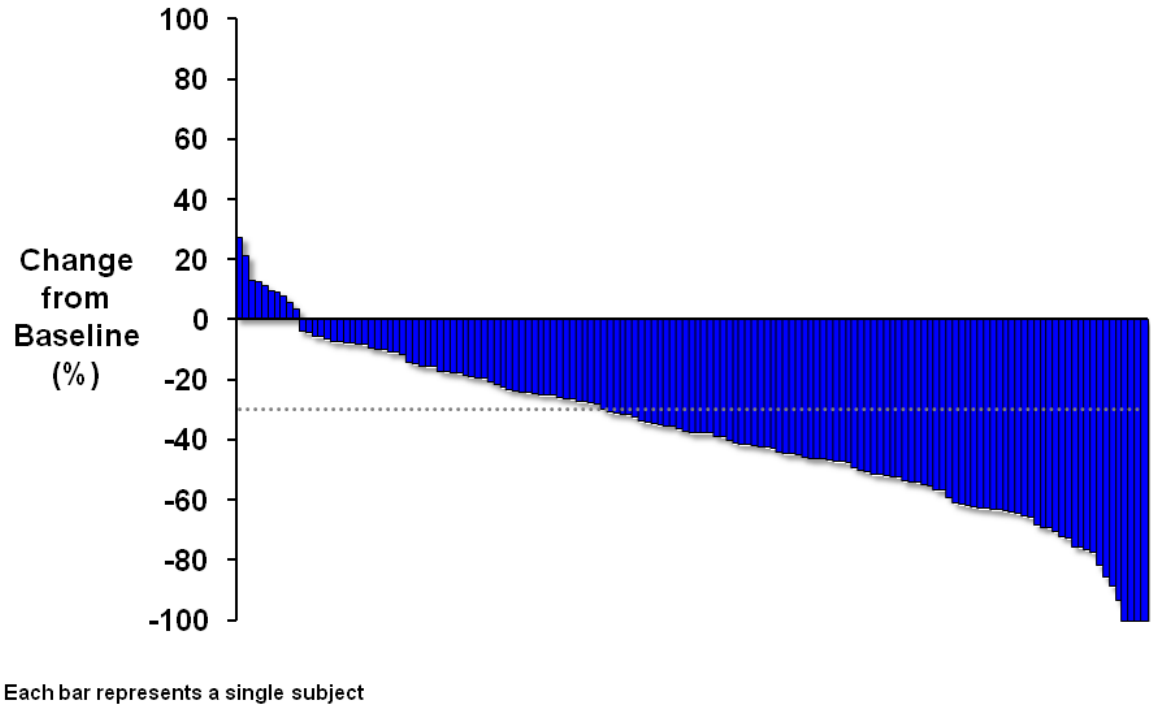


Abbreviations: BID = twice daily; CI = confidence interval

4.2.2 Target Lesion Reduction

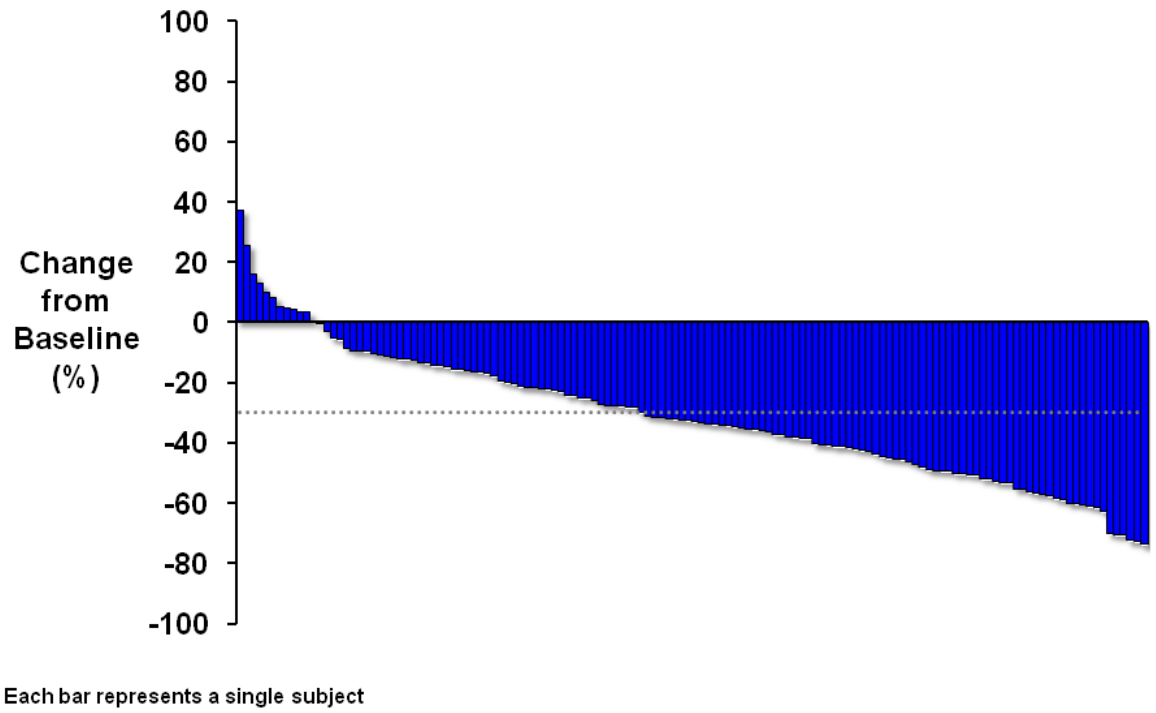
The direct assessment of anti-tumor activity is a reduction of measurable disease evident by tumor target lesion reduction, because in advanced NSCLC, tumor lesions rarely shrink spontaneously. In the largest dose group,625 mg BID, 149 patients (91.5%) of the 163 patients with target lesions present at baseline experienced target lesion reduction when compared to baseline based on IRR assessment. Two independent reviewers assessed each patient. Each reviewer separately evaluated target lesions and target lesions were not part of the adjudication process, so target lesions are presented separately for the 2 reviewers (Figure 9 and Figure 10).

Figure 9: Best Response in Sum of Target Lesions per RECIST as Assessed by IRR Reviewer 1



Note: Patients whodid not have target lesions were excluded from this analysis. Each bar represents a single patient. Patients with zero percent change from baseline are shown as 0.5 for visual clarity.

Figure 10: Best Response in Sum of Target Lesions per RECIST as Assessed by IRR Reviewer 2

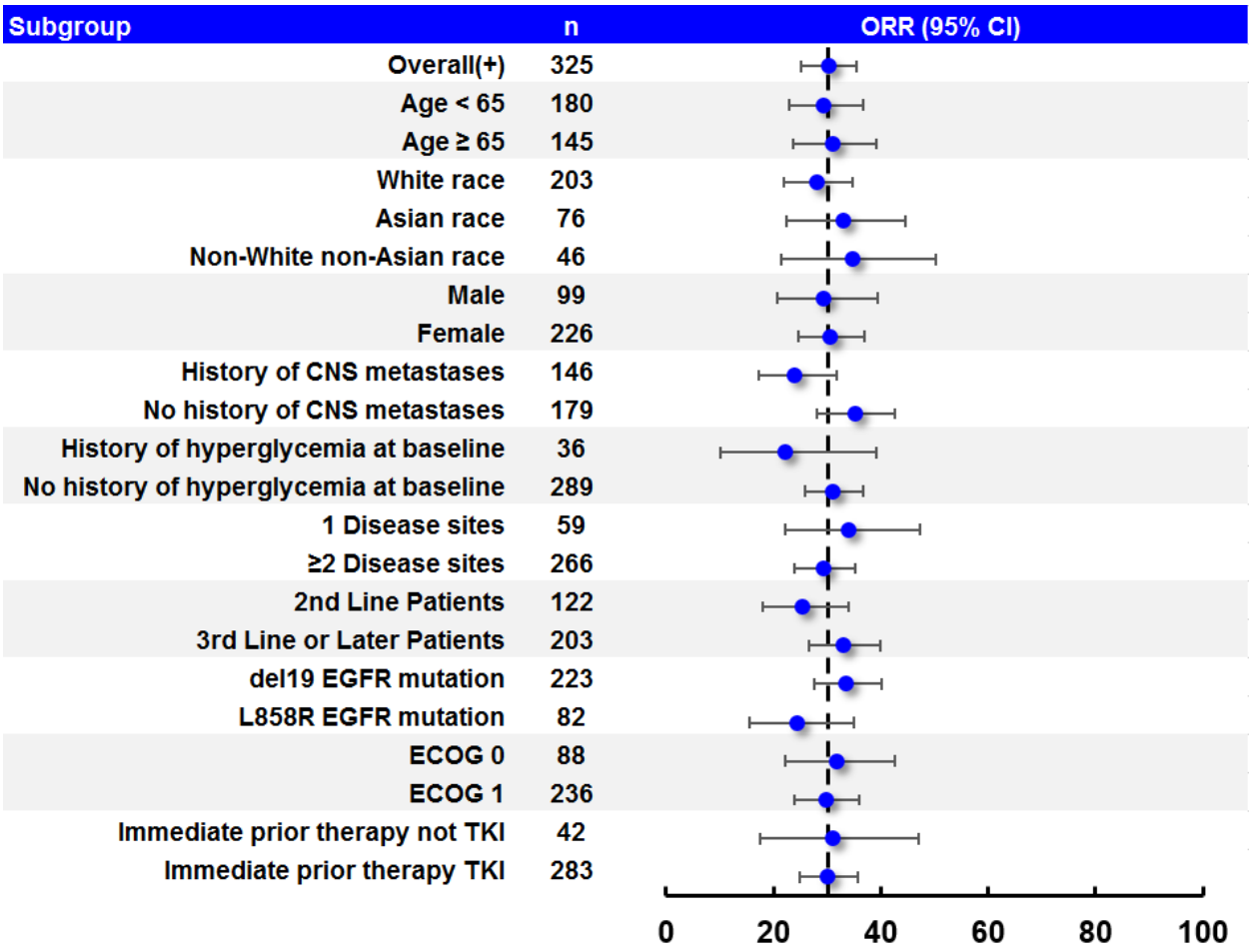


Note: Patients whodid not have target lesions were excluded from this analysis. Each bar represents a single patient. Patients with zero percent change from baseline are shown as 0.5 for visual clarity.

4.3 CONSISTENCY OF FINDINGS ACROSS PATIENT SUBGROUPS

ORR was consistent across all major clinically relevant subgroups. Figure 11 presents a forest plot of ORR based on IRR by subgroup for the rociletinib dose groups combined. Substantial tumor response was observed in patients with the following poor prognostic factors: over 65 years of age, ECOG 1 performance status, history of CNS disease, ≥ 2 sites of disease, and ≥2 previous lines of prior therapy, as well as patients with significant comorbidities, such as patients with a history of hyperglycemia and patients taking anti-hyperglycemia medications. Consistent findings were observed in the subgroup analysis of the rociletinib dose groups combined based on investigator assessment (Appendix 11.3, Figure 20).

Figure 11: ORR by IRR Assessment Across Subgroups for Doses Combined (T790M Positive)



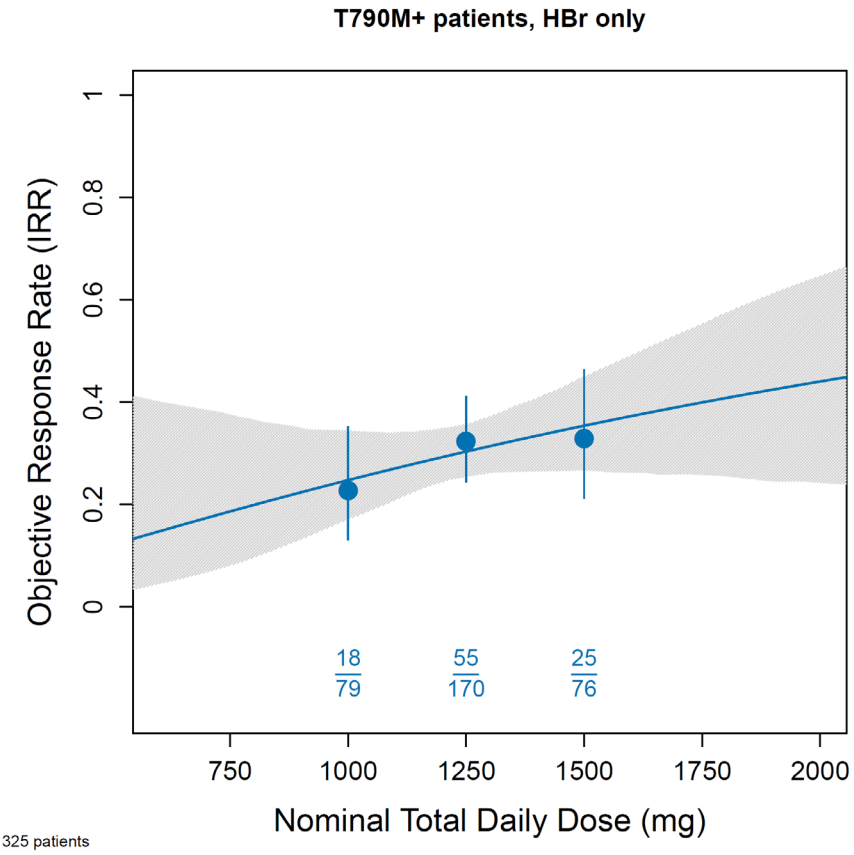
Dotted line represents the overall ORR across all doses in 325 patients (30.2%)

4.4 EXPOSURE RESPONSE ANALYSIS

4.4.1 Exposure and ORR Based on IRR

Dose response analysis by IRR in T790M-positive patients in the rociletinib 500 mg BID, 625 mg BID, and 750 mg BID dose groups is presented in Figure 12. In T790M-positive patients, there is a trend of increasing ORR with dose, however it is not statistically significant when limiting the analysis set to data from 500 mg BID, 625 mg BID, and 750 mg BID dose groups.

Figure 12: ORR by IRR Stratified by Daily Dose in T790M-positive Patients



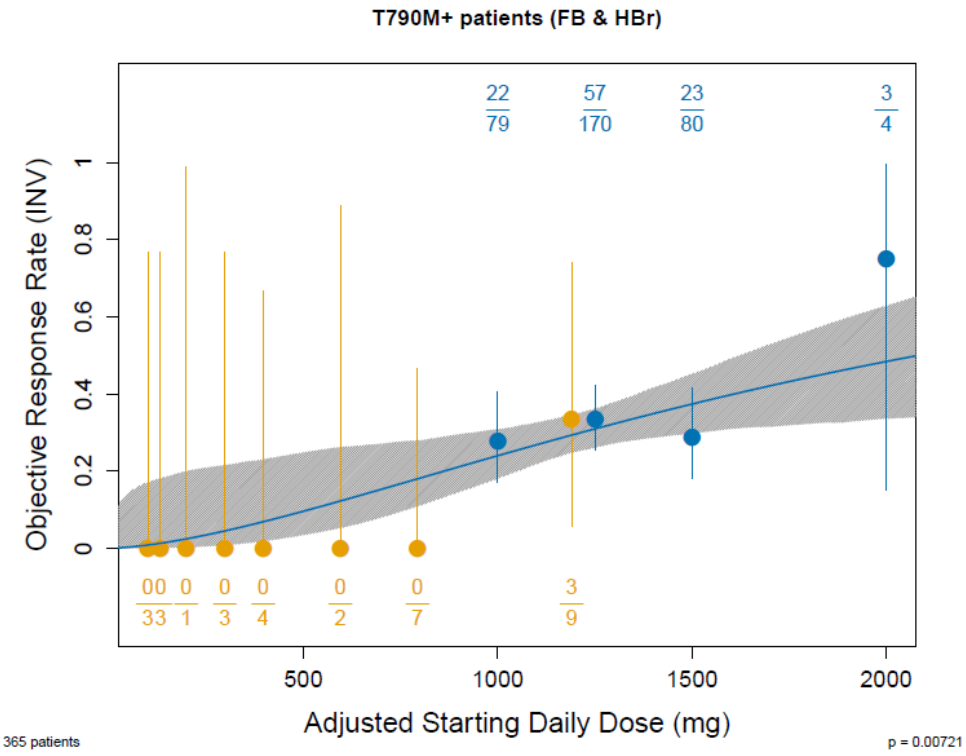
Individual PK parameter post-hoc estimates from the final population PK models were used to predict rociletinib exposure at steady state for each patient, assuming a nominal dosing history. The predicted maximum or minimum concentration at steady-state ($C_{max,ss}$, $C_{min,ss}$) and area under the 0 to 24 hour concentration curve at steady-state (AUC_{ss}) were calculated for all patients with PK parameter estimates. Rociletinib exposure (AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$) and ORR by IRR relationship is described in Appendix 11.4, Figure 21. Dose and exposure response relationships were assessed using logistic regression models, where the logit relationship could be linear or log-linear function of each exposure metric (AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$). In T790M-positive patients, the ORR by IRR relationship with exposure is flat when limiting the analysis set to data from 500 mg BID, 625 mg BID, and 750 mg BID dose groups. No significant relationships were identified with age, sex, weight, BMI, race, or history of hyperglycemia.

4.4.2 Exposure and ORR Based on Investigator Assessment

While assessment of ORR by IRR is limited to 500 mg BID, 625 mg BID, and 750 mg BID, response data based on investigator assessment is available for a wider range of doses from Phase 1 and Phase 2 of Study 008, including patients who received rociletinib FB early on during the dose escalation part of the study. Since bioavailability of rociletinib in the FB formulation is approximately 66.1% of the HBr

formulation, nominal dose of the FB formulation can be scaled to the HBr formulation equivalent and relationship with response rates based on investigator assessment can be evaluated. The dose-response analysis in the 365 T790M-positive patients who received rociletinib across several dose levels including doses that would be below 500 mg BID suggested that confirmed ORR by investigator assessment correlated significantly with the adjusted starting daily dose (ie, FB nominal daily dose was adjusted to HBr equivalent daily dose) (p=0.00721) (Figure 13).

