CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211288Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 2, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211288
Product Name and Strength:	Vizimpro (dacomitinib) tablets, 15mg, 30 mg, and 45 mg
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	July 6, 2018
OSE RCM #:	2018-249-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels for Vizimpro (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels for Vizimpro is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Little C. Label and Labeling Review for Vizimpro (NDA 211288). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 20. RCM No.: 2018-249.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 6, 2018

Container labels

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/s/

COLLEEN L LITTLE
08/02/2018

CHI-MING TU
08/02/2018

Clinical Inspection Summary

Date	July 31, 2018
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Felicia Diggs, M.S.N., Regulatory Project Manager Barbara Scepura, M.D., Clinical Reviewer Erin Larkins, M.D., Cross Discipline Team Leader Division of Oncology Products 2
NDA #	211288
Applicant	Pfizer, Inc.
Drug	Dacomitinib
NME (Yes/No)	Yes
Therapeutic Classification	Priority
Proposed Indication(s)	Treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) [redacted] (b) (4) mutations as detected by an FDA-approved test.
Consultation Request Date	March 27, 2017
Summary Goal Date	July 31, 2018
Action Goal Date	September 28, 2018
PDUFA Date	September 28, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study Protocol A7471050 (from now on called ARCHER 1050) was submitted to FDA in support of a proposed indication for NDA 211288. This was a randomized, open-label, Phase 3 efficacy and safety study of dacomitinib versus gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in subjects with EGFR activating mutations. The data for ARCHER 1050 submitted by the Sponsor to the Agency in support of NDA 211288 appear reliable based on available information from the inspections of three foreign clinical sites.

Three clinical sites, Dr. Seiji Niho, M.D. (Site 8107), Dr. Xiangdong Zhou, M.D. (Site 8616), and Dr. Ying Cheng, M.D. (Site 8624) were selected for audit.

There were no significant inspectional observations for the clinical investigators, Dr. Seiji Niho, M.D., Dr. Xiangdong Zhou, M.D., and Dr. Ying Cheng, M.D. The final compliance

classification for Dr. Xiangdong Zhou, M.D. and Dr. Ying Cheng, M.D. is No Action Indicated (NAI). The preliminary compliance classification for Dr. Seiji Niho is No Action Indicated (NAI).

A Clinical Inspections Summary Addendum will be provided if the final compliance classification of the inspection of the clinical investigator, Dr. Seiji Niho M.D. is significantly different following receipt and review of the Establishment Inspection Report (EIR).

II. BACKGROUND

Pfizer Inc., as sponsor of NDA 211288, seeks full marketing approval for the use of dacomitinib tablets for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test.

Dacomitinib is a pan-HER inhibitor, with clinical activity against mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21. Dacomitinib binds irreversibly to HER receptors, thereby providing prolonged inhibition of tumor growth.

ARCHER 1050 is an ongoing, randomized, open-label, Phase 3 efficacy and safety study comparing dacomitinib with gefitinib in patients with locally advanced or metastatic newly diagnosed, treatment-naïve NSCLC or with recurrent NSCLC. Patients with recurrent NSCLC could only have completed neoadjuvant/adjuvant therapy previously and have had a minimum 12-month disease-free interval between completion of prior systemic therapy and recurrence of NSCLC. All eligible patients were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The first patient visit was on May 9, 2013. The treatment period was preceded by a 28-day screening period. The study completed its enrollment on March 25, 2015 with 452 patients randomized (Intent-to-Treat [ITT] Population). Of these, 227 patients were randomized to the dacomitinib arm and 225 patients to the gefitinib arm. Randomization for this study was stratified by race (Japanese vs mainland Chinese vs other East Asian vs non-East Asian) and (EGFR)-activating mutation status (exon 19 deletion vs L858R mutation in exon 21).

Subjects in the dacomitinib arm received dacomitinib 45 mg orally (PO) once daily. Subjects in the comparator arm received gefitinib 250 mg PO once daily. The study treatment period was organized into 28-day cycles for operational purposes. Randomized patients were to receive continuous daily PO dosing of study treatment for up to 48 months from the date of first dosing or until 1 of the following criteria was met (whichever occurred first): disease progression; initiation of a new anti-cancer therapy; unacceptable toxicities; global deterioration of health-related symptoms; pregnancy; withdrawal of consent; loss to follow-up; death; investigator decision dictated by protocol noncompliance or termination by the Sponsor.

The primary endpoint was PFS per RECIST v1.1, as determined by blinded Independent Radiologic Central (IRC) review. Patients who had progressive disease (PD) per RECIST v1.1 and for whom the investigator believed it was in their best interest to continue on their respective study therapy were allowed to continue on their respective study therapy and were

to be followed for up to 48 months from the date of first dosing for serious adverse events (SAEs) related to study treatment. At the discretion of the investigator, patients who were randomized to either treatment arm (dacomitinib or gefitinib) and had not progressed at the conclusion of this study (up to 48 months from the date of first dosing) could continue on their respective study therapy, in accordance with the accepted local clinical practice standards.

ARCHER 1050 was conducted at 90 study sites worldwide including China, Hong Kong, Italy, Japan, Poland, Republic of Korea, and Spain. At the February 17, 2017 cut-off date, 55% of patients in the dacomitinib arm and 62% of patients in the gefitinib arm had discontinued the study. The primary reason for discontinuation from study was patient death (103 [45%] patients from the dacomitinib arm and 117 [52%] patients in the gefitinib arm).

GCP inspection was conducted at three clinical investigator (CI) sites. All the study data is from outside of the U.S. The CI sites for inspection were chosen because of high enrollment and high study drug efficacy rates.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	**Protocol # # of Subjects**	**Inspection Dates**	**Classification**
Seiji Niho, M.D. Site Number: 8107 National Cancer Center, Hospital East 6-5-1 Kashiwanoha Kashiwa-shi Chiba 277-8577 Japan	Study: ARCHER 1050 Enrolled: 13	June 25-28, 2018	*NAI
Xiangdong Zhou, M.D. Site Number: 8616 The First Affiliated Hospital of Third Military Medical University PLA No.30 Gaotanyan Main Street Shapingba District, Chongqing, 400038 China	Study: ARCHER 1050 Enrolled: 24	June 25-28, 2018	NAI
Ying Cheng, M.D. Site Number: 8624 Jilin Province Cancer Hospital No. 1018 Huguang Street Chaoyang District Changchun, Jilin 130012 China	Study: ARCHER 1050 Enrolled: 26	July 2-5, 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Seiji Niho, M.D. (Site 8107)

The site screened 13 subjects and all were enrolled into the study. Nine (9) subjects completed the study and 4 were in follow up. An inspection of all enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included review of 1572s, financial disclosures, staff training logs, Sponsor correspondences, subject eligibility, test article accountability, site monitoring logs, source documents, concomitant medications, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the inspected subjects were compared to the data listings and Case Report Forms (CRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. An item of General Discussion was discussed with the Primary Investigator (PI). Specifically, two subjects were enrolled into the study prior to a protocol which discouraged use of concomitant medication before they had time to wash out. The primary efficacy endpoint data, PFS, as determined by the Investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 8107 appear reliable based on available information.

2. Xiangdong Zhou, M.D. (Site 8616)

The site screened 33 subjects and 24 subjects were enrolled into the study. Twenty-two (22) subjects completed the study and 2 were in follow up. An audit of all enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included review of source documents, case report forms, regulatory binder containing sponsor/monitor/IRB correspondence, test article accountability, concomitant medications, eligibility criteria, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and Case Report Forms (CRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, PFS, as determined by the Investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 8616 appear reliable based on available information.

3. Ying Cheng, M.D. (Site 8624)

The site screened 51 subjects and 26 subjects were enrolled into the study. Twenty-five (25) subjects completed the study and one (1) subject was in follow up. An audit of all enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included review of source documents, case report forms, regulatory binder containing sponsor/monitor/IRB correspondence, test article accountability, concomitant medications, eligibility criteria, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and Case Report Forms (CRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, PFS, as determined by the Investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 8624 appear reliable based on available information.

{See appended electronic signature page}

Navid Homayouni, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Susan Thompson, M.D., Team Leader
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OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Navid Homayouni
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

NAVID R HOMAYOUNI
07/31/2018

SUSAN D THOMPSON
07/31/2018

KASSA AYALEW
07/31/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 20, 2018
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VIZIMPRO (dacomitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 211288
Applicant:	Pfizer Inc.

1 INTRODUCTION

On January 31, 2018, Pfizer Inc. submitted for the Agency's review an original New Drug Application (NDA) 211288 for VIZIMPRO (dacomitinib) tablets. The proposed indication for VIZIMPRO (dacomitinib) tablets is for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on March 23, 2018 and March 19, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VIZIMPRO (dacomitinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft VIZIMPRO (dacomitinib) PPI received on January 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2018.
- Draft VIZIMPRO (dacomitinib) Prescribing Information (PI) received on January 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
06/20/2018

NAZIA FATIMA
06/20/2018

SHARON R MILLS
06/20/2018

LASHAWN M GRIFFITHS
06/20/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 20, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211288
Product Name and Strength:	Vizimpro (dacomitinib) tablets, 15mg, 30 mg, and 45 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	January 31, 2018 and April 30, 2018
OSE RCM #:	2018-249
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this NDA, this review evaluates the proposed Vizimpro prescribing information (PI) and container labels to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B- N/A
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials found the proposed Vizimpro PI and container labels may be improved to promote safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

We conclude PI and container labels for Vizimpro may be improved to promote the safe use of the product as described in Section 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. Please see Appendix H for our PI recommendations in track changes.

4.2 RECOMMENDATIONS FOR PFIZER INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. Revise the product code in the NDC number to ensure that the middle 3 or 4 digits are nonsequential (-0197-, -0198-, -0199-). The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the product code is not and differentiating feature. If for some reason, the middle digits cannot be revised, then increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example, XXXX-**XXXX**-XX.
2. Ensure there is sufficient white space around the barcode while retaining the vertical orientation of the barcode. The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i).
3. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number.[a,b]
    a. Identify the format of the expiration date you intend to use. We recommend using a format such as MMMYYYY (e.g. JAN2019) or MMMDDYYYY (e.g. JAN312019) to minimize confusion and reduce the risk for deteriorated drug medication errors.[c]

[a] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

[b] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vizimpro received on April 30, 2018 from Pfizer Inc.

Table 2. Relevant Product Information for Vizimpro	
Initial Approval Date	N/A
Active Ingredient	dacomitinib
Indication	for the first-line treatment of patients with (b) (4) metastatic non small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test
Route of Administration	oral
Dosage Form	tablets
Strength	15 mg, 30 mg, and 45 mg
Dose and Frequency	45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. Dose reduction to 30 mg then 15 mg for adverse events.
How Supplied	30 count bottle
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Vizimpro labels and labeling submitted by Pfizer Inc.

- Container label received on January 31, 2018.
- Prescribing Information (Image not shown) received on April 30, 2018.