Figure 13: Dose-response Relationship for ORR by Investigator Assessment in T790M-positive Patients

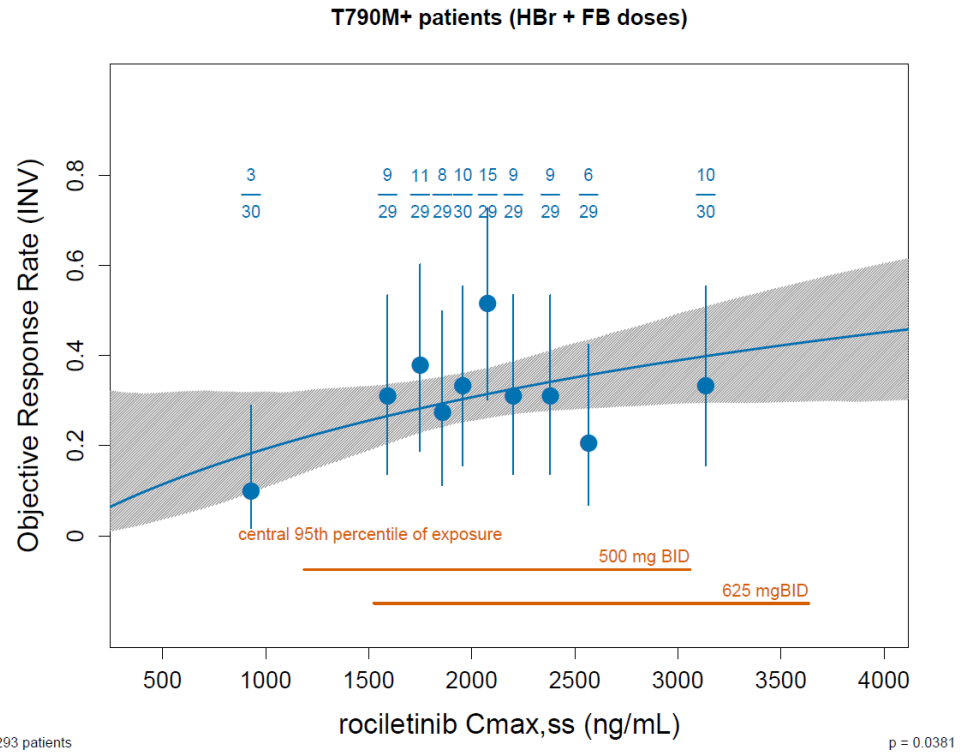


Twenty-three patients at doses below 900 mg FB, including 2 Phase 1 patients with no measurable disease, are included in the analysis.

Note: A univariate logistic regression relationship with the log of the adjusted daily dose is shown by the solid blue line with the gray shaded area representing the 95% confidence interval, visualized on a linear x-axis. A total of 108 events are shown for 365 patients. Each gold circle represents the confirmed ORR by investigator assessment for each FB dose group. Each blue circle represents the confirmed ORR by investigator assessment for each HBr dose group. The error bars on each point are the 95% confidence intervals calculated using the Clopper-Pearson method. The ratios at the top and bottom of the figure are the number of events (numerator) and total number of patients (denominator) in each dose group.

Using model-predicted steady state rociletinib exposures for all PK-evaluable patients, regardless of rociletinib formulation, logistic regression relationships with confirmed ORR by investigator assessment were evaluated. The confirmed ORR by investigator assessment correlated significantly with $C_{max,ss}$ in a log-linear relationship (p = 0.038)

Figure 14: Exposure-response Relationship Between Confirmed ORR by Investigator Assessment and $C_{max,ss}$ in T790M-positive Patients

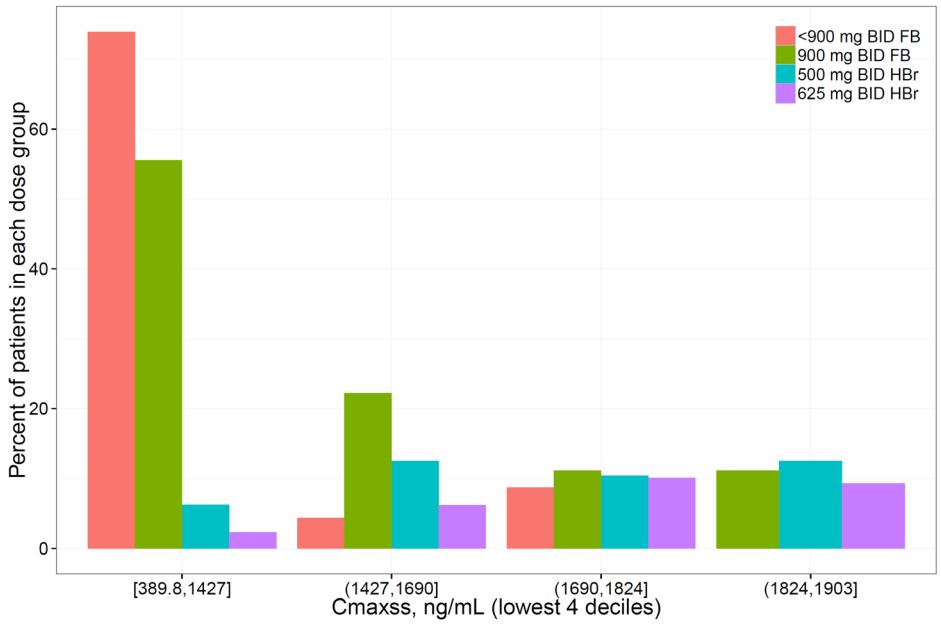


Twenty-three patients at doses below 900 mg FB, including 2 Phase 1 patients with no measurable disease, are included in the analysis.

Note: A univariate logistic regression relationship with the log of rociletinib $C_{max,ss}$ is shown by the solid blue line with the gray shaded area representing the 95% confidence interval, visualized on a linear x-axis. A total of 90 events are shown for 293 patients. Each solid circle represents the ORR in each of 10 equally sized bins (~30 patients each). The error bars on each point are the 95% confidence intervals calculated using the Clopper-Pearson method. The ratios at the top of the figure are the number of events (numerator) and total number of patients (denominator) in each bin of exposure.

The exposure-response analysis suggests that the threshold for response lies between the lowest 2 deciles of exposures in PK-evaluable T790M-positive patients. To compare the likelihood of patients in the 500 mg BID and 625 mg BID dose groups falling into the lower range of exposures, the fraction of patients in the 500 mg BID and 625 mg BID dose groups falling into the lower deciles of the model-predicted $C_{max,ss}$, AUC_{ss} or $C_{min,ss}$ were calculated. As shown in Figure 15, 78%, 78%, 19%, 9% of patients at the starting dose of less than 900 mg FB BID, 900 mg FB BID, 500 mg HBr BID, and 625 mg HBr BID, respectively, have rociletinib $C_{max,ss}$ that are in the lowest 2 deciles.

Figure 15: Percent of Patients from Selected Dose Groups Across the Lowest Four of 10 Quantiles for $C_{max,ss}$



In conclusion, ORR by investigator assessment correlated significantly with rociletinib doses when all doses, regardless of formulation, were included in the analysis. PopPK model- predicted rociletinib exposure at steady state, when based on a broad range of doses including rociletinib free base formulation, shows significant correlation between ORR by investigator assessment and rociletinib $C_{max,ss}$. PopPK model based on the larger patient population revealed that at the starting dose of 500 mg HBr BID, a higher percentage of patients have rociletinib exposure in the lowest 2 deciles than at 625 mg HBr BID dose.

4.5 EFFICACY CONCLUSIONS

Across the doses groups, rociletinib demonstrated clinically meaningful and durable responses in T790M-positive mutant EGFR NSCLC patients with recurrent disease. Overall, the ORR was 30.2% (95% CI 25.2 – 35.5%) for rociletinib doses combined (n=325). Logistic regression analyses of ORR by IRR revealed no statistically significant dose- or exposure-response relationships based on IRR.

The ORR and 95% CI were similar between the 625 mg BID dose group and rociletinib doses combined (32.4% [95% CI 25.4 - 39.9%] and 30.2% [95% CI 25.2 - 35.5%], respectively). Thus, the ORR for the 625 mg BID dose group, which represents 52% (n=170) of T790M-positive patients who received rociletinib, should provide the most robust estimate of efficacy. Similar findings were reported based on the investigator assessment of ORR.

Patients who responded to rociletinib experienced a significant DOR. For all rociletinib dose groups combined, the duration of confirmed response was 270 days (8.9 months) based on IRR. For rociletinib 625 mg BID, the DOR was 268 days (8.8 months).

ORRs were consistent across all major clinically-relevant subgroups, including patients with poor prognostic factors such as over 65 years of age, ECOG 1 performance status, history of CNS disease, ≥2 sites of disease, ≥ 2 lines of prior therapy.

ORR by investigator assessment correlated significantly with rociletinib doses when all doses, regardless of formulation, were included in the analysis. PopPK-model-predicted-rociletinib-exposure at steady state, when based on a broad range of doses including rociletinib FB formulation, shows significant correlation between ORR by investigator assessment and rociletinib $C_{max,ss}$. PopPK model based on a larger patient population revealed that at the starting dose of 500 mg HBr BID, a higher percentage of patients have rociletinib exposure that are in the lowest 2 deciles than for 625 mg HBr BID dose.

5 SAFETY FINDINGS IN STUDY 008 AND STUDY 019

5.1 EXTENT OF EXPOSURE

The safety population contains 400 patients who initiated treatment with rociletinib 500 mg BID (n=90), 625 mg BID (n=209), 750 mg BID (n=95), or 1000 mg BID (n=6) (Table 9). The median duration of treatment was 149.5 days (4.9 months) and ranged from 1 day to 571 days (18.8 months) across doses. Across all doses, 40% of patients were treated with rociletinib for longer than 6 months.

5.2 TREATMENT EMERGENT ADVERSE EVENTS

Almost all patients treated with rociletinib reported 1 or more treatment-emergent AE regardless of causality (Table 13). The rate of TEAEs leading to discontinuation was similar across all doses (21% overall) and included 38 (45%) events disease progression across all doses. The rate of serious adverse events (SAEs) across doses was 47%. Thirteen percent, 17%, and 15% of patients experienced an AE with an outcome of death in the 500 mg, 625 mg, and 750 mg dose groups, respectively. Overall 16% of patients experienced an AE with an outcome of death, however, 86% of these reported deaths were related to disease progression.

Table 13: Overall Summary of Treatment Emergent AEs in Patients Treated with Rociletinib 500-1000 mg BID

	500 mg BID N = 90	625 mg BID N = 209	750 mg BID N = 95	1000 mg BID N = 6	Overall (N = 400)
	n (%)	n (%)	n (%)	n (%)	n (%)
Number (%) of Patients with at Least 1:					
AE	9 (100)	207 (99.0)	95 (100)	6 (100)	398 (99.5)
SAE	40 (44.4)	97 (46.4)	45 (47.4)	5 (83.3)	187 (46.8)
Maximum Intensity					
Grade 1	5 (5.6)	15 (7.2)	4 (4.2)	0	24 (6.0)
Grade 2	22 (24.4)	40 (19.1)	15 (15.8)	1 (16.7)	78 (19.5)
Grade 3	45 (50.0)	101 (48.3)	55 (57.9)	2 (33.3)	203 (50.8)
Grade 4	6 (6.7)	16 (7.7)	7 (7.4)	0	29 (7.3)
AE with an outcome of death[a]	12 (13.3)	35 (16.7)	14 (14.7)	3 (50.0)	64 (16.0)
AE leading to rociletinib discontinuation[b]	18 (20.0)	45 (21.5)	19 (20.0)	3 (50.0)	85 (21.3)
AE leading to rociletinib discontinuation (excluding events of disease progression)	11 (12.2)	24 (11.5)	10 (10.5)	2 (33.3)	47 (11.8)
AE leading to rociletinib interruption	50 (55.6)	114 (54.5)	56 (58.9)	3 (50.0)	223 (55.8)
AE leading to rociletinib dose reduction	36 (40.0)	99 (47.4)	64 (67.4)	4 (66.7)	203 (50.8)
AE leading to rociletinib dose reduction or interruption	54 (60.0)	132 (63.2)	70 (73.7)	3 (50.0)	260 (65.0)
AE leading to rociletinib dose interruption, reduction or discontinuation[b]	60 (66.7)	154 (73.7)	77 (81.1)	5 (83.3)	296 (74.0)

Abbreviations: BID = twice daily; SAE = serious adverse event; AE = treatment-emergent adverse event.
[a] 55 of the 64 deaths were due to progressive disease.
[b] Includes TEAEs of disease progression.

The most common AEs were diarrhea, nausea, hyperglycemia, and fatigue across all doses (Table 14). Skin effects that are seen with non-selective EGFR inhibitors, including acneiform rash, stomatitis and paronychia, were not commonly observed. This confirms the WT sparing profile of rociletinib.

For the purposes of these analyses, the following adverse events have been analyzed using combined terms (MedDRA standardized medical queries [SMQs]): Hyperglycemia, QT prolongation, interstitial lung disease, and acute pancreatitis. A list of the preferred terms contained within each SMQ is in Appendix 11.6.

Table 14: Treatment Emergent AEs in ≥10% of Patients in 500 mg BID, 625 mg BID, or 750 mg BID Dose Groups or ≥33% of Patients in the 1000 mg BID Dose Group

System Organ Class Preferred Term	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID[a] (N=6)	Overall (N=400)
	n (%)				
≥ 1 AE					
Overall	90 (100.0)	207 (99.0)	95 (100.0)	6 (100.0)	398 (99.5)
Gastrointestinal Disorders					
Overall	77 (85.6)	174 (83.3)	76 (80.0)	5 (83.3)	332 (83.0)
Diarrhoea	50 (55.6)	115 (55.0)	50 (52.6)	4 (66.7)	219 (54.8)
Nausea	46 (51.1)	111 (53.1)	49 (51.6)	3 (50.0)	209 (52.3)
Vomiting	27 (30.0)	68 (32.5)	27 (28.4)	1 (16.7)	123 (30.8)
Constipation	20 (22.2)	63 (30.1)	22 (23.2)	2 (33.3)	107 (26.8)
Abdominal pain	8 (8.9)	30 (14.4)	15 (15.8)	0	53 (13.3)
Dry mouth	11 (12.2)	16 (7.7)	14 (14.7)	0	41 (10.3)
Gastrooesophageal reflux disease	12 (13.3)	18 (8.6)	9 (9.5)	0	39 (9.8)
Abdominal pain upper	8 (8.9)	12 (5.7)	11 (11.6)	1 (16.7)	32 (8.0)
Metabolism and Nutrition Disorders					
Overall	68 (75.6)	153 (73.2)	71 (74.7)	6 (100.0)	298 (74.5)
Hyperglycaemia SMQ[b]	49 (54.4)	115 (55.0)	63 (66.3)	4 (66.7)	231 (57.8)
Decreased appetite	29 (32.2)	72 (34.4)	40 (42.1)	4 (66.7)	145 (36.3)
Hypokalaemia	13 (14.4)	34 (16.3)	12 (12.6)	1 (16.7)	60 (15.0)
Dehydration	5 (5.6)	21 (10.0)	12 (12.6)	0	38 (9.5)
Hypomagnesaemia	9 (10.0)	18 (8.6)	8 (8.4)	2 (33.3)	37 (9.3)
General Disorders and Administration Site Conditions					
Overall	69 (76.7)	133 (63.6)	65 (68.4)	3 (50.0)	270 (67.5)
Fatigue	42 (46.7)	86 (41.1)	45 (47.4)	3 (50.0)	176 (44.0)
Oedema peripheral	14 (15.6)	27 (12.9)	12 (12.6)	0	53 (13.3)
Asthenia	12 (13.3)	22 (10.5)	14 (14.7)	1 (16.7)	49 (12.3)
Investigations					
Overall	57 (63.3)	130 (62.2)	70 (73.7)	6 (100.0)	263 (65.8)
Cardiac arrhythmias SMQ[b,c]	35 (38.9)	85 (40.7)	36 (37.9)	3 (50.0)	159 (39.8)
Torsades de Pointes/QT prolongation (narrow) SMQ[b,c]	30 (33.3)	77 (36.8)	33 (34.7)	3 (50.0)	143 (35.8)
Weight decreased	24 (26.7)	40 (19.1)	38 (40.0)	2 (33.3)	104 (26.0)

System Organ Class Preferred Term	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID[a] (N=6)	Overall (N=400)
	n (%)				
Blood bilirubin increased	6 (6.7)	16 (7.7)	13 (13.7)	1 (16.7)	36 (9.0)
Platelet count decreased	9 (10.0)	11 (5.3)	2 (2.1)	0	22 (5.5)
Musculoskeletal and Connective Tissue Disorders					
Overall	44 (48.9)	114 (54.5)	50 (52.6)	3 (50.0)	211 (52.8)
Muscle spasms	25 (27.8)	46 (22.0)	25 (26.3)	1 (16.7)	97 (24.3)
Back pain	8 (8.9)	30 (14.4)	10 (10.5)	0	48 (12.0)
Arthralgia	8 (8.9)	24 (11.5)	9 (9.5)	0	41 (10.3)
Musculoskeletal chest pain	1 (1.1)	17 (8.1)	10 (10.5)	1 (16.7)	29 (7.3)
Nervous System Disorders					
Overall	47 (52.2)	97 (46.4)	46 (48.4)	3 (50.0)	193 (48.3)
Headache	24 (26.7)	46 (22.0)	16 (16.8)	0	86 (21.5)
Dizziness	12 (13.3)	33 (15.8)	12 (12.6)	1 (16.7)	58 (14.5)
Respiratory, Thoracic and Mediastinal Disorders					
Overall	43 (47.8)	100 (47.8)	41 (43.2)	3 (50.0)	187 (46.8)
Cough	20 (22.2)	41 (19.6)	15 (15.8)	0	76 (19.0)
Dyspnoea	17 (18.9)	38 (18.2)	20 (21.1)	1 (16.7)	76 (19.0)
Infections and Infestations					
Overall	42 (46.7)	82 (39.2)	35 (36.8)	5 (83.3)	164 (41.0)
Urinary tract infection	7 (7.8)	18 (8.6)	11 (11.6)	0	36 (9.0)
Pneumonia	5 (5.6)	15 (7.2)	8 (8.4)	2 (33.3%)	30 (7.5)
Upper respiratory tract infection	11 (12.2)	13 (6.2)	5 (5.3)	0	29 (7.3)
Blood and Lymphatic System Disorders					
Overall	28 (31.1)	64 (30.6)	34 (35.8)	1 (16.7)	127 (31.8)
Anaemia	14 (15.6)	46 (22.0)	14 (14.7)	1 (16.7)	75 (18.8)
Thrombocytopenia	8 (8.9)	17 (8.1)	17 (17.9)	0	42 (10.5)
Skin and Subcutaneous Tissue Disorders					
Overall	23 (25.6)	50 (23.9)	25 (26.3)	2 (33.3)	100 (25.0)
Psychiatric Disorders					
Overall	18 (20.0)	52 (24.9)	20 (21.1)	1 (16.7)	91 (22.8)
Insomnia	7 (7.8)	22 (10.5)	9 (9.5)	0	38 (9.5)

System Organ Class Preferred Term	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID[a] (N=6)	Overall (N=400)
	n (%)				
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)					
Overall	14 (15.6)	40 (19.1)	22 (23.2)	1 (16.7)	77 (19.3)
Malignant neoplasm progression	13 (14.4)	37 (17.7)	20 (21.1)	1 (16.7)	71 (17.8)
Eye Disorders					
Overall	17 (18.9)	23 (11.0)	18 (18.9)	0	58 (14.5)
Renal and Urinary Disorders					
Overall	14 (15.6)	30 (14.4)	12 (12.6)	1 (16.7)	57 (14.3)
Vascular Disorders					
Overall	11 (12.2)	29 (13.9)	10 (10.5)	1 (16.7)	51 (12.8)
Injury, Poisoning, and Procedural Complications					
Overall	8 (8.9)	27 (12.9)	10 (10.5)	0	45 (11.3)
Cardiac Disorders					
Overall	11 (12.2)	23 (11.0)	9 (9.5)	0	43 (10.8)
Ear and Labyrinth Disorders					
Overall	13 (14.4)	9 (4.3)	3 (3.2)	0	25 (6.3)

Abbreviations: BID = twice daily; HBr = hydrobromide; PT = preferred term; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; SOC = system organ class; AE = treatment-emergent adverse event.
[a] Due to the low number of patients at 1000 mg BID, AEs reported in 2 or more patients (≥ 33% of patients) are presented.
[b] See Appendix 11.6 for the list of PTs included in each SMQ
[c] The Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ both contain PTs from multiple SOCs. These have been placed under the SOC of Investigations as most frequently reported PT was electrocardiogram QT prolonged from the Investigations SOC. In addition, there are several PTs common to both the Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ.
Note: SOCs and PTs are presented in terms of descending incidence.