(b) (4)

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

COLLEEN L LITTLE
06/20/2018

CHI-MING TU
06/20/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	NDA 211288
Brand Name	
Generic Name	Dacomitinib (PF-00299804)
Sponsor	Pfizer Incorporated
Indication	Indicated for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by a FDA-approved test
Dosage Form	Tablet
Drug Class	Inhibitor of the HER (human epidermal growth factor receptor) family of tyrosine kinases.
Therapeutic Dosing Regimen	45 mg QD
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	45 mg QD
Submission Number and Date	SDN#001, 1/31/2018
Review Division	DOP2

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1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Study A7471047 was a multi-center, phase 2 open-label trial of a loading dose of dacomitinib in patients with advanced NSCLC. 38 subjects were tested and included in this analysis. A summary of the analysis of ΔQTcF, showing the largest upper bounds for dacomitinib by study cycle and day, is given in Table 1. No large mean increase (i.e. >20 ms) was observed with administration of dacomitinib in study A7471047. The exposures observed in this study with a loading dose of dacomitinib is expected to cover the proposed maximum therapeutic dosing scenario (45 mg qd). The findings in this study are further supported by preclinical studies (hERG patch clamp, dog purkinje fiber and dog CV study) and completed clinical studies in NSCLC patients.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for dacomitinib in ΔQTcF (FDA Analysis)

Cycle/ Day*	TIME	LS mean (ms)	SE	90% CI	
				Lower (ms)	Upper (ms)
0/4	2	5.2453	2.3922	1.2065	9.2841
1/1	0	3.8145	1.9507	0.5186	7.1103
1/4	0	2.9426	1.6254	0.1942	5.6909

* In Cycle 0 (lead-in cycle) patients received 6 doses of 45 mg BID and in subsequent cycles patients received 6 doses of 60 mg BID.

2 PROPOSED LABEL

The Sponsor included the following language in the proposed label:

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of dacomitinib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 32 patients with advanced NSCLC. (b) (4) 5 mg once daily.

Reviewer's Comments: *The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.*

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of dacomitinib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 32 patients with advanced NSCLC. Dacomitinib had no large effect on QTc (i.e. >20 ms) at (b) (4) maximum concentrations (b) (4) 45 mg once daily.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Dacomitinib (PF-00299804) is an irreversible, small molecule inhibitor of the Human Epidermal Growth Factor Receptor (HER, erbB) family of Receptor tyrosine kinases (RTK), including epidermal growth factor receptor (EGFR) (HER1), HER2 (erbB2),

HER4 (erbB4), and their oncogenic variants (eg, EGFR with exon 19 deletions or exon 21 L858R mutation. It is being developed for proposed indication: for the treatment of patients with (b) (4) metastatic Non-Small Cell Lung Cancer (NSCLC).

3.2 MARKET APPROVAL STATUS

Dacomitinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Dacomitinib had no effect on the central nervous system or on respiratory function after oral administration. The IC50 of dacomitinib for the human ether-à-go-go related gene (hERG) potassium (IKr) channels, in vitro, was 1.58 μM (~283-fold the free Cmax of 2.6 ng/mL at 45 mg QD in cancer patients). Dacomitinib had no effect on cardiac action potentials in dog Purkinje fibers in vitro up to the maximum tested concentration of 10 μ M (>1000-fold the expected clinical exposure). There were no notable dacomitinib related cardiovascular (CV) effects observed at ≤30 mg/kg at any time point during the conduct of a telemetered, conscious dog CV safety study.

***Reviewer's Comments**: In vitro assessments of the effects of dacomitinib on the hERG potassium channel suggests a low potential for direct blockade of the hERG potassium channel (hERG IC_{50} was ~283 fold free C_{max}). This finding is further supported by dog Purkinje fiber experiments and a dog CV safety study.*

3.4 CLINICAL EXPERIENCE

There are 26 clinical studies (24 completed, 2 ongoing) as of the data cutoff date of 29 July 2016. Patient exposure to dacomitinib includes clinical trials (1975 patients single agent, 173 patients combination therapy), clinical pharmacology studies (143 patients/healthy volunteers), Investigator-initiated studies (382), compassionate use (28 patients).

The majority of the clinical experience with dacomitinib has utilized the 45 mg QD dosing regimen. A pool of 1473 patients with NSCLC irrespective of line of therapy or EGFR mutation status, treated with single-agent dacomitinib at 45 mg daily has been analyzed (Pool B).

In the pool of 1473 patients with NSCLC treated with single-agent dacomitinib at 45 mg daily (Pool B), the following E14 PT terms were reported: Syncope (9 patients, 0.6%, all Grade 3 severity), Seizure (6 patients, 0.4%; 1 Grade 1, 4 Grade 2, 1 Grade 3, no Grade 4-5), Sudden death (1 patient, <0.1%, Grade 5), Ventricular tachycardia (1 patient, <0.1%, Grade 2). There were no reports of Torsade de pointes, Ventricular fibrillation or Ventricular flutter.

Of the 1473 patients treated in Pool B, 1 (0.2%) patient had postbaseline QTcF of ≥ 500 msec, and in the pivotal Study 1050, there were no reports of QTcF ≥ 500 msec.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of dacomitinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 72775 and no outstanding issues were identified. The sponsor submitted the study report A7471047 for dacomitinib, including electronic datasets and waveforms to the ECG warehouse.

4.2 PHASE 2 STUDY

4.2.1 Title

Phase 2 Open Label Trial of Oral Intermittent Dacomitinib in Patients with Advanced NSCLC

4.2.2 Protocol Number

A7471047

4.2.3 Study Dates

Study Initiation Date: First Patient First Visit (FPFV): 31 July 2013

Primary Completion Date: 23 September 2015

Study Completion Date: Last Patient Last Visit (LPLV): 23 September 2015

4.2.4 QT/QTc Objective

- To determine the potential effect of maximum therapeutic plasma concentration of dacomitinib and its major circulating metabolite, PF-05199265 on the QT interval (Cohorts A and B).

4.2.5 Study Description

4.2.5.1 Design

This was a multi-center, single arm, Phase 2 open-label trial of dacomitinib to assess the Objective Response Rate (ORR) in 38 patients with advanced NSCLC whose tumor has a documented T790M mutation in exon 20 of EGFR.

4.2.5.2 Controls

The Sponsor did not use any controls.

4.2.5.3 Blinding

This study was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

This study has a single arm in which patients received intermittent dacomitinib as 6 doses on a b.i.d. schedule at the beginning of each cycle of either 45 mg (lead-in cycle [cycle 0]) or 60 mg (subsequent cycles)

4.2.6.2 Sponsor's Justification for Doses

The currently recommended dose and schedule for dacomitinib is 45 mg QD. The Phase I trial A7471001, explored an alternative loading dose (LD) schedule of 45 mg BID for 3 days in Cycle 1 only followed by 45 mg QD. Exposure (Cmax and AUCtau) to dacomitinib on Cycle 1, Day 4 was above that on Cycle 2, Day 1 at steady state, indicating that the LD regimen exceeded steady state concentrations for a 45 mg QD regimen. Steady state concentrations were also achieved earlier with a BID loading dose regimen than using a 45 mg QD schedule. Safety profiles of the LD regimen were similar to those of the continuous daily dosing regimen.

The PK samples and time-matched ECGs that will be generated in this trial after the sixth 45 mg dose during the Lead-In Cycle, will allow for an assessment of dacomitinib exposure-response on QT intervals at the maximum dacomitinib plasma concentrations that are expected to be achieved with the current recommended dose and schedule. Additionally, the shorter time from the ECG baseline assessments to the serial on treatment ECGs (3 days) with this proposed q12h dosing regimen will minimize the potential confounding effects of variability due to complications or rapid progression of NSCLC, comorbid illness, and dose adherence with a QD dosing schedule (requiring 14 days between baseline and at steady state exposure on treatment).

Reviewer's Comment*: Acceptable. The loading dose of 45 mg BID for 3 days is reasonable to achieve exposures similar to those observed at steady state for the intended therapeutic dose (45 mg QD). Of note, the study does not meet the requirement as a substitute for a TQT study to exclude small mean effects (<10 ms) as described in ICH E14, however, as the proposed indication is an oncology indication this is acceptable and the doses are adequate to exclude large mean increases at the maximum therapeutic dosing (45 mg qd).*

4.2.6.3 Instructions with Regard to Meals

No instructions with regard to meals were specified in the study protocol.

Reviewer's Comment: *Acceptable. A food effect study showed that mean Cmax was increased by 24% and AUCinf was increased by 14% when dacomitinib was administered with a high-fat, high calorie meal. Such PK changes were not determined to be clinically meaningful. Therefore, dacomitinib can be given with or without food.*

4.2.6.4 ECG and PK Assessments

On the morning of Day 1 of the Lead-In Cycle (Cycle 0), 12-lead ECGs were performed in triplicate (approximately 2 minutes apart) at time 0 and at 2, 4, 6, 8, and 10 hrs thereafter. On Day 4 of Cycle 0, 12-lead ECGs were performed in triplicate (approximately 2 minutes apart) at pre-dose, and at 2, 4, 6, 8, and 10 hrs post 6th 45 mg dacomitinib dose given q12h (time-matched to Day 1 of Cycle 0). On the mornings of Days 1 and 4 of Cycle 1, where dose was escalated to 60 mg q12h and any cycle where dose was escalated beyond 60 mg q12h, a 12-lead ECG was required to be performed in triplicate pre-dose (dosing started in the evening of Day 1). On Day 1 of any other Cycle (no dose escalation), a pre-dose 12-lead ECGs was to be performed in triplicate (approximately 2 minutes apart).

Whole blood for PK analysis was collected right after completion of ECGs and blood pressure and pulse rate. Assessments: On Day 4 of Cycle 0, whole blood samples were collected at pre-dose (0), and 2, 4, 6, 8, and 10 hours post dose. On Days 1 and 4 of Cycle 1, and any other cycle where dose is being escalated, a pre-dose PK sample was drawn.

Plasma concentrations of dacomitinib and PF 05199265 were analyzed using a high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) validated analytical method in compliance with the Pfizer's standard operating procedures.

Reviewer's Comment*: Acceptable. The proposed PK and ECG sampling schedule is acceptable to capture the* T_{max} *of dacomitinib and its metabolite (PF 05199265).*

4.2.6.5 Baseline

Time-matched baseline was used in this study.

4.2.7 ECG Collection

All ECGs were performed before blood pressure and pulse rate assessments and any type of blood draws. 12-lead ECGs were performed in triplicate (approximately 2 minutes apart) at time 0 and at 2, 4, 6, 8, and 10 h thereafter.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 52 patients were screened for entry into the study of which 41 patients were enrolled (16 patients in Cohort A and 25 patients in Cohort B), and 38 patients treated (16 patients in Cohort A and 22 patients in Cohort B). Three patients were enrolled in Cohort B but not treated: 2 patients withdrew consent before start of treatment, and the third patient experienced an SAE prior to initiation of study treatment.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Changes in time-matched QTc (QTcB, QTcF, and/or QTcS) from baseline to Day 4 of Cycle 0 and Day 4 of Cycle 1 were used to characterize the potential effect of dacomitinib on the QT interval.

QTcF was analyzed using analysis of variance (ANOVA) and results are summarized in

Table 2. The change in least square (LS) mean of QTcF post-dose on Cycle 0/Day 4 from time-matched baseline pre-treatment on Cycle 0/Day 1 did not appear to increase on dacomitinib treatment. The largest LS mean difference for the change from baseline was 4.4 msec reported at 2 hours post-dose on Cycle 0/Day 4 time points. All upper limits of the 95% CI for the LS mean change from baseline in QTcF at all Cycle 0/ Day 4 time points were <10 msec.