5.3 GRADE 3 OR HIGHER ADVERSE EVENTS

The most common AEs Grade 3 or higher by PT were hyperglycemia, electrocardiogram QT prolonged, fatigue, and anemia (Table 15). The majority of these events were Grade 3.

Table 15: Treatment Emergent AEs Grade 3 or Higher in ≥2% of Patients in any Dose Group

System Organ Class Preferred Term	500 mg BID (N=90)	625 mg BID (N=209)	750 mg BID (N=95)	1000 mg BID (N=6)	Overall (N=400)
	n (%)				
≥ 1 Grade 3 or Higher AE					
Overall	63 (70.0)	152 (72.7)	76 (80.0)	5 (83.3)	296 (74.0)
Metabolism and Nutrition Disorders					
Overall	34 (37.8)	78 (37.3)	41 (43.2)	4 (66.7)	157 (39.3)
Hyperglycaemia SMQ[a]	28 (31.1)	66 (31.6)	40 (42.1)	3 (50.0)	137 (34.3)
Hyponatraemia	4 (4.4)	6 (2.9)	5 (5.3)	1 (16.7)	16 (4.0)
Hypokalaemia	0	8 (3.8)	3 (3.2)	0	11 (2.8)
Dehydration	1 (1.1)	6 (2.9)	1 (1.1)	0	8 (2.0)
Decreased appetite	0	3 (1.4)	2 (2.1)	0	5 (1.3)
Investigations					
Overall	13 (14.4)	43 (20.6)	27 (28.4)	1 (16.7)	84 (21.0)
Cardiac arrhythmias SMQ[a,b]	7 (7.8)	28 (13.4)	15 (15.8)	0	50 (12.5)
Torsades de Pointes/QT prolongation (narrow) SMQ[a,b]	7 (7.8)	27 (12.9)	15 (15.8)	0	49 (12.3)
Aspartate aminotransferase increased	2 (2.2)	4 (1.9)	0	0	6 (1.5)
Weight decreased	0	2 (1.0)	4 (4.2)	0	6 (1.5)
Alanine aminotransferase increased	0	5 (2.4)	0	0	5 (1.3)
Lymphocyte count decreased	0	5 (2.4)	0	0	5 (1.3)
Blood bilirubin increased	0	1 (0.5)	3 (3.2)	0	4 (1.0)
Neutrophil count decreased	2 (2.2)	0	2 (2.1)	0	4 (1.0)
White blood cell count decreased	1 (1.1)	0	2 (2.1)	0	3 (0.8)
Blood phosphorus decreased	0	0	0	1 (16.7)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)					
Overall	12 (13.3)	37 (17.7)	20 (21.1)	1 (16.7)	70 (17.5)
Malignant neoplasm progression	12 (13.3)	37 (17.7)	19 (20.0)	1 (16.7)	69 (17.3)

Gastrointestinal Disorders					
Overall	15 (16.7)	26 (12.4)	13 (13.7)	1 (16.7)	55 (13.8)
Vomiting	6 (6.7)	5 (2.4)	5 (5.3)	0	16 (4.0)
Nausea	3 (3.3)	6 (2.9)	4 (4.2)	1 (16.7)	14 (3.5)
Diarrhoea	0	8 (3.8)	3 (3.2)	0	11 (2.8)
Abdominal pain	1 (1.1)	5 (2.4)	2 (2.1)	0	8 (2.0)
Acute Pancreatitis SMQ[a]	4 (4.4)	6 (2.9)	0	0	10 (2.5)
Gastrointestinal haemorrhage	0	1 (0.5)	2 (2.1)	0	3 (0.8)
General Disorders and Administration Site Conditions					
Overall	9 (10.0)	20 (9.6)	10 (10.5)	2 (33.3)	41 (10.3)
Fatigue	4 (4.4)	10 (4.8)	4 (4.2)	2 (33.3)	20 (5.0)
Asthenia	2 (2.2)	5 (2.4)	5 (5.3)	0	12 (3.0)
Infections and Infestations					
Overall	6 (6.7)	16 (7.7)	8 (8.4)	3 (50.0)	33 (8.3)
Pneumonia	2 (2.2)	9 (4.3)	6 (6.3)	2 (33.3)	19 (4.8)
Sepsis	1 (1.1)	2 (1.0)	2 (2.1)	0	5 (1.3)
Clostridium difficile infection	0	2 (1.0)	0	1 (16.7)	3 (0.8)
Lung infection	2 (2.2)	0	0	0	2 (0.5)
Blood and Lymphatic System Disorders					
Overall	8 (8.9)	13 (6.2)	4 (4.2)	0	25 (6.3)
Anaemia	3 (3.3)	10 (4.8)	1 (1.1)	0	14 (3.5)
Neutropenia	2 (2.2)	2 (1.0)	1 (1.1)	0	5 (1.3)
Lymphopenia	2 (2.2)	1 (0.5)	0	0	3 (0.8)
Thrombocytopenia	1 (1.1)	0	2 (2.1)	0	3 (0.8)
Respiratory, Thoracic and Mediastinal Disorders					
Overall	5 (5.6)	14 (6.7)	5 (5.3)	1 (16.7)	25 (6.3)
Dyspnoea	2 (2.2)	6 (2.9)	0	0	8 (2.0)
Interstitial lung disease SMQ[a]	1 (1.1)	2 (1.0)	2 (2.1)	0	5 (1.3)
Respiratory distress	0	0	0	1 (16.7)	1 (0.3)
Nervous System Disorders					
Overall	5 (5.6)	10 (4.8)	4 (4.2)	1 (16.7)	20 (5.0)
Headache	2 (2.2)	0	2 (2.1)	0	4 (1.0)
Vocal cord paralysis	0	0	0	1 (16.7)	1 (0.3)

Musculoskeletal and Connective Tissue Disorders					
Overall	1 (1.1)	7 (3.3)	4 (4.2)	0	12 (3.0)
Musculoskeletal chest pain	0	1 (0.5)	2 (2.1)	0	3 (0.8)
Hepatobiliary Disorders					
Overall	1 (1.1)	6 (2.9)	3 (3.2)	0	10 (2.5)
Cardiac Disorders					
Overall	1 (1.1)	6 (2.9)	2 (2.1)	0	9 (2.3)
Psychiatric Disorders					
Overall	1 (1.1)	6 (2.9)	2 (2.1)	0	9 (2.3)
Mental status changes	1 (1.1)	0	2 (2.1)	0	3 (0.8)
Vascular Disorders					
Overall	3 (3.3)	6 (2.9)	0	0	9 (2.3)
Hypertension	3 (3.3)	2 (1.0)	0	0	5 (1.3)
Renal and Urinary Disorders					
Overall	2 (2.2)	2 (1.0)	2 (2.1)	0	6 (1.5)

Abbreviations: BID = twice daily; HBr = hydrobromide; PT = preferred term; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; SOC = system organ class; AE = treatment-emergent adverse event.

[a] See Appendix 11.6 for the list of PTs included in each SMQ

[b] The Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ both contain PTs from multiple SOCs. These have been placed under the SOC of Investigations as most frequently reported PT was electrocardiogram QT prolonged from the Investigations SOC. In addition, there are several PTs common to both the Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ

Note: SOCs and PTs are presented in terms of descending incidence

5.4 ADVERSE EVENTS LEADING TO DOSE REDUCTION OR INTERRUPTION

Overall, 51% of patients experienced AEs leading to dose reduction. AEs that led to dose reduction or interruption of treatment, regardless of causality, are presented for all dose groups in Table 16. The most common AEs leading to dose reduction were hyperglycemia, electrocardiogram QT prolonged, nausea, diarrhea, and fatigue.

Table 16: Treatment Emergent AEs that Led to Dose Reduction or Interruption in ≥2% of Patients in Any Dose Group

System Organ Class Preferred Term	500 mg BID N = 90	625 mg BID N = 209	750 mg BID N = 95	1000 mg BID N = 6	Overall (N = 400)
	n (%)				
≥ 1 AE Leading to Dose Reduction	**36 (40.0)**	**99 (47.4)**	**64 (67.4)**	**4 (66.7)**	**203 (50.8)**
≥ 1 AE Leading to Dose Reduction or Interruption	**54 (60.0)**	**132 (63.2)**	**70 (73.7)**	**4 (66.7)**	**260 (65.0)**
Metabolism and Nutrition disorders					
Overall	25 (27.8)	65 (31.1)	44 (46.3)	3 (50.0)	137 (34.3)
Hyperglycaemia SMQ[a]	22 (24.4)	47 (22.5)	45 (47.4)	3 (50.0)	117 (29.3)
Decreased appetite	2 (2.2)	15 (7.2)	7 (7.4)	1 (16.7)	25 (6.3)
Hyponatraemia	2 (2.2)	2 (1.0)	3 (3.2)	0	7 (1.8)
Gastrointestinal Disorders					
Overall	18 (20.0)	51 (24.4)	24 (25.3)	1 (16.7)	94 (23.5)
Nausea	8 (8.9)	27 (12.9)	14 (14.7)	1 (16.7)	50 (12.5)
Diarrhoea	3 (3.3)	25 (12.0)	10 (10.5)	1 (16.7)	39 (9.8)
Vomiting	6 (6.7)	14 (6.7)	6 (6.3)	0	26 (6.5)
Acute pancreatitis SMQ[a]	4 (4.4)	5 (2.4)	0	0	9 (2.3)
Abdominal pain	1 (1.1)	6 (2.9)	1 (1.1)	0	8 (2.0)
Constipation	0	1 (0.5)	2 (2.1)	0	3 (0.8)
Investigations					
Overall	19 (21.1)	43 (20.6)	27 (28.4)	2 (33.3)	91 (22.8)
Cardiac Arrhythmias SMQ[a]	12 (13.3)	26 (12.4)	13 (13.7)	0	51 (12.8)
Torsades de Pointes/QT prolongation (narrow) SMQ[a]	10 (11.1)	26 (12.4)	13 (13.7)	0	49 (12.3)
AST increased	2 (2.2)	6 (2.9)	1 (1.1)	0	9 (2.3)
Weight decreased	1 (1.1)	4 (1.9)	3 (3.2)	0	8 (2.0)
ALT increased	0	6 (2.9)	1 (1.1)	0	7 (1.8)
Blood bilirubin increased	0	2 (1.0)	3 (3.2)	0	5 (1.3)
Blood creatinine increased	0	2 (1.0)	1 (1.1%)	1 (16.7)	4 (1.0)

Neutrophil count decreased	2 (2.2)	0	2 (2.1)	0	4 (1.0)
General Disorders and Administration Site Conditions					
Overall	7 (7.8)	30 (14.4)	20 (21.1)	2 (33.3)	59 (14.8)
Fatigue	4 (4.4)	23 (11.0)	16 (16.8)	2 (33.3)	45 (11.3)
Asthenia	2 (2.2)	4 (1.9)	5 (5.3)	0	11 (2.8)
Infections and Infestations					
Overall	4 (4.4)	15 (7.2)	4 (4.2)	1 (16.7)	24 (6.0)
Pneumonia	0	7 (3.3)	0	0	7 (1.8)
Clostridium difficile infection	0	2 (1.0)	0	1 (16.7)	3 (0.8)
Lung infection	2 (2.2)	0	0	0	2 (0.5)
Blood and Lymphatic System Disorders					
Overall	5 (5.6)	7 (3.3%)	5 (5.3)	0	17 (4.3)
Thrombocytopenia	2 (2.2)	2 (1.0)	4 (4.2)	0	8 (2.0)
Anaemia	2 (2.2)	3 (1.4)	1 (1.1)	0	6 (1.5)
Respiratory, Thoracic and Mediastinal Disorders					
Overall	3 (3.3)	9 (4.3)	5 (5.3)	0	17 (4.3)
Dyspnoea	0	4 (1.9)	2 (2.1)	0	6 (1.5)
Pleural effusion	1 (1.1)	2 (1.0)	2 (2.1)	0	5 (1.3)
Nervous System Disorders					
Overall	2 (2.2)	6 (2.9)	4 (4.2)	0	12 (3.0)
Renal and Urinary Disorders					
Overall	1 (1.1)	5 (2.4)	4 (4.2)	0	10 (2.5)
Acute kidney injury	1 (1.1)	3 (1.4)	2 (2.1)	0	6 (1.5)
Hepatobiliary Disorders					
Overall	1 (1.1)	6 (2.9)	3 (3.2)	0	10 (2.5)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)					
Overall	0	4 (1.9)	5 (5.3)	0	9 (2.3)
Malignant neoplasm progression	0	3 (1.4)	4 (4.2)	0	7 (1.8)
Musculoskeletal and Connective Tissue Disorders					
Overall	0	2 (1.0)	5 (5.3)	0	7 (1.8)
Muscle spasms	0	0	4 (4.2)	0	4 (1.0)
Psychiatric Disorders					
Overall	1 (1.1)	3 (1.4)	2 (2.1)	0	6 (1.5)

Cardiac Disorders					
Overall	3 (3.3)	1 (0.5)	1 (1.1)	0	5 (1.3)
Vascular Disorders					
Overall	2 (2.2)	3 (1.4)	0	0	5 (1.3)
Hypertension	2 (2.2)	0	0	0	2 (0.5)

Abbreviations: BID = twice daily; HBr = hydrobromide; PT = preferred term; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; SOC = system organ class; AE = treatment-emergent adverse event.
[a] See Appendix 11.6 for the list of PTs included in each SMQ
[b] The Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ both contain PTs from multiple SOCs. These have been placed under the SOC of Investigations as most frequently reported PT was electrocardiogram QT prolonged from the Investigations SOC. In addition, there are several PTs common to both the Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ
Note: SOCs and PTs are presented in terms of descending incidence.

5.5 ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION

Overall, 21% of patients discontinued rociletinib across all doses (Table 17). Approximately half (49%) of treatment discontinuations were due to disease progression. Discontinuation rates for other AEs, including QT prolonged and hyperglycemia were low and similar across doses (3% and 1%, respectively).

Table 17: Treatment Emergent AEs Leading to Discontinuation of Rociletinib in ≥ 2% of Patients in Any Dose Group

System Organ Class Preferred Term	500 BID (N=90)	625 BID (N=209)	750 BID (N=95)	1000 BID (N=6)	Overall (N=400)
	n (%)				
≥ 1 AE Leading to Discontinuation					
Overall	18 (20.0)	45 (21.5)	19 (20.0)	3 (50.0)	85 (21.3)
≥ 1 AE Leading to Discontinuation excluding malignant neoplasm progression					
Overall	11 (12.2)	24 (11.5)	10 (10.5)	2 (33.3)	47 (11.8)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)					
Overall	8 (8.9)	22 (10.5)	11 (11.6)	1 (16.7)	42 (10.5)
Malignant neoplasm progression	8 (8.9)	22 (10.5)	11 (11.6)	1 (16.7)	42 (10.5)
Investigations					
Overall	3 (3.3)	6 (2.9)	2 (2.1)	0	11 (2.8)
Torsades de Pointes/QT prolongation (narrow) SMQ[a,b]	3 (3.3)	7 (3.3)	3 (3.2)	0	13 (3.3)
Cardiac Arrhythmias SMQ[a,b]	3 (3.3)	6 (2.9)	3 (3.2)	0	12 (3.0)
Respiratory, Thoracic and Mediastinal Disorders					
Overall	1 (1.1)	5 (2.4)	3 (3.2)	1 (16.7)	10 (2.5)
Interstitial lung disease SMQ[a]	0	2 (1.0)	2 (2.1)	0	4 (1.0)
Respiratory distress	0	0	0	1 (16.7)	1 (0.3)
General Disorders and Administration Site Conditions					
Overall	2 (2.2)	5 (2.4)	2 (2.1)	0	9 (2.3)
Infections and Infestations					
Overall	2 (2.2)	2 (1.0)	2 (2.1)	2 (33.3)	8 (2.0)
Pneumonia	1 (1.1)	2 (1.0)	2 (2.1)	2 (33.3)	7 (1.8)
Metabolism and Nutrition Disorders					
Overall	2 (2.2)	5 (2.4)	0	0	7 (1.8)
Hyperglycaemia SMQ[a]	2 (2.2)	3 (1.4)	0	0	5 (1.3)

System Organ Class Preferred Term	500 BID (N=90)	625 BID (N=209)	750 BID (N=95)	1000 BID (N=6)	Overall (N=400)
	n (%)				
Gastrointestinal Disorders					
Overall	1 (1.1)	1 (0.5)	2 (2.1)	0	4 (1.0)
Nausea	0	1 (0.5)	2 (2.1)	0	3 (0.8)

Abbreviations: BID = twice daily; HBr = hydrobromide; PT = preferred term; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; SOC = system organ class; AE = treatment-emergent adverse event.
[a] See Appendix 11.6 for the list of PTs included in each SMQ
[b] The Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ both contain PTs from multiple SOCs. These have been placed under the SOC of Investigations as most frequently reported PT was electrocardiogram QT prolonged from the Investigations SOC. In addition, there are several PTs common to both the Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ
Note: SOCs and PTs are presented in terms of decreasing incidence.

5.6 SERIOUS ADVERSE EVENTS

Overall, 47% of patients reported SAEs across all dose groups (Table 18). The most common SAE across all doses was progression of the underlying disease (preferred term neoplasm progression), with 16% of patients experiencing the SAE. Aside from hyperglycemia in the 500 mg BID dose group (13%), all other SAEs occurred in less than 10% of patients.