As all the upper limits were below the pre-defined non-inferiority margin of 20 msec, the key secondary objective was met. Therefore, it was considered that the post-baseline change of QTcF interval on dacomitinib treatment was non-inferior to the baseline and the effect of dacomitinib on QTcF was acceptable.

Table 2: Statistical Analysis of ECG Data: QTc Change from Baseline to Cycle 0/Day 4 and Cycle 1, QTc Evaluable Population

				Change from Baseline	
		Planned Time Post-dose		LS Mean (SE)	95% CI of LS Mean
Parameter	Visit	(Hours)	N		
Cohort A + Cohort B					
QTcF interval (msec)	Cycle 0/Day 4	0	32	1.7 (2.05)	-1.7, 5.1
		2	32	4.4 (2.05)	1.0, 7.8
		4	32	0.4 (2.05)	-3.0, 3.8
		6	31	-0.4 (2.08)	-3.9, 3.0
		8	31	0.1 (2.08)	-3.3, 3.5
		10	31	0.6 (2.08)	-2.9, 4.0
	Cycle 1/Day 1	0	32	4.1 (2.05)	0.7, 7.5
	Cycle 1/Day 4	0	32	3.4 (2.05)	0.0, 6.8
QTcB interval (msec)	Cycle 0/Day 4	0	32	-0.8 (2.07)	-4.3, 2.6
		2	32	1.1 (2.07)	-2.3, 4.5
		4	32	-0.2 (2.07)	-3.6, 3.2
		6	31	-3.1 (2.09)	-6.5, 0.4
		8	31	-1.7 (2.09)	-5.1, 1.8
		10	31	-2.1 (2.09)	-5.5, 1.4
	Cycle 1/Day 1	0	32	1.8 (2.07)	-1.6, 5.3
	Cycle 1/Day 4	0	32	2.6 (2.07)	-0.8, 6.0
QTcS interval (msec)	Cycle 0/Day 4	0	32	-1.3 (2.14)	-4.8, 2.3
		2	32	0.4 (2.14)	-3.1, 4.0
		4	32	-0.2 (2.14)	-3.8, 3.3
		6	31	-3.5 (2.17)	-7.1, 0.1
		8	31	-2.1 (2.17)	-5.7, 1.5
		10	31	-2.5 (2.17)	-6.1, 1.1
	Cycle 1/Day 1	0	32	1.5 (2.14)	-2.0, 5.1
	Cycle 1/Day 4	0	32	2.4 (2.14)	-1.1, 6.0

Reviewer's Comment: *The reviewer's analysis agrees with the sponsor's analysis, that there are no large QT effects observed in the study. FDA independent analysis is presented in section 0.*

4.2.8.2.2 Assay Sensitivity

Not applicable.

4.2.8.2.3 Categorical Analysis

Sponsor's outlier analyses are presented in Table 3.

Table 3: Categorization of ECG Outliers by Cohort and Overall

Parameter (Units)	Criteria	Cohort A (N=16) n (%)	Cohort B (N=22) n (%)	Overall (N=38) n (%)
QTcF (msec)	Maximum Absolute Value > 450	2 (12.5)	2 (9.1)	4 (10.5)
	Maximum Absolute Value > 480	0	1 (4.5)	1 (2.6)
	Maximum Absolute Value > 500	0	0	0
	Maximum Increase from Baseline > 30	4 (25.0)	2 (9.1)	6 (15.8)
	Maximum Increase from Baseline > 60	0	0	0
QTcB (msec)	Maximum Absolute Value > 450	2 (12.5)	6 (27.3)	8 (21.1)
	Maximum Absolute Value > 480	0	1 (4.5)	1 (2.6)
	Maximum Absolute Value > 500	0	0	0
	Maximum Increase from Baseline > 30	2 (12.5)	2 (9.1)	4 (10.5)
	Maximum Increase from Baseline > 60	0	0	0
QTcS (msec)	Maximum Absolute Value > 450	2 (12.5)	8 (36.4)	10 (26.3)
	Maximum Absolute Value > 480	0	1 (4.5)	1 (2.6)
	Maximum Absolute Value > 500	0	0	0
	Maximum Increase from Baseline > 30	2 (12.5)	4 (18.2)	6 (15.8)
	Maximum Increase from Baseline > 60	0	0	0
QT (msec)	Maximum Absolute Value > 450	2 (12.5)	1 (4.5)	3 (7.9)
	Maximum Absolute Value > 480	0	1 (4.5)	1 (2.6)
	Maximum Absolute Value > 500	0	1 (4.5)	1 (2.6)
	Maximum Increase from Baseline > 30	7 (43.8)	10 (45.5)	17 (44.7)
	Maximum Increase from Baseline > 60	2 (12.5)	2 (9.1)	4 (10.5)
QRS (msec)	Maximum Absolute Value > 110	2 (12.5)	2 (9.1)	4 (10.5)
PR (msec)	Maximum Absolute Value > 200	4 (25.0)	3 (13.6)	7 (18.4)
	Maximum Absolute Value > 220	2 (12.5)	1 (4.5)	3 (7.9)
HR (msec)	Maximum Absolute Value < 50	0	0	0
	Maximum Absolute Value < 40	0	0	0
	Maximum Absolute Value < 30	0	0	0
	Maximum Absolute Value > 90	8 (50.0)	6 (27.3)	14 (36.8)

Baseline is defined as the ECGs recorded on Day 1 of Cycle 0. The triplicate data is averaged and the averaged data was used in the summary. Maximum absolute value includes all baseline and post baseline measurements.
Unplanned readings have been included in the presentation.