Table 18:SAEs Reported in ≥2% of Patients in Any Dose Group

System Organ Class Preferred Term	500 BID (N=90)	625 BID (N=209)	750 BID (N=95)	1000 BID (N=6)	Overall (N=400)
	n (%)				
≥ 1 Serious AE					
Overall	40 (44.4)	97 (46.4)	45 (47.4)	5 (83.3)	187 (46.8)
Neoplasms Benign, Malignant and unspecified (Including Cysts and Polyps)					
Overall	12 (13.3)	37 (17.7)	17 (17.9)	1 (16.7)	67 (16.8)
Malignant neoplasm progression	11 (12.2)	36 (17.2)	16 (16.8)	1 (16.7)	64 (16.0)
Metabolism and Nutrition Disorders					
Overall	12 (13.3)	20 (9.6)	10 (10.5)	2 (33.3)	44 (11.0)
Hyperglycaemia SMQ[a]	12 (13.3)	13 (6.2)	7 (7.4)	2 (33.3)	34 (8.5)
Gastrointestinal Disorders					
Overall	11 (12.2)	20 (9.6)	7 (7.4)	0	38 (9.5)
Acute Pancreatitis SMQ[a]	4 (4.4)	5 (2.4)	0	0	9 (2.3)
Nausea	3 (3.3)	4 (1.9)	1 (1.1)	0	8 (2.0)
Vomiting	5 (5.6)	1 (0.5)	1 (1.1)	0	7 (1.8)

System Organ Class Preferred Term	500 BID (N=90)	625 BID (N=209)	750 BID (N=95)	1000 BID (N=6)	Overall (N=400)
	n (%)				
Gastrointestinal haemorrhage	0	1 (0.5)	2 (2.1)	0	3 (0.8)
Infections and Infestations					
Overall	5 (5.6)	16 (7.7)	7 (7.4)	3 (50.0)	31 (7.8)
Pneumonia	2 (2.2)	8 (3.8)	6 (6.3)	2 (33.3)	18 (4.5)
Clostridium difficile infection	0	3 (1.4)	0	1 (16.7)	4 (1.0)
Respiratory, Thoracic and Mediastinal Disorders					
Overall	3 (3.3)	12 (5.7)	4 (4.2)	0	19 (4.8)
Interstitial lung disease SMQ[a]	1 (1.1)	2 (1.0)	2 (2.1)	0	5 (1.3)
Nervous System Disorders					
Overall	3 (3.3)	6 (2.9)	6 (6.3)	0	15 (3.8)
Headache	0	1 (0.5)	3 (3.2)	0	4 (1.0)
Seizure	1 (1.1)	0	2 (2.1)	0	3 (0.8)
General Disorders and Administration Site Conditions					
Overall	2 (2.2)	8 (3.8)	3 (3.2)	1 (16.7)	14 (3.5)
Fatigue	1 (1.1)	1 (0.5)	0	1 (16.7)	3 (0.8)
Cardiac Disorders					
Overall	2 (2.2)	5 (2.4)	3 (3.2)	0	10 (2.5)
Hepatobiliary Disorders					
Overall	0	7 (3.3)	2 (2.1)	0	9 (2.3)
Investigations					
Overall	1 (1.1)	3 (1.4)	1 (1.1)	0	5 (1.3)
Cardiac Arrhythmias SMQ[a,b]	3 (3.3)	9 (4.3)	4 (4.2)	0	16 (4.0)
Torsades de Pointes/QT prolongation (narrow) SMQ[a,b]	1 (1.1)	8 (3.8)	2 (2.1)	0	11 (2.8)
Renal and Urinary Disorders					
Overall	2 (2.2)	2 (1.0)	1 (1.1)	0	5 (1.3)
Psychiatric Disorders					
Overall	0	2 (1.0)	2 (2.1)	0	4 (1.0)
Mental status changes	0	0	2 (2.1)	0	2 (0.5)
Blood and Lymphatic System Disorders					
Overall	2 (2.2)	1 (0.5)	0	0	3 (0.8)

Abbreviations: BID = twice daily; HBr = hydrobromide; PT = preferred term; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; SOC = system organ class; AE = treatment-emergent adverse event.

[a] See Appendix 11.6 for the list of PTs included in each SMQ
[b] The Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ both contain PTs from multiple SOCs. These have been placed under the SOC of Investigations as most frequently reported PT was electrocardiogram QT prolonged from the Investigations SOC. In addition, there are several PTs common to both the Cardiac arrhythmias SMQ and Torsades de Pointes/QT prolongation (narrow) SMQ
Note: SOCs and PTs are presented in terms of decreasing incidence.

5.7 ADVERSE EVENTS WITH FATAL OUTCOME

Overall, 16% of patients experienced at least 1 TEAE with an outcome of death across dose groups (Table 19). Importantly, 55 of 64 (86%) of these events were related to disease progression and were judged to be unrelated to rociletinib treatment by the investigator. Additionally, 5 patients died of pneumonia, 1 of sepsis, 1 of aspiration, and 2 patients died with no cause identified. One patient where the investigator reported cause of death was disease progression had experienced a ventricular tachyarrhythmia on the day of death (see Appendix 11.5.3).

Table 19: Treatment Emergent AEs with an Outcome of Death in Patients Treated with Rociletinib 500-1000 mg BID

SOC PT	**500 mg BID** **N = 90**	**625 mg BID** **N = 209**	**750 mg BID** **N = 95**	**1000 mg BID** **N = 6**	**Overall** **(N = 400)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥ 1 AE with an outcome of death					
Overall	12 (13.3)	35 (16.7)	14 (14.7)	3 (50.0%)	64 (16.0%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)					
Malignant neoplasm progression	9 (10.0)	33 (15.8)	12 (12.6)	1 (16.7%)	55 (13.8%)
Infections and Infestations					
Pneumonia	1 (1.1)	1 (0.5)	1 (1.1)	2 (33.3%)	5 (1.3%)
Sepsis	1 (1.1)	0	0	0	1 (0.3%)
General Disorders and Administration Site Conditions					
Sudden death	0	1 (0.5)	1 (1.1)	0	2 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders					
Aspiration	1 (1.1)	0	0	0	1 (0.3%)

Abbreviations: AE = adverse event; BID = twice daily; PT = preferred term; SOC = System Organ Class.
Note: SOCs and PTs are presented in terms of descending incidence.
Patients could have > 1 AE leading to death.
Includes AEs with an outcome of death and/or CTCAE Grade 5 AEs.

5.8 LABORATORY EVALUATION

With the exception of elevation in serum glucose measurements (see Section 5.9.1), laboratory changes occurred infrequently. Assessment of vital sign data collected on patients during the studies did not elicit any safety concerns. Glucose measurements above the threshold value of 13.9 mmol/L (> 250 mg/dL; CTCAE Grade 3 or higher) and above the threshold value of 27.8 mmol/L (> 500 mg/dL; Grade 4) are summarized In Table 20. Two patients experienced a single Grade 4 glucose reading of > 500 mg/dL in each of the 500 mg BID, 625 mg BID, and 750 mg BID dose groups. Additionally, 1 patient in the 500 mg BID dose group experienced 2 or more events.

Table 20: Summary of Glucose Values

	500 BID (N=90)	625 BID (N=209)	750 BID (N=95)	1000 BID (N=6)	Overall (N=400)
	n (%)	n (%)	n (%)	n (%)	n (%)
Any Post-Baseline Glucose > 13.875 mmol/L (>250 mg/dL)	24 (26.7)	59 (28.2)	33 (34.7)	2 (33.3)	118 (29.5)
≥ 2 Post-Baseline Glucose > 13.875 mmol/L (>250 mg/dL)	12 (13.3)	26 (12.4)	12 (12.6)	0	50 (12.5)
≥ 3 or more Post-Baseline Glucose > 13.875 mmol/L (>250 mg/dL)	4 (4.4)	12 (5.7)	8 (8.4)	0	24 (6.0)
Any Post-Baseline Glucose > 27.75 mmol/L (>500 mg/dL)	2 (2.2)	2 (1.0)	2 (2.1)	0	6 (1.5)
≥ 2 or more Post-Baseline Glucose > 27.75 mmol/L (>500 mg/dL)	1 (1.1)	0	0	0	1 (0.3)
≥ 3 or more Post-Baseline Glucose > 27.75 mmol/L (>500 mg/dL)	0	0	0	0	0

5.9 SPECIAL SAFETY TOPICS

The following adverse drug reactions are discussed in detail: hyperglycemia, QTc prolongation, ILD, pancreatitis, and cataracts. ILD is a class effect of EGFR TKIs.

5.9.1 Hyperglycemia

Hyperglycemia was the most common AE associated with rociletinib, occurring in 58% of patients across the dose groups.(Table 21). Grade 3 and above hyperglycemia was reported in 34% of patients across the dose groups. Most of the Grade 3 events occurred early in treatment. Twenty-four percent and 23% of patients in the 500 mg BID and 625 mg BID dose groups, respectively, required dose modification, compared to 47% and 50% in the 750 mg BID and 1000 mg BID dose groups.

Overall, 1% of patients discontinued rociletinib because of hyperglycemia, and 9% of patients experienced SAEs of hyperglycemia across dose groups. These data suggest that hyperglycemia was managed effectively in most cases by following guidance that was developed once the MOA was understood.

Table 21: Hyperglycemia Events in Studies 008 and 019

Hyperglycemia [a]	**500 mg BID N=90**	**625 mg BID N=209**	**750 mg BID N=95**	**1000 mg BID N=6**	**Overall N=400**
All AEs	54%	55%	66%	67%	58%
Any Grade ≥ 3 AE[b]	31%	32%	42%	50%	34%
AE leading to dose modification	24%	23%	47%	50%	29%
AE leading to discontinuation	2%	1%	0	0	1%
SAE	13%	6%	7%	33%	9%
AE with outcome of death	0	0	0	0	0

[a] See Appendix 11.6 for the list of preferred terms included in hyperglycemia SMQ
[b] Grading based on laboratory value, and does not need to be symptomatic

The mechanism of the effect of hyperglycemia was elucidated during the rociletinib development program, after it was first observed in patients. Hyperglycemia was not observed in the preclinical toxicology studies probably because the bioactive metabolite responsible is not present at high concentrations in animals. Once it was understood that the effect was likely caused by reversible inhibition of IGF1R/INSR kinases by rociletinib metabolite, M502 (see Section 3.4.2.1 for more details), investigators were advised to use oral medications that were effective at managing a state of insulin resistance, such as metformin, glitazones and sodium-glucose co-transporter-2 inhibitors. If symptomatic hyperglycemia is not controlled by anti-hyperglycemic medication, a brief dose interruption will result in symptom control and blood glucose reduction. Rociletinib may then be restarted concurrently with the selected anti-hyperglycemic medication. Table 22 shows the most commonly used anti-hyperglycemic medications in Studies 008 and 009.

Table 22: Concomitant Medication Given to > 5% of Patients for Hyperglycemia in Studies 008 and 019

ATC Code (Standardized Name)	**500 mg BID N=90**	**625 mg BID N=209**	**750 mg BID N=95**
Patients with at least 1 concomitant medication for hyperglycemia	43%	40%	50%
Biguanides (Metformin)	39%	32%	42%
Insulin and analogs- fast acting	12%	12%	14%
Insulin and analogs- long acting	4%	8%%	5%
Sulfonylureas	11%	10%	18%
Thiazolidinediones (pioglitazone)	2%	8%	5%

Because most cases of Grade 3 or higher hyperglycemia occurred early in treatment, regular glucose monitoring in the initial weeks of therapy followed by periodic monitoring can effectively manage potential hyperglycemia. Hyperglycemia may be managed with hypoglycemic agents that are effective against insulin resistance, such as metformin. Rociletinib dose reductions are recommended for symptomatic or severe events.

5.9.2 QTc Prolongation and Cardiac Dysrhythmia

Rociletinib causes QT prolongation. This effect is likely caused by the metabolite, M460 (Section 3.4.2.2).

A comprehensive ECG monitoring program was included in the clinical trials, and all ECGs were collected and analyzed centrally. More than 25,000 individual ECG tracings were included in the NDA. Therefore, the signal has been comprehensively evaluated. The frequency of QTcF changes based on central laboratory evaluation are summarized in Table 23.

Table 23: Summary of QTc Values in Patients Treated with Rociletinib 500-1000 mg BID

	500 BID (N=90)	625 BID (N=209)	750 BID (N=95)	1000 BID (N=6)	Overall (N=400)
	n (%)	n (%)	n (%)	n (%)	n (%)
QTcF Post-Baseline					
>=450 msec	47 (52.2)	118 (56.5)	60 (63.2)	4 (66.7)	229 (57.3)
>=481 msec	19 (21.1)	45 (21.5)	28 (29.5)	2 (33.3)	94 (23.5)
>=501 msec	11 (12.2)	24 (11.5)	17 (17.9)	0	52 (13.0)
Two or more within 3 days >=501 msec	4 (4.4)	9 (4.3)	10 (10.5)	0	23 (5.8)
QTcF Change from Baseline					
>30 msec	68 (75.6)	151 (72.2)	81 (85.3)	5 (83.3)	305 (76.3)
>60 msec	23 (25.6)	69 (33.0)	43 (45.3)	2 (33.3)	137 (34.3)
QTcF Mean Change From Baseline at Week 2 (msec)	36	39	48	48	41

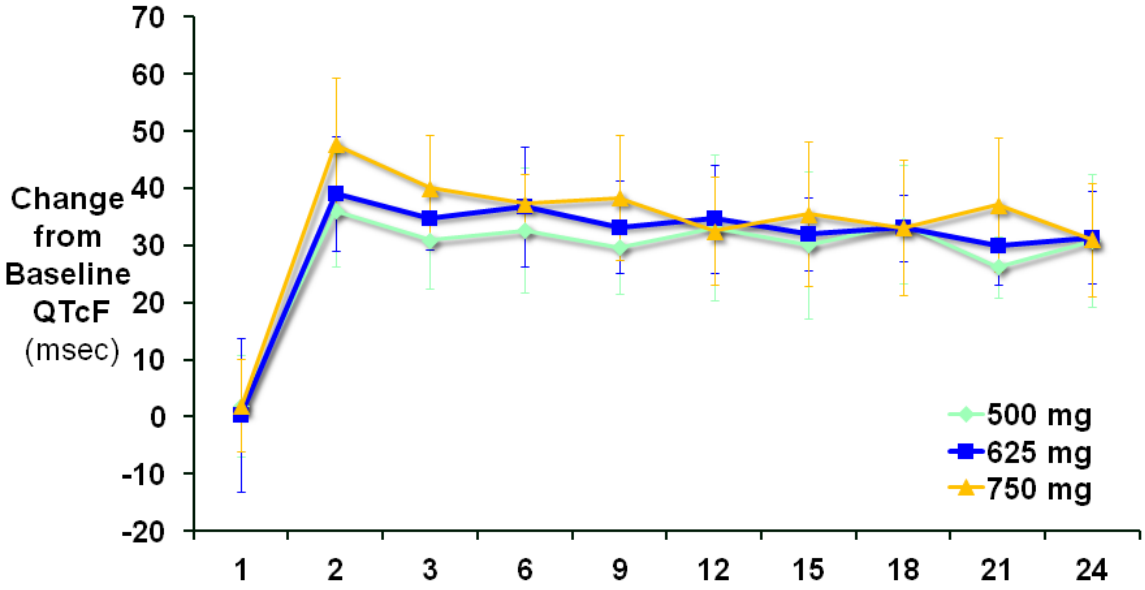
* Database contains > 25,000 Tracings
Abbreviations: BID = twice daily; QTcF = QT interval corrected using Fridericia's method.
Note: Data are presented for the number of patients with QTc above the specified threshold. For all other patients, QTc values were below the specified threshold.

The maximum mean change from baseline in the 3 largest dose groups occurred at Week 2 in all dose groups.

QTc was >500 ms in 13% of patients overall across doses. QTc was measured on Day 1, Day 15, and every 21 days (Study 008) or 28 days (Study 019) days thereafter. The effect of rociletinib on the QT interval did not occur on Day 1 of therapy, which is consistent with the M460 half-life of approximately

50 hours. QTc prolongation was evident by Day 15 of treatment (Figure 16) and generally did not increase further. The effect on QTc is reversible once rociletinib is stopped.

Figure 16: Effect of Rociletinib on QT Interval Over Time



The X axis shows sequential sampling points. Point 1 is Cycle 1 Day 1. Point 2 is Cycle 1 Day 15. Thereafter, ECGs were taken at the beginning of each treatment cycle.

Overall 36% of patients experienced a AE of QTc prolongation across all doses, with 12% reported as Grade 3 or higher. Thirteen percent of patients had dose modifications, and 3% discontinued treatment due to AEs of QTc prolongation.

The 3% of patients who experienced SAEs included 3 events of ventricular tachyarrhythmia. These events all occurred in the 625mg BID dose group. Two patients with ventricular tachyarrhythmia recovered, and the other patient was successfully converted to sinus tachycardia but died on the same day. Full vignettes of these patients can be found in Appendix 11.5.

There were 2 unexplained deaths (1 at 625mg BID and 1 at 750mg BID). Both were judged related to rociletinib by the investigators. Full vignettes of these patients can be found in Appendix 11.5.

Table 24: Events of QTc Prolongation

QTc Prolongation [a]	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95	1000 mg BID N=6	Overall (N=400)
All AEs	33%	37%	35%	50%	36%
Any Grade ≥ 3 AE	8%	13%	16%	0	12%
AE leading to dose reduction	11%	12%	14%	0	12%
AE leading to discontinuation	3%	3%	3%	0	3%
SAE	1%	4%	2%	0	3%
AE with outcome of death	0	0	0	0	0

[a] See Appendix 11.6 for the list of preferred terms included in hyperglycemia SMQ

A risk minimization strategy has been developed to address QT prolongation. The strategy contains 5 elements. First, patient selection criteria have been identified. Proposed labeling will contain clear guidance on which patients are not suitable for rociletinib based on baseline risk factors that increase the risk of QT complications. Second, ECG monitoring should be conducted during therapy. Data shows that the ECG effect is stable by Day 15, so the product labeling recommends ECG monitoring at baseline, after 15 days of therapy, and periodically thereafter. Third, patients and prescribers should be educated on the effect of electrolyte depletion on the risk of QT prolongation. The proposed label contains a warning that electrolytes should be checked and normalized before starting therapy and whenever clinically indicated (e.g. should the patient develop persistent or severe diarrhea). Fourth, co-administration of drugs that cause QT prolongation should be avoided while taking rociletinib. Fifth, the proposed label contains clear guidance on when to interrupt rociletinib for prolonged QTc and how to restart. Additional information on proposed labeling and risk management is provided in Section 8, and discussions are ongoing between the sponsor and FDA regarding content of the minimization plan, and the implementation method.