Source Data: Listing 16.2.8.3.1
Source: /pub/studies/pfizer/9002_075/CSR/tables/t_ecg_cat_out_at.sas Table Generation: 12MAR2016 (11:20) Data Extraction: 21JAN2016

Reviewer's Comment*: The reviewer's conclusion matches with the sponsor's conclusion. FDA independent analysis is presented in section 0.*

4.2.8.3 Safety Analysis

Most deaths and SAEs that occurred in this study were associated with progression of disease or events associated with concurrent diseases. Two deaths were associated with sepsis, and 2 deaths had an unknown cause (both post 28 days after last dose). Five treatment- related SAEs were reported in 3 patients: 1 with nausea and dehydration, 1 with diarrhea and dehydration, and 1 with diarrhea only. Most treated-related SAEs were expected as related to the mechanism of action of dacomitinib and there were no unexpected SAEs. Other significant AEs, including events of special interest, did not reveal any unexpected findings.

Reviewer's comment: *There were no reports of TdP, sudden death, ventricular tachycardia, ventricular arrhythmia or syncope. One patient (Patient* (b) (6) *experienced a non-serious AE of seizure (Grade 2).*

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 4. C_{max} and C_{min} values of dacomitinib and PF-05199265 in the study A7471047 were comparable to those previously observed at steady state following 45 mg QD dosing (the intended clinical dose) in study A7471042. Dacomitinib and PF-05199265 PK profiles on Cycle 0, Day 4 are presented in Figure 1 and Figure 2.

Table 4: Summary of Descriptive Statistics for Pharmacokinetic Parameters of Plasma Dacomitinib and PF-05199265

	N (dacomitinib)| N (PF-05199265)	Dacomitinib	PF-05199265
		Mean (CV%) [Median]	
Cycle 0, Day 4[a]			
Pre-dose (0 hr) (ng/mL)	36|36	76.4 (43) [68.4]	7.1 (161) [4.6]
AUC_{0-10} (ng.hr/mL)	33|33	793.8 (40) [728.0]	75.0 (148) [50.8]
C_{max} (ng/mL)	37|37	96.8 (39) [90.7]	8.5 (150) [5.9]
C_{min} (ng/mL)	37|37	71.3 (39) [65.6]	6.8 (157) [4.5]
T_{max}[b] (hr)	37|37	6.1 (1.3-10.9)	5.6 (0-11.0)
Cycle 1, Day 1[c]			
Pre-dose	35|35	32.1 (65) [26.9]	3.8 (158) [2.8]
Cycle 1, Day 4[d]			
Pre-dose	33|33	108.1 (39) [100]	9.0 (161) [7.43]

Note: N (dacomitinib)|N (PF-05199265)=The total number of patients contributing to the summary statistics for dacomitinib|The total number of patients contributing to the summary statistics for PF-05199265. Abbreviations: AUC_{0-10}=area under the concentration-time curve from 0 time to 10 hours; C_{max}=maximum observed concentration; C_{min}=lower concentration reported on Day 4 of Cycle 0; CV%=coefficient of variation; q12h=once every 12 hours; T_{max}=time for C_{max}

a. Following 6 q12h doses of 45 mg dacomitinib.
b. T_{max}: Median, minimum and maximum.
c. Following 3 day washout after 6 q12h doses of 45 mg dacomitinib.
d. Following 5 q12h doses of 60 mg dacomitinib.

Figure 1: Individual and Mean Dacomitinib Plasma Concentration-Time Plot on Cycle 0, Day 4 (Semi-logarithmic Scale)

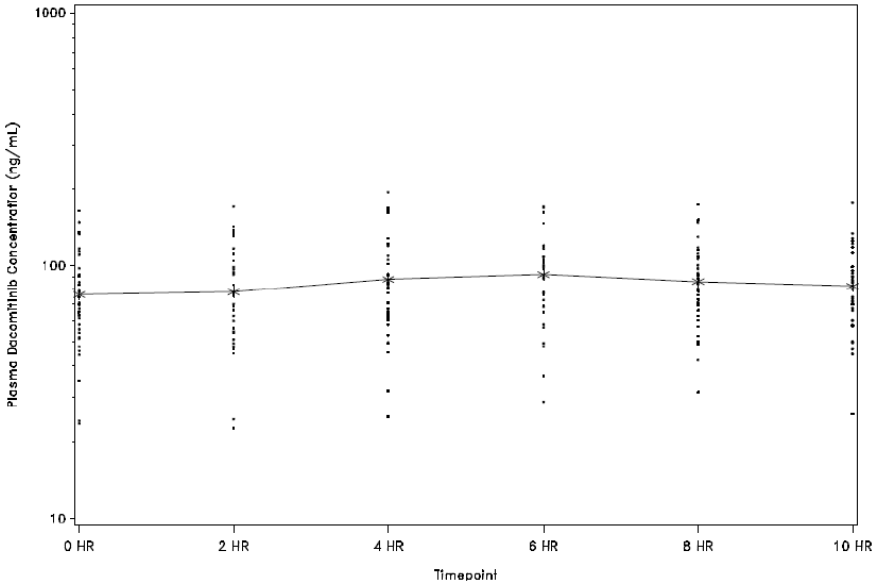
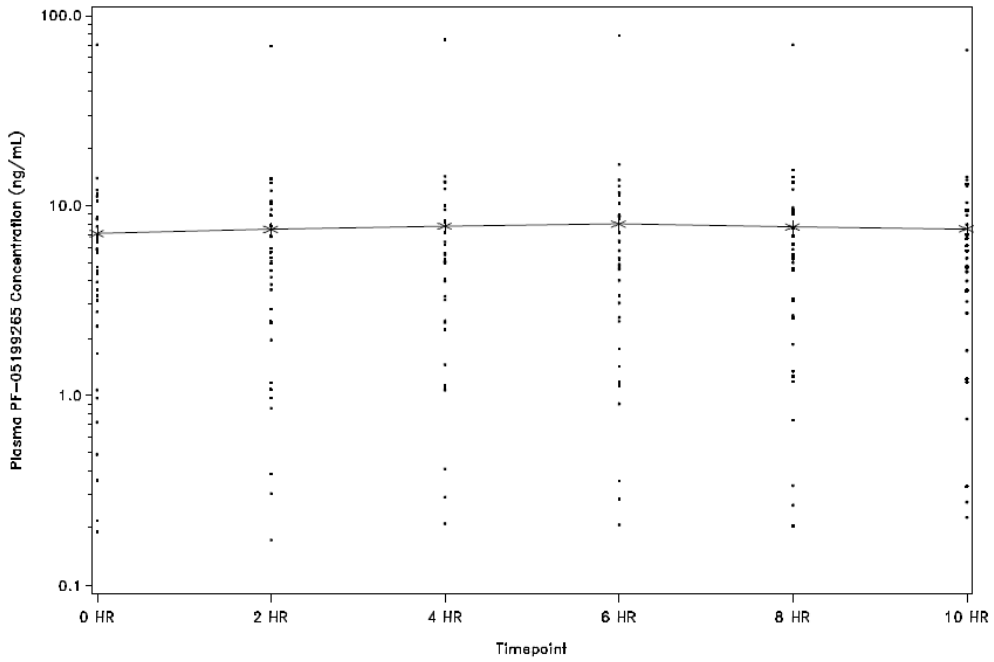