5.9.3 Interstitial Lung Disease

ILD is a well-characterized class effect of EGFR inhibitors and other TKIs. The incidence of ILD SMQ associated with rociletinib falls within the expected range, with 11 (2.8%) cases observed overall. Nine cases in the ILD SMQ were pneumonitis with 6 (2.9%) cases in the 625 mg BID and 3 (3.2%) in the 750 mg BID dose groups. Four of the 11 total cases resulted in discontinuation of rociletinib.

5.9.4 Acute Pancreatitis

Fifteen patients (4%) reported an AE of acute pancreatitis, of which 10 (2.5%) were Grade 3 or higher.

5.9.5 Diarrhea

Although overall 55% of patients reported diarrhea, most of the events were Grade 1 or 2, with Grade ≥3 in only 3% of patients. Diarrhea has particular relevance in the context of a QTc prolonging agent due to electrolyte depletion that can increase the risk of prolonged QTc. The proposed rociletinib product labeling will inform prescribers that electrolytes and ECG should be monitored in patients with diarrhea, and electrolytes should be repleted as necessary in order to mitigate the potential risk of QTc prolongation.

5.9.6 Cataracts

Cataract is a late effect of rociletinib treatment, as the median time to cataract AE was 241 days. At the time of the data cutoff for the NDA 60-day Safety Update, there were 12 patients (3%) with cataract(s) reported across all doses. As this can be a very late onset event, the NDA database was re-analyzed with a cut-off date of January 2016, and at that time there were 41 total cases of cataracts. The sponsor will propose that the labeling, including patient information labeling, will advise of the risk of cataract formation and of the potential long latency, and that patients who develop visual disturbance should be referred for ophthalmological assessment.

5.9.7 Effect of NAT2 Genotype on Adverse Events

As described in Section 3.4.2, 2 of rociletinib's major metabolites cause the adverse effects of hyperglycemia and QT prolongation. These metabolites, M502 and M460, are cleared by the enzyme NAT2. NAT2 gene is polymorphic, and the polymorphisms are associated with different levels of enzymatic activity (acetylator status). Depending on which polymorphism is present, patients can be categorized into 3 phenotypes: slow, intermediate, and rapid, based on acetylation activity. Slow acetylators, therefore, would be expected to have higher plasma levels of M502 and M460. Clinically, slow acetylator status might result in higher frequency of QTc prolongation and hyperglycemia.

In Studies 008 and 019, NAT2 genotyping was performed on patients who had provided informed consent for genomic testing, which was optional. Acetylator status is available for 303 patients within the 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID dose groups.

5.9.7.1 Analysis of Adverse Event and Dose Modification Frequency by Acetylator Status

AE and laboratory data based on NAT2 phenotype are summarized in Table 25. Individual event analyses were performed for hyperglycemia, cardiac adverse events, and laboratory tests (including ECGs). Analyses are presented by acetylator status for all doses combined, since the combined dose findings were consistent with the findings within each dose group.

The frequency of events related to hyperglycemia and QTc was highest in the slow acetylator group compared to the intermediate and rapid acetylator groups.

Table 25: Summary of Adverse Events and Laboratory Values In Patients with "Slow", "Intermediate", and "Rapid" NAT2 Phenotype

	NAT2 Phenotype		
	Rapid N=35	**Intermediate N=111**	**Slow N=157**
	n (%)	**n (%)**	**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	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 laboratory ECG Assessment			
QTcF Post Baseline			
≥450ms	18 (51.4)	52 (46.8)	108 (68.8)
≥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			
>30ms	27 (77.1)	73 (65.8)	131 (83.4)
>60ms	8 (22.9)	26 (23.4)	80 (51.0)
SMQ Hyperglycemia			
Overall	12 (34.3)	65 (58.6)	106 (67.5)
Combined terms of Hyperglycemia	12 (34.3)	65 (58.6)	106 (67.5)
Blood glucose increased	1 (2.9)	7 (6.3)	9 (5.7)
Glycosylated hemoglobin increased	1 (2.9)	3 (2.7)	4 (2.5)
Glucose tolerance impaired	2 (5.7)	9 (8.1)	9 (5.7)
Glucose urine present	0	0	3 (1.9)
Hyperglycemia	10 (28.6)	52 (46.8)	96 (61.1)
Diabetic ketoacidosis	1 (2.9)	0	1 (0.6)

Glucose Values (Laboratory Testing)			
Any post baseline glucose >13.875 mmol/L (>250 mg/dL)	5 (14.3)	30 (27.0)	63 (40.1)
2 or more post baseline glucose >13.875 mmol/L (>250 mg/dL)	0	18 (16.2)	22 (14.0)
Any post baseline glucose >27.75 mmol/L (>500mg/dL)	0	1 (0.9)	5 (3.2)
2 or more post baseline glucose >27.75 mmol/L (>500mg/dL)	0	0	1 (0.6)

The frequencies of dose modifications were also analyzed by acetylator status. Overall frequency of all adverse events, and events of QTc prolongation or hyperglycemia leading to dose reduction, dose interruption, dose discontinuation, and dose modification (combining dose reduction and interruption) by NAT2 phenotype are summarized in Table 26.

Table 26: Summary of Adverse Events Leading to Dose Reductions, Dose Interruptions, and Dose Discontinuations in Patients with "Slow", "Intermediate", and "Rapid" NAT2 Phenotype Studies CO-1686-008 and CO-1686-019

	NAT2 Phenotype		
	Rapid N=35	**Intermediate N=111**	**Slow N=157**
	n (%)	n (%)	n (%)
AEs Leading to Dose Reductions			
Overall	9 (25.7)	59 (53.2)	95 (60.5)
QTc Prolongation*	1 (2.9)	9 (8.1)	23 (14.6)
Hyperglycemia*			
AEs Leading To Dose Interruptions			
Overall	12 (34.3)	56 (50.5)	102 (65.0)
QTc Prolongation *	1 (2.9)	8 (7.2)	22 (14.0)
Hyperglycemia*	2 (5.7)	22 (19.8)	55 (35)
AEs Leading To Dose Reduction or Interruption			
Overall	16 (45.7)	66 (59.5)	119 (75.8)
QTc Prolongation *	1 (2.9)	9 (8.1)	28 (17.8)
Hyperglycemia*	3 (8.6)	27 (24.3)	69 (43.9)
AEs Leading To Dose Discontinuations			
Overall**	4 (11.4)	25 (22.5)	33 (21.0)
QTc Prolongation *	0	1 (0.9)	6 (3.8)
Hyperglycemia*	0	0	3 (1.9)

* combined terms; ** includes AEs of disease progression

The frequency of dose modifications/discontinuations was highest in the slow acetylators, and lowest in the rapid acetylator group. This relationship was driven by events of hyperglycemia and QTc prolongation, and was not seen across other events. In the slow acetylator group, although more

common than the other groups, discontinuation rate for hyperglycemia or QTc prolongation was low (1.9% and 3.8% respectively).

5.9.7.2 Frequency of Adverse Events By Dose, Normalized For Acetylator Status

AEs were analyzed by dose within each acetylator phenotype. This analysis normalizes the datasets for acetylator status, minimizing its potential confounding effect on frequency by dose level, since the number of patients with slow acetylator status were not balanced amongst the treatment arms.

In the intermediate and slow acetylator groups, there was a relationship with dose for QTc events and QTc laboratory abnormalities. In the intermediate group, more patients had ≥481ms QTc measured on study or change from baseline >60ms with ascending dose. In the slow group, more patients had change from baseline >60ms with ascending dose, and more patients had ≥481ms QTc measured on study in the 750mg BID group compared with the lower doses. In both acetylator groups, the frequency of Grade 3 or above QTc adverse events increased with dose. There was no relationship with dose in the small, rapid acetylator group (n=35).

5.9.7.3 Feasibility of Reducing QTc Prolongation Risk by Genotyping Patients for NAT2 Alleles

The analysis of cardiac events showed an association between change in baseline QTc>60ms and acetylator status, with an increased event frequency in the slow group compared with the intermediate or rapid groups. In addition, ventricular tachyarrhythmia events, although infrequent, were only observed in the slow acetylator group.

However, QTc prolongation was observed across all acetylator subgroups. Therefore, the risk minimization measures for QTc prolongation described in Section 5.9.2 should be applied to all patients, irrespective of acetylator status

Clovis plans to investigate the potential utility of the NAT2 genotype further. Plans include the following:

- NAT2 genotyping on all consenting patients in ongoing studies of rociletinib to increase the sample size.
- Further examine whether heterogeneity exists within slow acetylator genotype

5.10 SAFETY CONCLUSIONS

Overall, rociletinib has a well-defined, manageable, and differentiated safety profile. Overall across all doses, 36% of patients had treatment duration greater than 6 months. Effective risk management, as described in Section 8 includes dose reduction recommendations, prescriber education, and patient selection should reduce the risk of potentially serious sequelae.

6 SELECTION OF RECOMMENDED DOSE

Three doses of rociletinib, 500 mg BID (n=79), 625 mg BID (n=170), and 750 mg BID (n=76), have been evaluated for efficacy and safety in Studies 008 and 019 (625 mg BID only). The rationale for selecting rociletinib 625 mg BID as the recommended dose for patients with T790M-positive mutant EGFR NSCLC is based on a comprehensive evaluation of clinical efficacy, understanding of rociletinib exposure and response relationship, and assessment of clinical safety. A summary of the key findings are presented below.Efficacy of rociletinib at 500 mg BID (n = 79), 625 mg BID (n = 170). and 750 mg BID (n = 76) was evaluated in T790M-positive patients using both investigator assessment and IRR. The 750 mg BID dose was not pursued because of higher rates of dose modifications and AEs compared with the other doses. There was no significant difference in the ORR (Table 12) and median DOR (Figure 8) results based on IRR at 500 mg BID and 625 mg BID doses (investigator assessment data showed similar results, Appendix 11.3). For IRR, the 95% CIs were overlapping for the 500 mg BID and 625 mg BID dose groups. Because there was no dose relationship identified based on IRR analysis (Figure 12), robust assessment of efficacy based on IRR can be performed using all doses combined (500 mg BID, 625 mg BID, 750 mg BID). The ORR by IRR was similar for 625 mg BID and for all rociletinib doses combined: 32.4% and 30.2%, respectively (Table 12). The ORR for the 500 mg BID dose group (22.8%) was slightly below the lower boundary of 95% CI for ORR for all rociletinib doses combined (25.2%). While robust efficacy was demonstrated for rociletinib at and above 500 mg BID, confirmed responses were not observed during Phase 1 in patients who received rociletinib FB below 900 mg BID dose levels (Figure 13). This is relevant to the dose-response evaluation because the relative bioavailability of the FB formulation is 66.1% of the HBr formulation based on the popPK model, thus allowing calculation of an “HBr equivalent” dose and evaluation of rociletinib activity at doses below 500 mg BID. The highest FB dose studied, 900 mg BID, is equivalent to 595 mg BID HBr. Therefore, as expected, responses were observed at this dose level (Figure 13). However, at the next lower dose tested (equivalent to 397 mg BID HBr) and at doses below that, no responses were observed (Figure 13). This finding suggests that a threshold of exposure is needed for response, and that the threshold of exposure lies between that observed with the 500 mg BID dose and that observed with the 397 mg BID HBr equivalent dose.

While assessment of ORR by IRR is limited to 500 mg BID, 625 mg BID, and 750 mg BID (Figure 12), the dose-response analysis in the 365 T790M-positive patients who received rociletinib across several dose levels including doses that would be below 500 mg BID suggested that confirmed ORR by investigator assessment correlated significantly with the adjusted starting daily dose (Figure 13). In addition, the ORR by investigator assessment correlated significantly with $C_{max,ss}$ in a log-linear relationship (Figure 14). The exposure-response analysis suggests that the threshold for response lies between the lowest 2 deciles of exposures in PK-evaluable T790M-positive patients (Figure 15) indicating that at the starting dose of 500 mg HBr BID, a higher percentage of patients have rociletinib exposure in the lowest 2 deciles than at 625

mg HBr BID dose. This is consistent with an observation of no responses at dose levels below 500 mg BID (Figure 13).

The safety profile of rociletinib was generally similar at 500 mg BID and 625 mg BID (Table 13). Between the 500 mg BID and 625 mg BID dose groups, there was approximately a 2% difference in the frequency of SAEs (44% vs 46%) and a 3% difference in the occurrence of ≥ Grade 3 AEs (70% vs 73%).

Approximately 33% and 34%, of patients experienced an AE of QTc prolongation in the 500 mg BID and 625 mg BID dose groups, respectively, with 8% and 10% reported as ≥ Grade 3, respectively. Based on central laboratory measurements, the rates of ≥ 501 ms post-baseline QTc were comparable between 500 mg BID and 625 mg BID, however a higher frequency of > 60 ms change from baseline was observed with 625 mg BID as compared to 500 mg BID (33% vs 26%). The 1% of patients who experienced SAEs included 3 events of ventricular tachyarrhythmia all occurred at the 625 mg BID dose. There were 2 unexplained deaths (1 at 625 mg BID and 1 at 750 mg BID). Both were judged related to rociletinib by the investigators. Similarly, with hyperglycemia, there was approximately a 1% difference between the 500 mg and 625 mg BID dose groups in the frequency across all grades (54% vs 55%) and those of ≥ Grade 3 (31% vs 32%).

In conclusion, based on the above summary of efficacy and safety at 500 mg BID and 625 mg BID, and considering that there appears to be a threshold of exposure to rociletinib that drives tumor response, the sponsor has selected 625 mg BID as the recommended dose in order to give each patient the greatest chance to benefit from rociletinib therapy. A recommended dose of 625 mg BID also provides dose modification flexibility without potentially compromising clinical benefit since a dose reduction to 500 mg BID will allow patients to continue to be treated at a dose known to be active.

7 BENEFIT RISK DISCUSSION

Most first-line patients achieve an initial response and receive durable clinical benefit following treatment with EGFR TKIs, however, eventually, after 9-14 months of PFS, these patients will develop treatment resistant disease due to T790M ((Mok et al 2009, Rosell et al 2012, Sequist et al 2013). Survival rates of patients with advanced NSCLC who progress following treatment with EGFR-TKI remain very low, with a median OS of 1 to 2 years (Yu et al 2013).

Rociletinib has been studied primarily in the US in a patient population with predominantly poor baseline prognostic factors. For example, 24% and 32% of patients treated at 625 mg BID had 4 or more prior therapies and more than 1 prior EGFR TKI, respectively. In addition, 41% had previously been treated with both platinum doublet chemotherapy and an EGFR TKI. Therefore, the majority of patients would have been candidates for single agent cytotoxic chemotherapy as the only remaining therapeutic option.

Despite the poor prognostic factors of patients in the rociletinib studies, the ORR in patients receiving 625 mg BID rociletinib was 32% by IRR and 34% by investigator assessment. Responses were durable, with a median duration of confirmed response of 8.8 months by IRR and 7.2 months by investigator assessment.

In determining if rociletinib provides a meaningful advantage over available therapy as one of the conditions for accelerated approval, the FDA only considers agents with full approval with includes platinum doublet chemotherapy, single-agent chemotherapy, and the immunotherapy nivolumab. Limited data are available regarding efficacy of platinum doublet chemotherapy in patients with recurrent disease, however, data from several front line Phase 3 randomized clinical trials are available. The ORR in these studies is generally 20-25% with a median DOR ranging from 4-6 months (Table 3). Given that these are earlier line patients, and that some of these studies include predominantly Asian patients who have a better prognosis, the clinical benefit observed in these studies is likely to be an overestimate of the efficacy expected for patients with recurrent disease in the US. Importantly, only one-third of patients who progress on first-line EGFR TKIs will receive platinum based chemotherapy, and single agent chemotherapy will be the choice for many patients. Single agent docetaxel and pemetrexed are commonly used in this setting, with response rates below ≤ 10% and a reported median DOR of 4.6 to 9.1 months. (Table 4). In additional, chemotherapy is associated with well-known toxicities which present a significant burden to patients' everyday lives.

Although immunotherapies have shown great promise and are approved in many indications, early data with the PD-1 inhibitor nivolumab suggests that tumor responses in mutant EGFR NSCLC patients are less common than those observed in unselected patients (Gettinger et al 2015). While no definitive conclusions regarding the efficacy of these agents in mutant EGFR patients can be made at present,

these data are consistent with the hypothesis that immunotherapy might be less active in patients with lower mutational burden such as mutant EGFR NSCLC (Rizvi et al 2015).

Rociletinib has a well-defined, manageable, and differentiated safety profile. Overall across all doses, 36% of patients had treatment duration greater than 6 months. Based on the understanding of the underlying mechanisms, monitoring and treatment guidelines have been developed for adverse events of hyperglycemia and QT prolongation. Thus, prescribers will be provided with effective risk management strategy, as described in Section 8, which will include patient selection, dose reduction and treatment recommendations, and prescriber education. This comprehensive approach to risk management will minimize the risk of potentially serious sequelae in the intended population of patients with recurrent mutant EGFR NSCLC.

In determining if rociletinib provides a meaningful advantage over available therapy, the FDA only considers agents with full regulatory approval to be appropriate comparator benchmarks. However, 1 other agent targeting T790M mutation, osimertinib, has recently been granted accelerated approval. The safety and efficacy of osimertinib were demonstrated in 2 single-arm studies which enrolled patients mostly in Asia (60%). Continued approval for this indication may be contingent upon further confirmatory studies (AstraZeneca Pharmaceuticals LP November 2015). The response rate in the subgroup (n=108) enrolled in North America was 52%. While osimertinib is associated with significant rates of skin rash (41%), stomatitis (12%) and nail toxicity (25%), (AstraZeneca Pharmaceuticals LP November 2015), these events are uncommon with rociletinib. Some patients may be unable or unwilling to endure additional skin toxicity while others may have a cardiac exclusion that makes osimertinib inappropriate. For these patients, rociletinib is an important treatment alternative that can deliver meaningful clinical benefit. Thus the safety profiles of osimertinib and rociletinib are clearly unique. In addition to unique toxicities, emerging data suggest that the patterns of acquired resistance differ between the 2 agents (Section 2.1.4). The importance of these resistance mechanisms and their implications for treatment decisions are currently under study.

In conclusion, rociletinib 625 mg BID has a favorable benefit:risk profile in patients with recurrent T790M-positive mutant EGFR NSCLC based on clinically meaningful and durable responses and well established and acceptable safety profile in this patient population with terminal lung cancer, for whom chemotherapy is often the only available option.

8 PROPOSED LABELING AND RISK MANAGEMENT PLAN

The sponsor is in discussion with FDA regarding the details of labeling and risk management for rociletinib. The proposed labeling includes warnings and precautions for the following: QTc prolongation, hyperglycemia, ILD, and embryofetal toxicity. The most common AEs are diarrhea, nausea, fatigue, decreased appetite, vomiting, constipation, muscle spasms and hyperglycemia.

QTc Prolongation

QTc prolongation is likely due to the rociletinib metabolite M460. The effect of rociletinib on QTc is well characterized through analysis of centrally read ECGs from patients in Study 008 and Study 019. The effect on QT interval does not occur on the first day of dosing but is generally apparent by Day 15 and remains prolonged for the duration of therapy thereafter. Therefore, ECGs should be monitored more frequently during initial treatment to establish the effect in each patient, and periodically thereafter once the effect has plateaued. Once rociletinib therapy is stopped, QTc returns to normal over several days, consistent with the relatively short half-life (approximately 50 hours) of M460.

Based on these data, Clovis has developed a structured management plan to minimize the risk of QT-related AEs.

1. Avoidance of prescribing in patients at risk for QTc prolongation.
   Proposed language in label:
   Avoid use of rociletinib in patients with congenital long QT syndrome, resting heart rate less than 55 beats/min, or baseline QTc interval greater than 450 msec.
2. Routine ECG monitoring, pre-treatment ECG (needed to detect patients with LQTS and bradycardia), 15 days after treatment initiation and monthly or as clinically indicated while on treatment with dose modification when Grade 3 prolongation occurs.
   Proposed language in label:
   Monitor ECG 15 days after treatment initiation and then monthly, or as clinically indicated, while on treatment.
3. Avoidance of arrhythmogenic concomitant medications.
   Proposed language in label:
   When possible, avoid use of medications that prolong the QT interval while taking rociletinib.
4. Prompt correction of electrolyte disturbances that may exacerbate the risk of QTc prolongation.
   Proposed language in label:
   Monitor for and correct hypomagnesemia, hypokalemia and hypocalcemia at baseline and monitor on treatment and correct as needed.

Diarrhea: Inform patients that XEGAFRI can cause mild or moderate diarrhea which may require medication for treatment. Advise patients to contact their healthcare team at the start of diarrhea or signs of dehydration *[see Adverse Reactions (6)]*.

Additionally, the proposed labeling contains guidance on when to interrupt rociletinib for prolonged QTc and how to restart at a reduced dose.

Proposed language in label:

Withhold XEGAFRI for:

- QTc interval greater than 500 msec until QTc interval is less than 481 msec, then resume XEGAFRI with the appropriate dose reduction *[see Warnings and Precautions (5.1)]*

Permanently discontinue XEGAFRI for:

- QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia *[see Warnings and Precautions (5.1)]*

Hyperglycemia

Hyperglycemia likely results from reversible inhibition of IGF1R and INSR kinases by rociletinib metabolite M502. Therefore, rociletinib therapy causes a reversible state of insulin resistance. Guidance has been developed to address this and primarily includes management of hyperglycemia with oral agents such as biguanides, glitazones, and SGLT2 inhibitors that are suitable for insulin resistance management. Since the majority of hyperglycemia events develop within the first 6 weeks, blood glucose should be monitored weekly for the first 6 weeks of treatment. Recommendations on the management of hyperglycemia are included in the proposed Prescribing Information.

9 CONFIRMATORY STUDY 020

9.1 OVERVIEW

Study 020 is a Phase 3, open-label, multicenter, randomized study of oral rociletinib monotherapy versus single-agent cytotoxic chemotherapy in patients with EGFR NSCLC after failure of at least 1 previous EGFR-directed TKI and platinum doublet chemotherapy. This population represents patients with the most advanced disease. Patients are to be randomized 1:1:1 to receive rociletinib at 500 mg BID or 625 mg BID or investigator choice standard of care chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel).

9.1.1 Population includes T790M-positive and T790M-negative Patients

Study 020 is enrolling both patients that are T790M-positive and T790M-negative by central testing. Patients that are T790M-negative may respond to rociletinib due to tumor heterogeneity, and inter-tumoral, intra-tumoral, and temporal heterogeneity has been observed in patients with mutant EGFR NSCLC (Gerlinger et al 2012) (Piotrowska et al 2015). In addition, rociletinib may have activity in T790M-negative patients due to off-target activity against other kinases such as IGF1R and INSR. There are also challenges with molecular testing. In a recent Phase 4 study of gefitinib in newly diagnosed patients with late-stage NSCLC, approximately 15% of patients had inadequate tumor sample for molecular analysis, and a number of patients were poor candidates for biopsy due to comorbidities (Douillard et al 2014). Thus to comprehensively explore the activity of rociletinib, both T790M-positive and T790M-negative are included in Study 020.

9.1.2 Study Design

In the initial Study 020 protocol (dated 10 October 2014), there was a single rociletinib arm in which patients were treated at 625 mg BID with rociletinib. This starting dose was based on the clinical safety and efficacy data available at that time. Maturing data from the CO-1686-008 study suggested that patients treated with rociletinib at 500 mg BID and 625 mg BID experienced comparable responses with an overall acceptable safety profile. To further describe the benefit:risk profile of the rociletinib 500 mg BID dose, Study 020 was amended (Protocol Amendment 2, dated 27 April 2015) for the rociletinib arm to receive 500 mg BID. The protocol was recently amended (Protocol Amendment 3, dated 22 February 2016) to explore both the 500 mg BID and 625 mg BID doses of rociletinib by implementing a 1:1:1 randomization scheme and increasing the sample size accordingly to 900 patients:

- 500 mg rociletinib BID (300 patients)
- 625 mg rociletinib BID (300 patients)
- Investigator's choice of single agent chemotherapy (300 patients)

Randomization is stratified according to history of brain metastases (yes vs no), ECOG performance status (0 vs 1), and geographic location (East Asian vs non-East Asian).

Treatment is to continue, until disease progression or until other withdrawal criteria are met (including completion of a single-agent chemotherapy regimen). Tumor assessment occurs every 6 ± 1 weeks, irrespective of regimen. Enrolled patients who are randomized to chemotherapy will be given the opportunity to cross-over to rociletinib after disease progression. An independent data monitoring committee (IDMC) will review safety and efficacy data on a periodic basis to ensure an acceptable overall risk and benefit for patients participating in the study, and to make recommendations to Clovis for any potential changes to study conduct. The end of study evaluation is to be conducted 28 days after the last dose, and patients are followed every 2 months thereafter for subsequent therapy and survival.

The primary endpoint for this study is PFS based on disease progression according to RECIST Version 1.1 as determined by investigator assessment. Key secondary endpoints include ORR and duration of response according to RECIST Version 1.1 as determined by investigator assessment, and OS. The primary and key secondary endpoints will be tested among the centrally confirmed T790M-positive and all randomized patients, using an ordered step-down multiple comparisons procedure separately for the 500 mg BID and 625 mg BID dose groups as compared to the chemotherapy arm. The study is 90% powered to detect a 40% improvement in PFS (hazard ratio of 0.6) at the 0.025 significance level for either rociletinib 500 mg BID or 625 mg BID dose groups compared to chemotherapy, but is not powered for formal comparison of 500 mg BID versus 625 mg BID.

9.1.3 Number Enrolled

Study 020 is currently open for enrollment in the US, Europe, South Korea, Taiwan, and Australia. The first patient was enrolled in the US on 04 May 2015. As of 26 February2016, a total of 114 patients have been randomized at 80 study sites, including 45 patients that have been randomized at 33 study sites in the US. An additional 45-50 study centers will be opened outside of the US to compensate for the availability of third-generation EGFR TKIs. New territories currently undergoing site selection include Canada, China, Malaysia, Philippines, Thailand, Romania, and Russia. Study 020 is projected to complete in 2018, with the last patient visit in the second half of 2018.

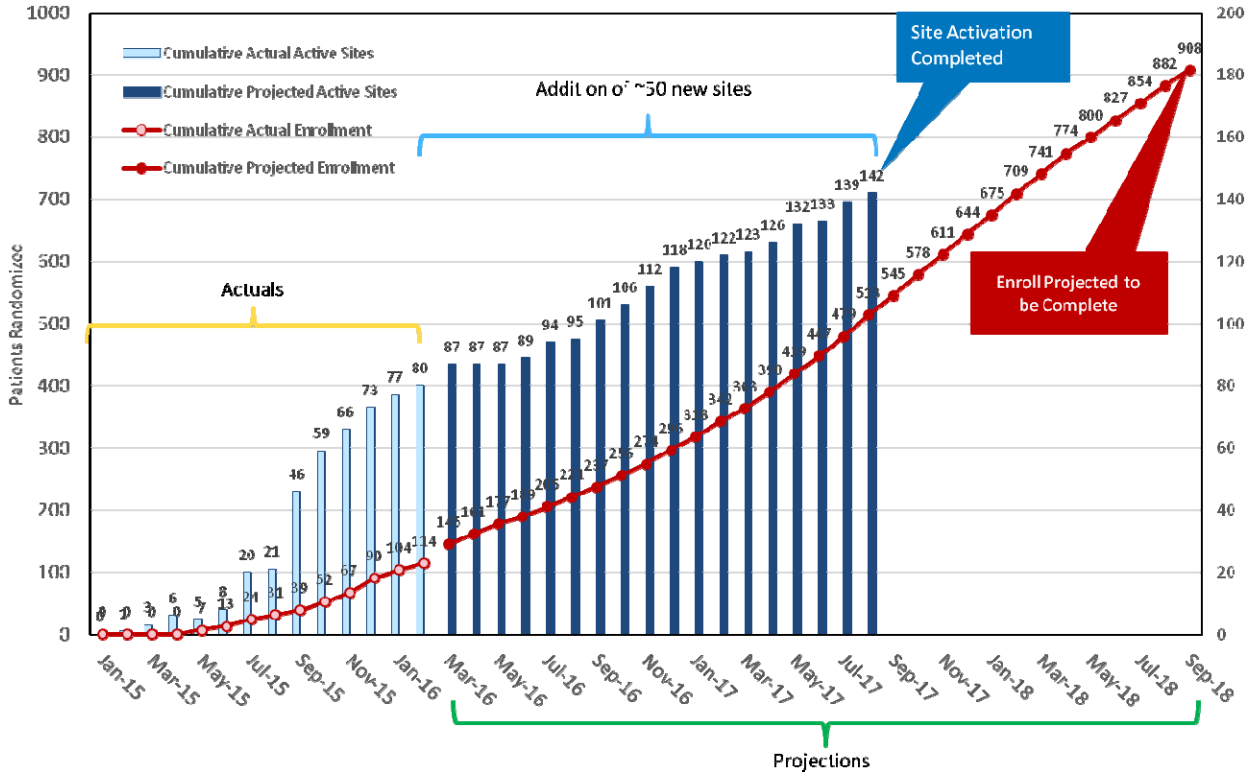
A total of 114 patients have been randomized in Study 020. The first patient was randomized in May 2015. Of the patients who have received rociletinib, 41 patients were randomized under Protocol Amendment 1 (dated 31 October 2014) and patients randomized to rociletinib began treatment with the 625 mg BID dose. The remaining 73 of 114 patients were randomized under Amendment 2 and received rociletinib at the 500 mg BID dose. Table 27 provides an overview of the status of the study, including the countries in which the study protocol has been approved, the number of sites currently enrolling under each protocol amendment, and the number of patients randomized.

Table 27: Status of Study 020 as of 26 February 2016

Amendment 1 (625 mg BID)		
Country	**Sites Activated**	**Total Number of Patients Randomized**
Australia	3	1
France	9	0
Germany	5	0
Italy	5	7
Netherlands	3	4
South Korea	6	1
Spain	7	0
Taiwan	5	0
UK	5	1
USA	32	27
Protocol Amendment 1 Subtotal	80	41
Amendment 2 (500 mg BID)		
Country	**Sites Activated**	**Total Number of Patients Randomized**
Australia	3	1
France	9	4
Germany	5	0
Italy	5	5
Netherlands	3	8
South Korea	6	11
Spain	7	7
Taiwan	5	15
UK	5	4
USA	32	18
Protocol Amendment 2 Subtotal	80	73
Study 020 Total	**80**	**114**

Figure 17 shows Study 020 site activation, patient screening, and enrollment. The first site was activated in the US in February 2015, followed by regulatory approvals and the first site opening in Europe in June 2015 and in Asia in July 2015. As of 26 February 2016, 80 of a projected 134 sites have been open around the world, including 32 in the US. Both screening and enrollment continue to increase according to projections.

Figure 17: Study 020 Enrollment Projections



In summary, the confirmatory study is appropriately designed to evaluate the activity of rociletinib 500 mg BID and 625 mg BID compared with single agent cytotoxic chemotherapy. To mitigate the risk of enrollment delay following availability of third generation EGFR inhibitors in certain countries including in the US, the sponsor has identified additional investigational sites in existing and new countries, and site activations are in progress. Therefore, appropriate measures are in place to ensure enrollment completion according to the specified timeline.

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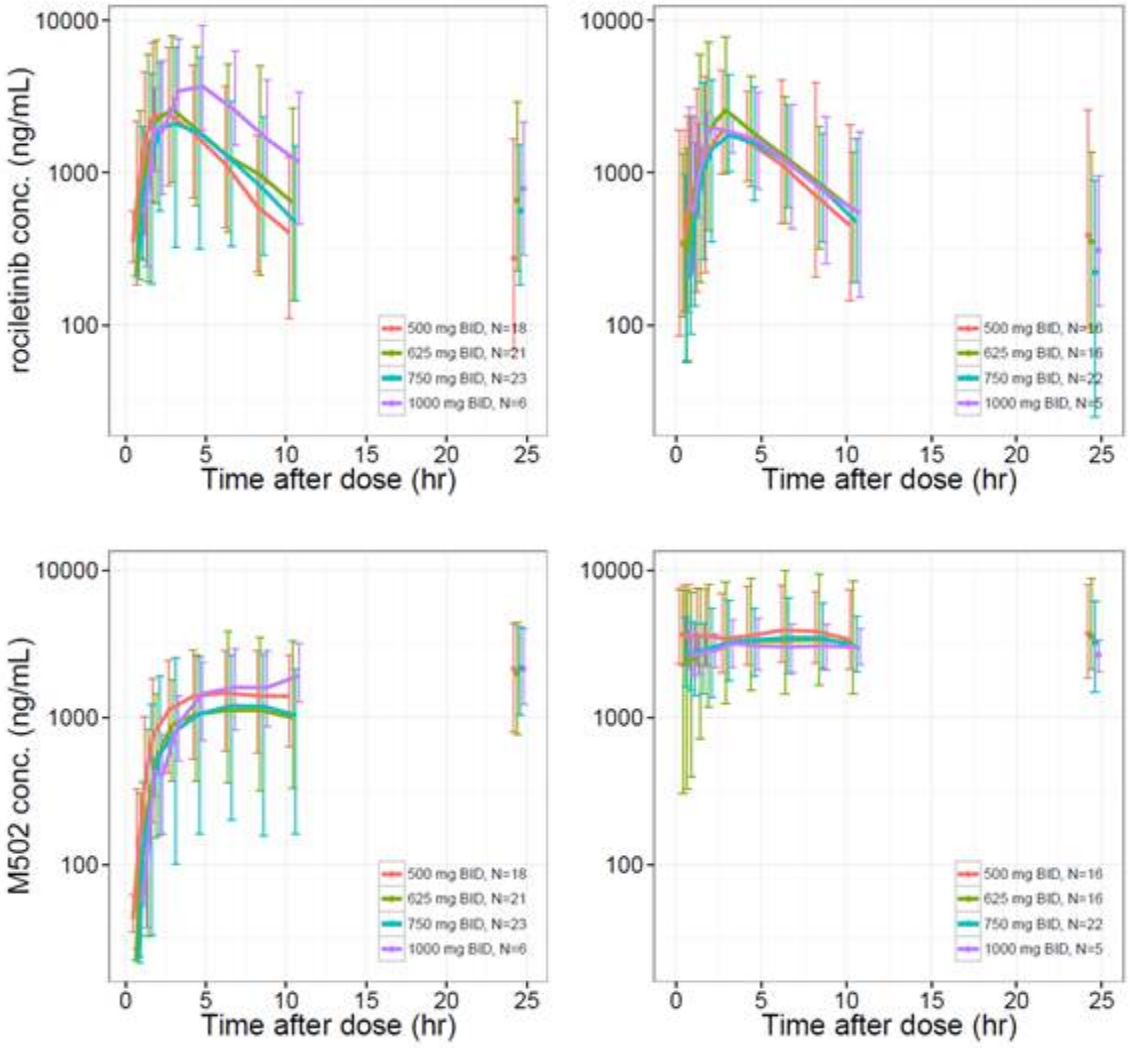
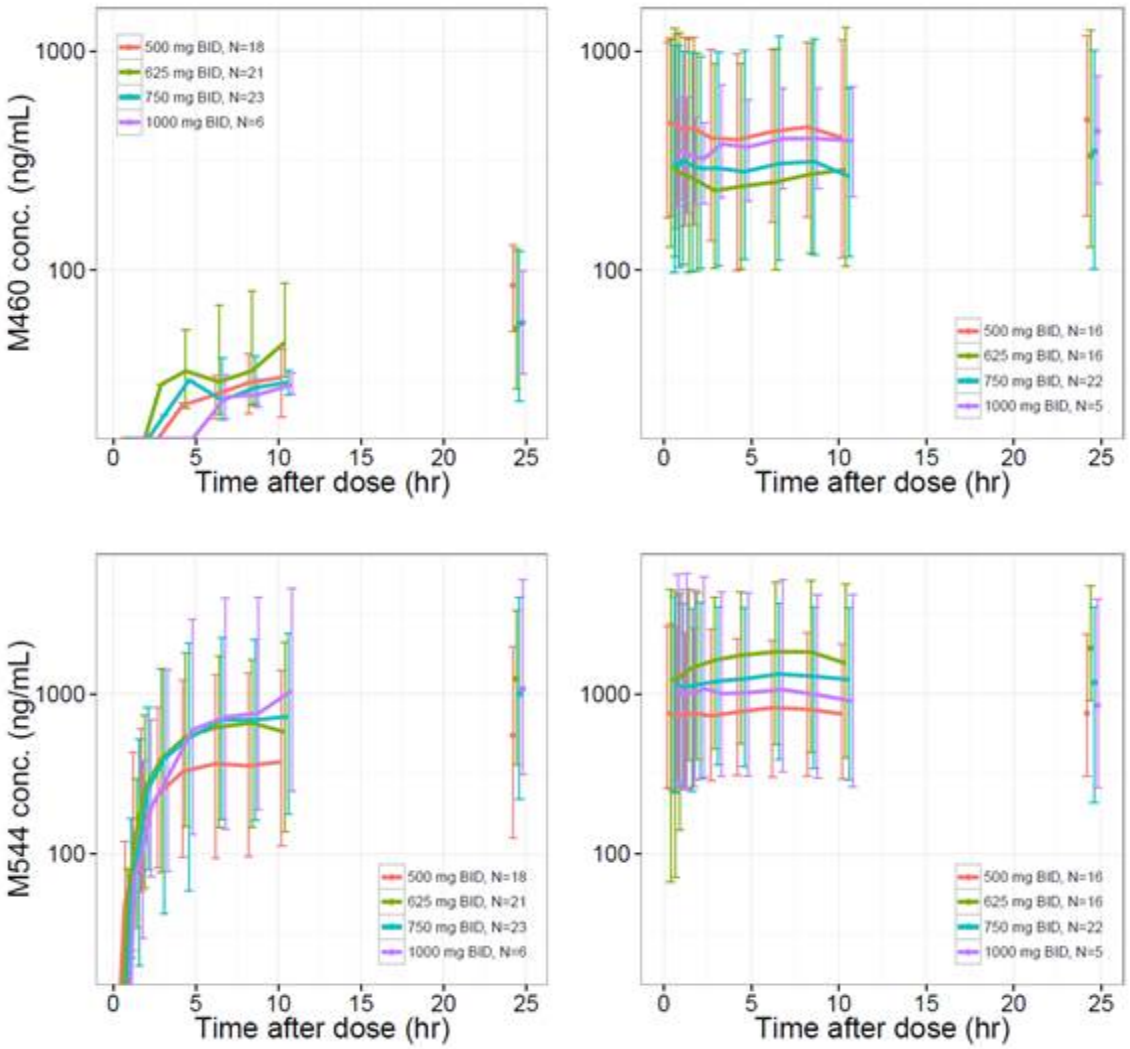
11 APPENDICES