Figure 2: Individual and Mean PF-05199265 Plasma Concentration-Time Plot on Cycle 0, Day 4 (Semi-logarithmic Scale)



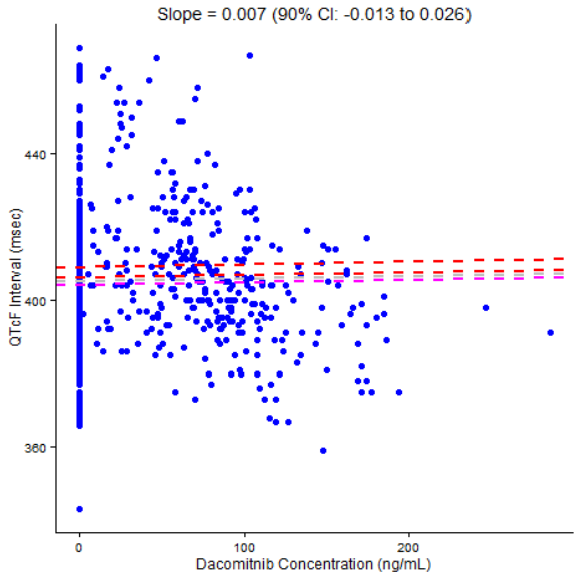
4.2.8.4.2 Exposure-Response Analysis

A linear mixed effects model was used to model QTc-concentration relationship. The 90% CI for the slope of relationships between QTcB, QTcS or QTcF and dacomitinib included the null value indicating a lack of a significant relationship between change in

QTcB, QTcF or QTcS and plasma concentration of dacomitinib. The relationship between QTcF and dacomitinib concentration, the typical population slope estimate was 0.007 (90% CI: -0.013, 0.026).

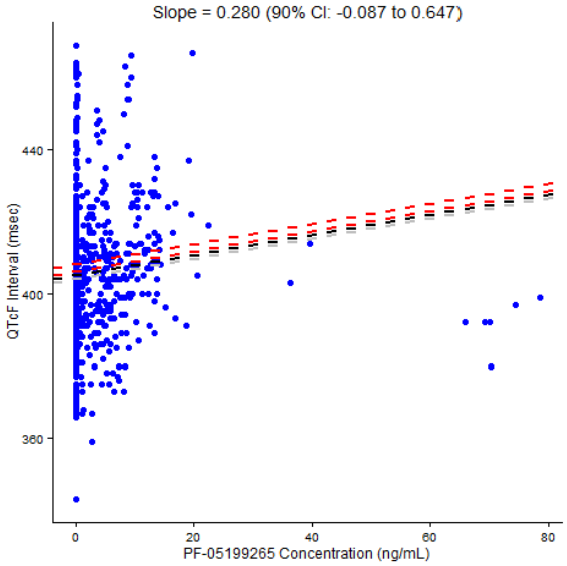
The 90% CI for the slope of relationships between QTcB, QTcS or QTcF and PF-05199265 included the null value indicating a lack of a significant relationship between change in QTcB, QTcF or QTcS and plasma concentration of PF-05199265. For the relationship between QTcF and PF-05199265 concentration, the typical population slope estimate was 0.280 (90% CI: -0.087, 0.647).

Figure 3: QTcF Versus Dacomitinib Plasma Concentration With Predicted Slope



ePharmacology artifact ID RA12766085.
Dashed lines represent best fit lines from the linear mixed effects model. Slope and 90% CI from the NONMEM estimates are also presented.
CI=confidence interval; msec=millisecond; ng/ml=nanogram per milliliter; QTcF=QT interval corrected using Fridericia's formula; RR=heart rate interval.

Figure 4: QTcF Versus PF-05199265 Plasma Concentration With Predicted Slope



ePharmacology artifact ID RA12766409.
Dashed lines represent best fit lines from the linear mixed effects model. Slope and 90% CI from the NONMEM estimates are also presented.
CI=confidence interval; msec=millisecond; ng/ml=nanogram per milliliter; QTcF=QT interval corrected using Fridericia's formula; RR=heart rate interval.