11.1 PLASMA ROCILETINIB, M502, M544, AND M460 CONCENTRATION VERSUS TIME PROFILES IN PATIENTS STARTED ON ROCILETINIB HBR

Figure 18: Geometric Mean (90% CI) Plasma Rociletinib, M502, M544, and M460 Concentration Versus Time Profiles on Day 1 (Left Panel) and on Day 15 (Right Panel) in Patients Started on Rociletinib HBr





11.2 PATIENT DISPOSITION AND BASELINE DEMOGRAPHICS IN THE T790M POSITIVE POPULATION

Table 28: Baseline Demographics in the T790M Positive Population

	500 mg BID (N=79)	625 mg BID (N=170)	750 mg BID (N=76)	Overall (N=325)
Age (yr)				
Mean (SD)	61.6 (11.02)	62.2 (11.26)	60.9 (11.79)	61.7 (11.31)
Median	62.0	62.5	61.0	62.0
Age Group				
≤50	8 (10.1%)	30 (17.6%)	12 (15.8%)	50 (15.4%)
51-64	35 (44.3%)	64 (37.6%)	31 (40.8%)	130 (40.0%)

	500 mg BID (N=79)	625 mg BID (N=170)	750 mg BID (N=76)	Overall (N=325)
65-80	33 (41.8%)	68 (40.0%)	30 (39.5%)	131 (40.3%)
≥81	3 (3.8%)	8 (4.7%)	3 (3.9%)	14 (4.3%)
Gender				
Female	59 (74.7%)	117 (68.8%)	50 (65.8%)	226 (69.5%)
Race				
Asian	15 (19.0%)	42 (24.7%)	19 (25.0%)	76 (23.4%)
Black	3 (3.8%)	7 (4.1%)	1 (1.3%)	11 (3.4%)
White	51 (64.6%)	97 (57.1%)	55 (72.4%)	203 (62.5%)
Other	10 (12.7%)	24 (14.1%)	1 (1.3%)	35 (10.8%)
Geographic Region				
North America	61 (77.2%)	139 (81.8%)	66 (86.8%)	266 (81.8%)
Europe	12 (15.2%)	16 (9.4%)	3 (3.9%)	31 (9.5%)
Other	6 (7.6%)	15 (8.8%)	7 (9.2%)	28 (8.6%)
ECOG at Baseline				
0	18 (22.8%)	46 (27.1%)	24 (31.6%)	88 (27.1%)
1	60 (75.9%)	124 (72.9%)	52 (68.4%)	236 (72.6%)
>=2	1 (1.3%)	0	0	1 (0.3%)
Time Since Diagnosis of NSCLC (months)				
n	79	170	76	325
Mean (SD)	36.6 (21.19)	31.3 (26.57)	36.0 (28.22)	33.7 (25.83)
Median	32.6	22.6	26.9	26.0
Time Since Diagnosis of NSCLC Group (months)				
≤3	0	1 (0.6%)	0	1 (0.3%)
>3-6	0	0	1 (1.3%)	1 (0.3%)
>6-12	6 (7.6%)	20 (11.8%)	8 (10.5%)	34 (10.5%)
>12-24	25 (31.6%)	70 (41.2%)	24 (31.6%)	119 (36.6%)
>24	48 (60.8%)	79 (46.5%)	43 (56.6%)	170 (52.3%)
History of CNS Metastases				
Yes	34 (43.0%)	76 (44.7%)	36 (47.4%)	146 (44.9%)
Metastatic Disease Site *				
Lung	72 (91.1%)	161 (94.7%)	72 (94.7%)	305 (93.8%)
Lymph Node	35 (44.3%)	78 (45.9%)	35 (46.1%)	148 (45.5%)

	500 mg BID (N=79)	625 mg BID (N=170)	750 mg BID (N=76)	Overall (N=325)
Liver	26 (32.9%)	55 (32.4%)	29 (38.2%)	110 (33.8%)
Bone	25 (31.6%)	58 (34.1%)	34 (44.7%)	117 (36.0%)
CNS	24 (30.4%)	81 (47.6%)	34 (44.7%)	139 (42.8%)
Other	14 (17.7%)	38 (22.4%)	18 (23.7%)	70 (21.5%)
Number of Metastatic Disease Sites				
1	14 (17.7%)	33 (19.4%)	12 (15.8%)	59 (18.2%)
2	31 (39.2%)	40 (23.5%)	16 (21.1%)	87 (26.8%)
3	19 (24.1%)	47 (27.6%)	21 (27.6%)	87 (26.8%)
4	8 (10.1%)	30 (17.6%)	18 (23.7%)	56 (17.2%)
5	5 (6.3%)	18 (10.6%)	8 (10.5%)	31 (9.5%)
6	2 (2.5%)	2 (1.2%)	1 (1.3%)	5 (1.5%)
Number of Previous Therapies				
Mean (SD)	3.0 (1.76)	2.5 (1.87)	2.8 (2.08)	2.7 (1.90)
Median	3.0	2.0	2.0	2.0
Min, Max	1.0, 8.0	1.0, 13.0	1.0, 9.0	1.0, 13.0
Number of Previous Therapies Group				
0	0	0	0	0
1	21 (26.6%)	68 (40.0%)	33 (43.4%)	122 (37.5%)
2	14 (17.7%)	39 (22.9%)	11 (14.5%)	64 (19.7%)
3	17 (21.5%)	23 (13.5%)	8 (10.5%)	48 (14.8%)
4	14 (17.7%)	22 (12.9%)	7 (9.2%)	43 (13.2%)
5	5 (6.3%)	6 (3.5%)	6 (7.9%)	17 (5.2%)
>5	8 (10.1%)	12 (7.1%)	11 (14.5%)	31 (9.5%)
Number of Previous TKI Therapies				
Mean (SD)	1.5 (0.73)	1.4 (0.72)	1.6 (0.82)	1.5 (0.75)
Median	1.0	1.0	1.0	1.0
Number of Previous TKI Therapies Group				
0	0	0	0	0
1	49 (62.0%)	115 (67.6%)	45 (59.2%)	209 (64.3%)
≥2	30 (38.0%)	55 (32.4%)	31 (40.8%)	116 (35.7%)
EGFR Activating Mutations				
Exon 19 Deletion	48 (60.8%)	118 (69.4%)	57 (75.0%)	223 (68.6%)
L858R	24 (30.4%)	40 (23.5%)	18 (23.7%)	82 (25.2%)

	500 mg BID (N=79)	625 mg BID (N=170)	750 mg BID (N=76)	Overall (N=325)
Other	3 (3.8%)	6 (3.5%)	1 (1.3%)	10 (3.1%)
Time Between Last Dose of a TKI and First Dose of Study Drug (days)				
n	79	170	76	325
Mean (SD)	77.0 (138.05)	39.4 (92.47)	27.9 (89.32)	45.8 (105.97)
Median	8.0	6.0	5.0	5.0
Min, Max	1.0, 642.0	1.0, 775.0	1.0, 589.0	1.0, 775.0
Time Between Last Dose of a TKI and First Dose of Study Drug Group (days)				
0-15	48 (60.8%)	116 (68.2%)	66 (86.8%)	230 (70.8%)
16-30	4 (5.1%)	19 (11.2%)	2 (2.6%)	25 (7.7%)
31-60	7 (8.9%)	10 (5.9%)	1 (1.3%)	18 (5.5%)
>60	20 (25.3%)	25 (14.7%)	7 (9.2%)	52 (16.0%)

Table 29: Patient Disposition in the T790M Positive Population

	500 mg BID (N=79)	625 mg BID (N=170)	750 mg BID (N=76)	Overall (N=325)
	n (%)	n (%)	n (%)	n (%)
End of Treatment Status				
Ongoing	33 (41.8%)	60 (35.3%)	31 (40.8%)	124 (38.2%)
Discontinued	46 (58.2%)	110 (64.7%)	45 (59.2%)	201 (61.8%)
Primary Reason for Discontinuation of Study Drug				
Progressive Disease	34 (73.9%)	80 (72.7%)	38 (84.4%)	152 (75.6%)
Adverse Event	7 (15.2%)	15 (13.6%)	3 (6.7%)	25 (12.4%)
Death	1 (2.2%)	0	0	1 (0.5%)
Withdrawal by Subject	1 (2.2%)	5 (4.5%)	1 (2.2%)	7 (3.5%)
Physician Decision	1 (2.2%)	3 (2.7%)	0	4 (2.0%)
Other	1 (2.2%)	5 (4.5%)	2 (4.4%)	8 (4.0%)
Lost to Follow-up	0	1 (0.9%)	0	1 (0.5%)
Pregnancy	0	0	0	0
Protocol Deviation	0	1 (0.9%)	0	1 (0.5%)
Missing	1 (2.2%)	0	1 (2.2%)	2 (1.0%)

Abbreviations: BID = twice daily.

[a] Percentages based on the number of patients who discontinued rociletinib at each dose.

11.3 EFFICACY DATA BY INVESTIGATOR ASSESSMENT IN THE T790M POSITIVE POPULATION

Table 30: Confirmed Objective Response Rate by Investigator Assessment (T790M Positive Population)

	500 mg BID N = 79	625 mg BID N = 170	750 mg BID N = 76	Overall N = 325
	n (%)	n (%)	n (%)	n (%)
Confirmed Response Rate	22 (27.8)	57 (33.5)	23 (30.3)	102 (31.4)
95% CI	18.3 - 39.1%	26.5 - 41.2%	20.2 - 41.9%	26.4 - 36.7%
Best Overall Confirmed Response				
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	22 (27.8)	57 (33.5)	23 (30.3)	102 (31.4)
SD[a]	44 (55.7)	66 (38.8)	36 (47.4)	146 (44.9)
PD	8 (10.1)	34 (20.0)	16 (21.1)	58 (17.8)
Not evaluable[b]	5 (6.3)	13 (7.6)	1 (1.3)	19 (5.8)

[a] All SD patients including SD ongoing without progressive disease.
[b] Patients without sufficient data to evaluate a tumor response due to one of the following reasons: patient died before the scan, patient discontinued before the scan, patient had no valid baseline lesions, or no data available for technical reasons.

Figure 19: Duration of Confirmed Response by Investigator Assessment for 500 mg BID, 625 mg BID, 750 mg BID and for All Doses (T790M Positive Patients)

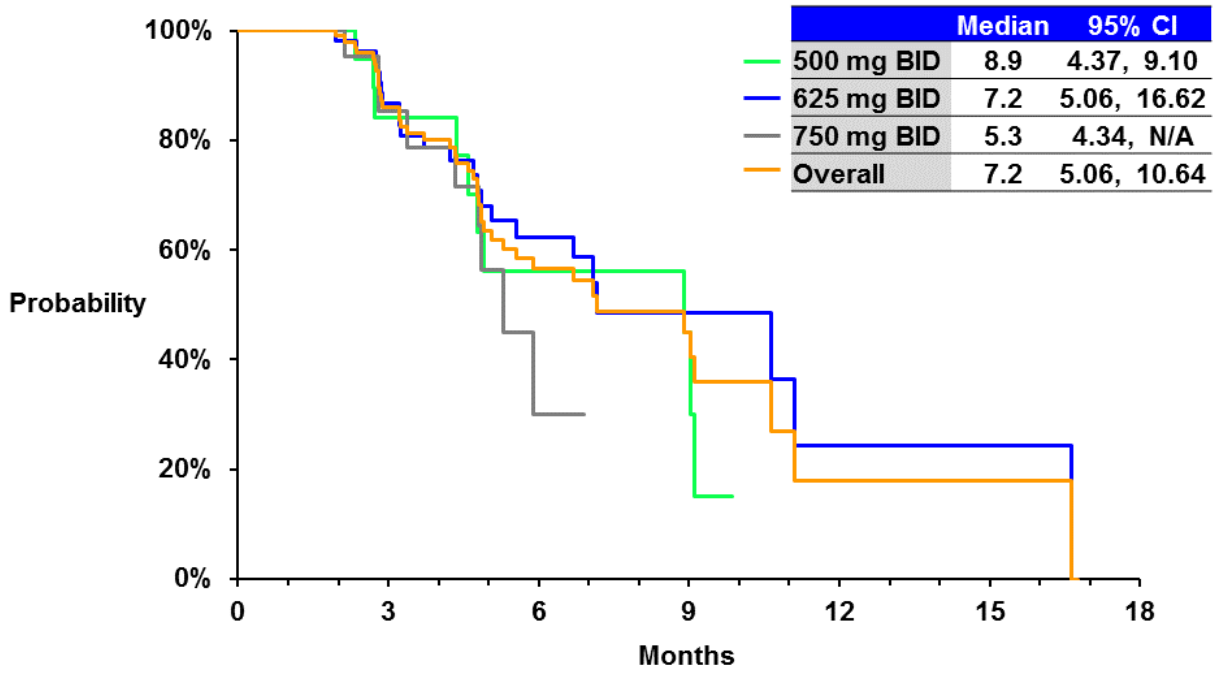
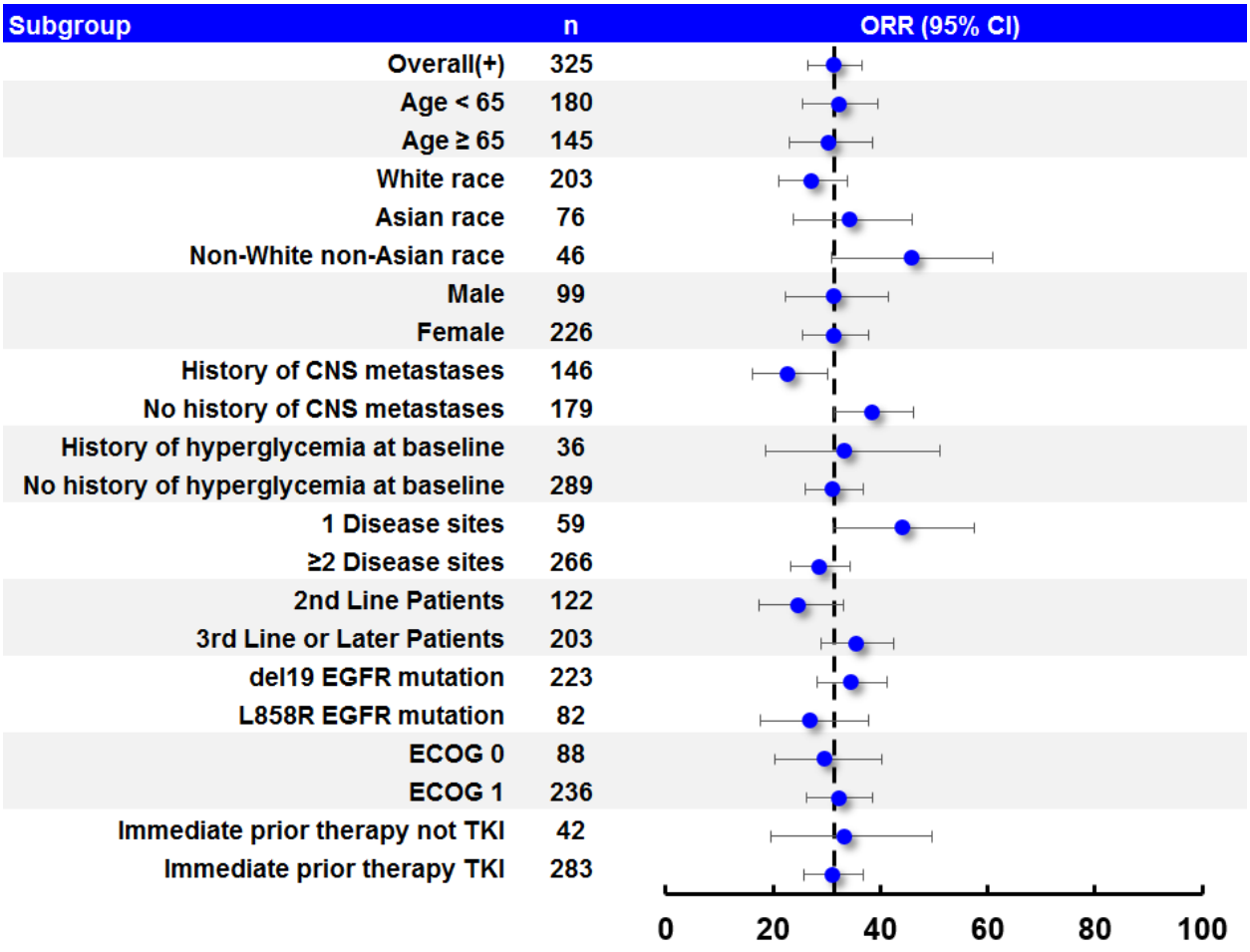


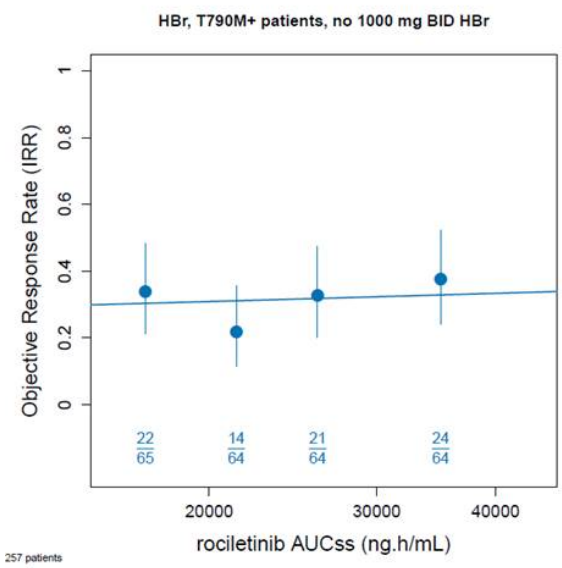
Figure 20: Subgroup Analyses by Investigator Assessment for All Doses (T790M Positive Patients)

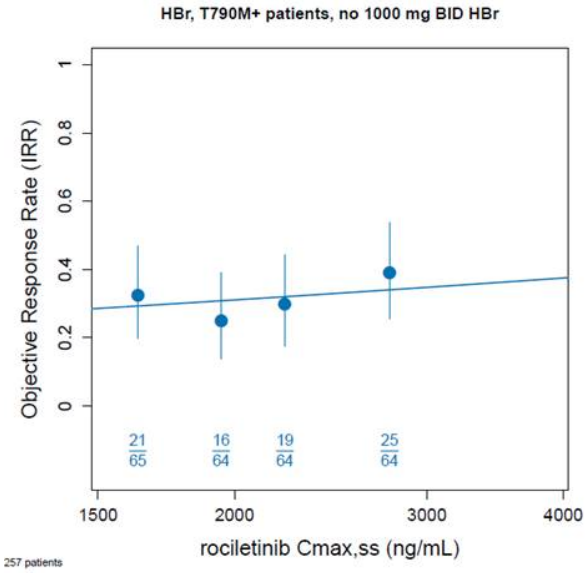


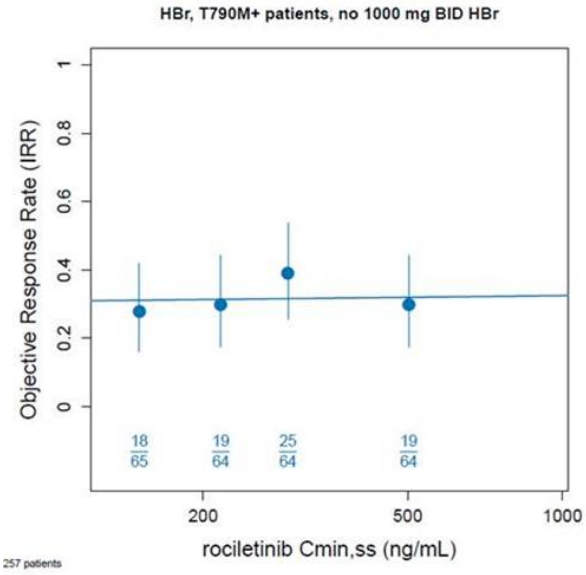
Dotted line represents the overall ORR across all doses in 325 patients (31.4%)

11.4 EXPOSURE RESPONSE ANALYSIS OF ORR BY IRR

Figure 21: Exposure (AUCss, Cmax,ss, Cmin,ss) and ORR by IRR in T790M-positive Patients







11.5 ADVERSE EVENT VIGNETTES

11.5.1 Ventricular Fibrillation and Cardiac Arrest

A 66-year-old woman in study -019 with a history of NSCLC metastatic to brain and pericardium, had received previous treatment with pulmonary lobectomy, stereotactic brain metastasis resection, and brain radiotherapy before starting rociletinib 625mg BID. Relevant past medical history included bilateral deep vein thromboses with vena cava filter, stroke with right sided hemiplegia. Baseline QTcF was 400 ms. Adverse events of diarrhea and nausea were reported beginning on Day 9 of rociletinib therapy, treated with loperamide and metoclopramide. On Day 14, ECG revealed QTcF of 443 ms. The patient discontinued rociletinib on Day 20 of her own accord. On Day 22, the patient was hospitalized with dehydration. ECG showed normal rate and sinus rhythm; full evaluation of the QTc interval was not possible due to ventricular bigeminy and ventricular couplets. The patient was treated with intravenous fluids and discharged home. On Day 23, the patient collapsed while at home and an initial ECG showed Grade 4 ventricular fibrillation with subsequent asystole requiring shock treatment, adrenaline and intubation. ECG thereafter showed sinus tachycardia with QTc interval of 452 ms. Per the patient's do not resuscitate order, she was extubated and died shortly afterwards. No autopsy was performed. The investigator assessed the events of ventricular fibrillation and cardiac arrest as secondary to rapid malignant neoplasm progression and not related to rociletinib. The sponsor assessed the event of ventricular arrhythmia as related to rociletinib, although acknowledged that other factors (including use of metoclopramide and the pericardial tumor infiltration) could also have played a causative role.

11.5.2 Torsades de Pointes

An 86-year-old man in study -008 with NSCLC metastatic to brain, pleura and adrenal, had received treatment with erlotinib before starting rociletinib 625mg BID. Relevant past medical history included hypomagnesemia and hyperlipidemia. Concomitant medications included magnesium oxide, simvastatin, brinzolamide, timolol ophthalmic drops, latanoprost ophthalmic drops, ondansetron, insulin and metformin. Baseline QTcF was 438 ms. Grade 3 hyperglycemia requiring treatment was reported on Day 8 of rociletinib therapy. He had a syncopal event on Day 10. Initial ECG showed polymorphic ventricular tachycardia and prolonged QTc (> 500 ms); subsequent ECG revealed Torsades de Pointes. The event resolved without sequelae following medical management; rociletinib was permanently discontinued. This event was judged related to rociletinib by the investigator and the sponsor.

11.5.3 Ventricular tachycardia

A 55-year-old woman in study -008 with NSCLC metastatic to lymph nodes, liver and bone, had received treatment with erlotinib, carboplatin and pemetrexed, pemetrexed and erlotinib maintenance, and additional erlotinib monotherapy before starting rociletinib 625mg BID. Relevant past medical history included malignant pleural effusion and hypothyroidism. Concomitant medications included pantoprazole sodium, levothyroxine sodium, ondansetron, and promethazine with codeine. Baseline QTcF was 443ms. Rociletinib was reduced to 500mg BID after 21 days on study. On Day 85 of rociletinib therapy, an AE of Grade 2 QT prolongation was reported (QTcF 484 ms). 114 days after initiation of rociletinib, the patient had several episodes of syncope, nausea, vomiting, palpitations, and dizziness. On Day 115 of therapy, she attended the emergency room, and while there (no cardiac monitor) she had a syncopal event and required cardiopulmonary resuscitation. Subsequently a non sustained 15-beat run of ventricular tachycardia was observed. The event resolved without sequelae following medical management; rociletinib was permanently discontinued. This event was judged related to rociletinib by the investigator and by the sponsor.

11.6 SMQS ASSOCIATED WITH ADVERSE EVENTS OF SPECIAL INTEREST

Table 31: Preferred Terms in the SMQs Associated with Adverse Events of Special Interest

SMQ (Scope)	PTs	Code
Hyperglycaemia/new onset diabetes mellitus (narrow)	Blood 1,5-anhydroglucitol decreased	10065367
	Blood glucose increased	10005557
	Diabetes complicating pregnancy	10012596
	Diabetes mellitus	10012601
	Diabetes mellitus inadequate control	10012607
	Diabetes with hyperosmolarity	10012631
	Diabetic coma	10012650
	Diabetic hepatopathy	10071265
	Diabetic hyperglycaemic coma	10012668
	Diabetic hyperosmolar coma	10012669
	Diabetic ketoacidosis	10012671
	Diabetic ketoacidotic hyperglycaemic coma	10012672
	Fructosamine increased	10017395
	Gestational diabetes	10018209
	Glucose tolerance impaired	10018429
	Glucose tolerance impaired in pregnancy	10018430
	Glucose urine present	10018478
	Glycosuria	10018473
	Glycosuria during pregnancy	10018475

	Glycosylated haemoglobin increased	10018484
	Hyperglycaemia	10020635
	Hyperglycaemic hyperosmolar nonketotic syndrome	10063554
	Hyperglycaemic seizure	10071394
	Hyperglycaemic unconsciousness	10071286
	Impaired fasting glucose	10056997
	Insulin resistance	10022489
	Insulin resistance syndrome	10022490
	Insulin resistant diabetes	10022491
	Insulin-requiring type 2 diabetes mellitus	10053247
	Ketoacidosis	10023379
	Ketonuria	10023388
	Ketosis	10023391
	Latent autoimmune diabetes in adults	10066389
	Metabolic syndrome	10052066
	Neonatal diabetes mellitus	10028933
	Pancreatogenous diabetes	10033660
	Type 1 diabetes mellitus	10067584
	Type 2 diabetes mellitus	10067585
	Urine ketone body present	10057597
SMQ (Scope)	**PTs**	**Code**
Acute pancreatitis (narrow)	Cullen's sign	10059029
	Hereditary pancreatitis	10056976
	Ischaemic pancreatitis	10066127
	Oedematous pancreatitis	10052400
	Pancreatic abscess	10048984
	Pancreatic haemorrhage	10033625
	Pancreatic necrosis	10058096
	Pancreatic phlegmon	10056975
	Pancreatic pseudocyst	10033635
	Pancreatic pseudocyst drainage	10033636
	Pancreatitis	10033645
	Pancreatitis acute	10033647
	Pancreatitis haemorrhagic	10033650
	Pancreatitis necrotising	10033654
	Pancreatitis relapsing	10033657
	Pancreatorenal syndrome	10056277
	Amylase abnormal	10072327
	Amylase increased	10002016
Acute pancreatitis (broad)	Amylase abnormal	10072327
	Amylase increased	10002016

	Hyperamylasaemia	10062770
	Hyperlipasaemia	10067725
	Lipase abnormal	10054821
	Lipase increased	10024574
	Lipase urine increased	10024578
	Pancreatic enzyme abnormality	10033619
	Pancreatic enzymes abnormal	10061899
	Pancreatic enzymes increased	10061900
SMQ (Scope)	**PTs**	**Code**
Interstitial lung disease (narrow)	Acute interstitial pneumonitis	10066728
	Allergic granulomatous angiitis	10048594
	Alveolar proteinosis	10001881
	Alveolitis	10001889
	Alveolitis allergic	10001890
	Alveolitis fibrosing	10001892
	Alveolitis necrotising	10050343

	Bronchiolitis	10006448
	Diffuse alveolar damage	10060902
	Eosinophilia myalgia syndrome	10014952
	Eosinophilic pneumonia	10014962
	Eosinophilic pneumonia acute	10052832
	Eosinophilic pneumonia chronic	10052833
	Idiopathic pneumonia syndrome	10063725
	Idiopathic pulmonary fibrosis	10021240
	Interstitial lung disease	10022611
	Lung infiltration	10025102
	Necrotising bronchiolitis	10070831
	Obliterative bronchiolitis	10029888
	Pneumonitis	10035742
	Progressive massive fibrosis	10036805
	Pulmonary fibrosis	10037383
	Pulmonary necrosis	10058824
	Pulmonary radiation injury	10061473
	Pulmonary toxicity	10061924
	Pulmonary vasculitis	10037457
	Radiation alveolitis	10037754
	Radiation fibrosis - lung	10037758
	Radiation pneumonitis	10037765
	Transfusion-related acute lung injury	10052235
SMQ (Scope)	**PTs**	**Code**
Interstitial lung disease (broad)	Acute lung injury	10069351
	Acute respiratory distress syndrome	10001052
	Antisynthetase syndrome	10068801
	Complications of transplanted lung	10010187
	Goodpasture's syndrome	10018620
	Langerhans' cell histiocytosis	10069698
	Lung transplant rejection	10051604
	Lupus pneumonitis	10057481
	Lymphangioleiomyomatosis	10049459
	Organising pneumonia	10067472
	Pneumonitis chemical	10035745
	Polyarteritis nodosa	10036024
	Pulmonary alveolar haemorrhage	10037313
	Pulmonary eosinophilia	10037382

	Pulmonary granuloma	10037391
	Pulmonary haemosiderosis	10037396
	Pulmonary renal syndrome	10068513
	Pulmonary sarcoidosis	10037430
	Rheumatoid lung	10039081
	Sarcoidosis	10039486
	Systemic sclerosis pulmonary	10042954
	Toxic oil syndrome	10051222
	Wegener's granulomatosis	10047888
SMQ (Scope)	**PTs**	**Code**
Torsades de Pointes/QT prolongation (narrow)	Electrocardiogram QT interval abnormal	10063748
	Electrocardiogram QT prolonged	10014387
	Long QT syndrome	10024803
	Long QT syndrome congenital	10057926
	Torsade de pointes	10044066
	Ventricular tachycardia	10047302
Torsades de Pointes/QT prolongation (broad)	Cardiac arrest	10007515
	Cardiac death	10049993
	Cardiac fibrillation	10061592
	Cardio-respiratory arrest	10007617
	Electrocardiogram repolarisation abnormality	10052464
	Electrocardiogram U-wave abnormality	10055032
	Electrocardiogram U-wave biphasic	10055068
	Loss of consciousness	10024855
	Sudden cardiac death	10049418
	Sudden death	10042434
	Syncope	10042772
	Ventricular arrhythmia	10047281
	Ventricular fibrillation	10047290
	Ventricular flutter	10047294
	Ventricular tachyarrhythmia	10065341

Sub-SMQs (PTs) Associated with Cardiac Events (SMQ: Cardiac Arrhythmias)		
Sub-SMQ(s) (Scope)	**PTs**	**Code**
Arrhythmia related investigations, signs and symptoms (narrow)	Chronotropic incompetence	10068627
	Electrocardiogram repolarisation abnormality	10052464
	Electrocardiogram RR interval prolonged	10067652
	Electrocardiogram U-wave abnormality	10055032
	Electrocardiogram U-wave biphasic	10055068
	Gallop rhythm present	10017648
	Sudden cardiac death	10049418
Arrhythmia related investigations, signs and symptoms (broad)	Bradycardia	10006093
	Cardiac arrest	10007515
	Cardiac death	10049993
	Cardiac telemetry abnormal	10053450
	Cardio-respiratory arrest	10007617
	Electrocardiogram abnormal	10014363
	Electrocardiogram ambulatory abnormal	10014369
	Electrocardiogram change	10061116
	Heart rate abnormal	10019300
	Heart rate decreased	10019301
	Heart rate increased	10019303
	Loss of consciousness	10024855
	Palpitations	10033557
	Rebound tachycardia	10067207
	Sudden death	10042434
	Syncope	10042772
	Tachycardia	10043071
	Tachycardia paroxysmal	10043079

Sub-SMQ(s) (Scope)			PTs	Code
Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	Cardiac arrhythmia terms, nonspecific (narrow)		Arrhythmia	10003119
			Heart alternation	10058155
			Heart rate irregular	10019304
			Pacemaker generated arrhythmia	10053486
			Pacemaker syndrome	10051994
			Paroxysmal arrhythmia	10050106
			Pulseless electrical activity	10058151
			Reperfusion arrhythmia	10058156
			Withdrawal arrhythmia	10047997
	Bradyarrhythmias (incl conduction defects and disorders of sinus node function)	Bradyarrhythmia terms, nonspecific (narrow)	Bradyarrhythmia	10049765
			Ventricular asystole	10047284
		Conduction defects (narrow)	Accessory cardiac pathway	10067618
			Adams-Stokes syndrome	10001115
			Agonal rhythm	10054015
			Atrial conduction time prolongation	10064191
			Atrioventricular block	10003671
			Atrioventricular block complete	10003673
			Atrioventricular block first degree	10003674
			Atrioventricular block second degree	10003677
			Atrioventricular conduction time shortened	10068180
			Atrioventricular dissociation	10069571
			Bifascicular block	10057393
			Brugada syndrome	10059027
			Bundle branch block	10006578
			Bundle branch block bilateral	10006579
			Bundle branch block left	10006580
			Bundle branch block right	10006582

Sub-SMQ(s) (Scope)			PTs	Code
			Conduction disorder	10010276
			Electrocardiogram delta waves abnormal	10014372
			Electrocardiogram PQ interval prolonged	10053656
			Electrocardiogram PR prolongation	10053657
			Electrocardiogram PR shortened	10014374
			Electrocardiogram QRS complex prolonged	10014380
			Electrocardiogram QT prolonged	10014387
			Electrocardiogram repolarisation abnormality	10052464
			Lenegre's disease	10071710
			Long QT syndrome	10024803
			Sinoatrial block	10040736
			Trifascicular block	10044644
			Ventricular dyssynchrony	10071186
			Wolff-Parkinson-White syndrome	10048015
		Disorders of sinus node function (narrow)	Nodal arrhythmia	10029458
			Nodal rhythm	10029470
			Sick sinus syndrome	10040639
			Sinus arrest	10040738
			Sinus arrhythmia	10040739
			Sinus bradycardia	10040741
			Wandering pacemaker	10047818
	Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias)	Supraventricular tachyarrhythmias (narrow)	Arrhythmia supraventricular	10003130
			Atrial fibrillation	10003658
			Atrial flutter	10003662
			Atrial parasystole	10071666
			Atrial tachycardia	10003668

Sub-SMQ(s) (Scope)			PTs	Code
			Supraventricular extrasystoles	10042602
			Supraventricular tachyarrhythmia	10065342
		Supraventricular tachyarrhythmias (broad)	ECG P wave inverted	10057526
			Electrocardiogram P wave abnormal	10050384
			Retrograde p-waves	10071187
			Sinus tachycardia	10040752
			Supraventricular tachycardia	10042604
		Tachyarrhythmia terms, nonspecific (narrow)	Anomalous atrioventricular excitation	10002611
			Atrioventricular extrasystoles	10051644
			Cardiac flutter	10052840
			Extrasystoles	10015856
			Tachyarrhythmia	10049447
		Ventricular tachyarrhythmias (narrow)	Accelerated idioventricular rhythm	10049003
			Cardiac fibrillation	10061592
			Parasystole	10033929
			Rhythm idioventricular	10039111
			Torsade de pointes	10044066
			Ventricular arrhythmia	10047281
			Ventricular extrasystoles	10047289
			Ventricular fibrillation	10047290
			Ventricular flutter	10047294
			Ventricular parasystole	10058184
			Ventricular pre-excitation	10049761
			Ventricular tachyarrhythmia	10065341
		Ventricular tachyarrhythmias (broad)	Ventricular tachycardia	10047302