Reviewer's Analysis: *Our independent analyses results in Section 4.3 are consistent with those provided by the sponsor.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

Since no large changes in heart rate were observed, no assessment of the QT/RR correction methodology is necessary (section 0), QTcF is used in this reviewer's analysis.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Dacomitinib

The statistical reviewer used a linear mixed model to analyze the ΔQTcF effect. The model includes cohort, time as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 5: Analysis Results of ΔQTcF for Dacomitinib

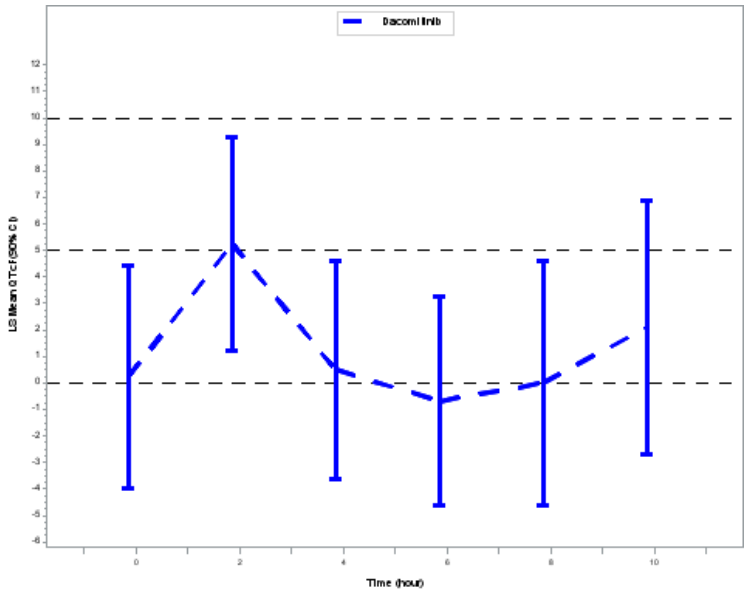
Cycle	Cycle Day	TIME	LS mean (ms)	SE	90% CI

					Lower (ms)	Upper (ms)
0	4	0	0.2385	2.4966	-3.9766	4.4536
0	4	2	5.2453	2.3922	1.2065	9.2841
0	4	4	0.4979	2.4302	-3.6050	4.6009
0	4	6	-0.6828	2.3421	-4.6369	3.2713
0	4	8	0.000182	2.7249	-4.6002	4.6006
0	4	10	2.1031	2.8323	-2.6788	6.8849
1	1	0	3.8145	1.9507	0.5186	7.1103
1	4	0	2.9426	1.6254	0.1942	5.6909

5.2.1.2 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for Dacomitinib.

Figure 5: Mean and 90% CI ΔQTcF for Dacomitinib (Cycle 0/Day 4)



5.2.1.3 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. One subject's QTcF was above 480 ms in cohort B.

Table 6: Categorical Analysis for QTcF

	Total (N)		Value<=450 ms		450 ms<Value<=480 ms		Value>=480 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Cohort A	16	341	14 (87.5%)	334 (97.9%)	2 (12.5%)	7 (2.1%)	0 (0.0%)	0 (0.0%)
Cohort B	22	463	20 (90.9%)	426 (92.0%)	1 (4.5%)	36 (7.8%)	1 (4.5%)	1 (0.2%)
ALL	38	804	34 (89.5%)	760 (94.5%)	3 (7.9%)	43 (5.4%)	1 (2.6%)	1 (0.1%)

Table 7 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 7: Categorical Analysis of ΔQTcF

	Total (N)		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cohort A	16	245	12 (75.0%)	239 (97.6%)	4 (25.0%)	6 (2.4%)
Cohort B	22	331	20 (90.9%)	326 (98.5%)	2 (9.1%)	5 (1.5%)
ALL	38	576	32 (84.2%)	565 (98.1%)	6 (15.8%)	11 (1.9%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper limits of 90% CI for the HR mean differences between Cycle 0 Day 4 and baseline was 1.3 bpm at 4 hours post dose.

Table 8: Analysis Results of ΔHR for Dacomitinib

Cycle	Cycle Day	TIME	LS mean (bpm)	SE	90% CI	
					Lower	Upper
0	4	0	-3.3744	1.2763	-5.5291	-1.2197
0	4	2	-4.3650	1.1335	-6.2787	-2.4514
0	4	4	-0.7259	1.1800	-2.7180	1.2663
0	4	6	-3.5686	1.1354	-5.4854	-1.6518
0	4	8	-2.3415	1.2666	-4.4799	-0.2031
0	4	10	-3.1497	1.1494	-5.0902	-1.2092
1	1	0	-2.9959	1.5817	-5.6682	-0.3236
1	4	0	-1.2771	1.6262	-4.0268	1.4727

The outlier analysis results for HR are presented in Table 9. There were 4 and 2 subjects who experienced HR interval greater than 100 bpm in cohort A and cohort B, respectively.

Table 9: Categorical Analysis of HR

	Total (N)		Value<=100 bpm		Value>100 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Cohort A	16	249	12 (75.0%)	239 (96.0%)	4 (25.0%)	10 (4.0%)
Cohort B	22	331	20 (90.9%)	322 (97.3%)	2 (9.1%)	9 (2.7%)
ALL	38	580	32 (84.2%)	561 (96.7%)	6 (0.16%)	19 (3.3%)

5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 10. There was a total of 7 subjects who experienced PR interval greater than 200 ms in two cohorts. Among those 7 subjects, 3 subjects experienced PR interval greater than 220 ms.

Table 10: Categorical Analysis for PR

	Total (N)		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Cohort A	16	247	12 (75.0%)	225 (91.1%)	2 (12.5%)	13 (5.3%)	2 (12.5%)	9 (3.6%)
Cohort B	22	331	19 (86.4%)	290 (87.6%)	2 (9.1%)	11 (3.3%)	1 (4.5%)	30 (9.1%)
ALL	38	578	31 (81.6%)	515(89.1%)	4 (10.5%)	24 (4.2%)	3(7.9%)	39(6.7%)

5.2.4 QRS Analysis

The outlier analysis results for QRS are presented in Table 11. There were 4 subjects who experienced QRS interval greater than 110 ms in both cohorts.

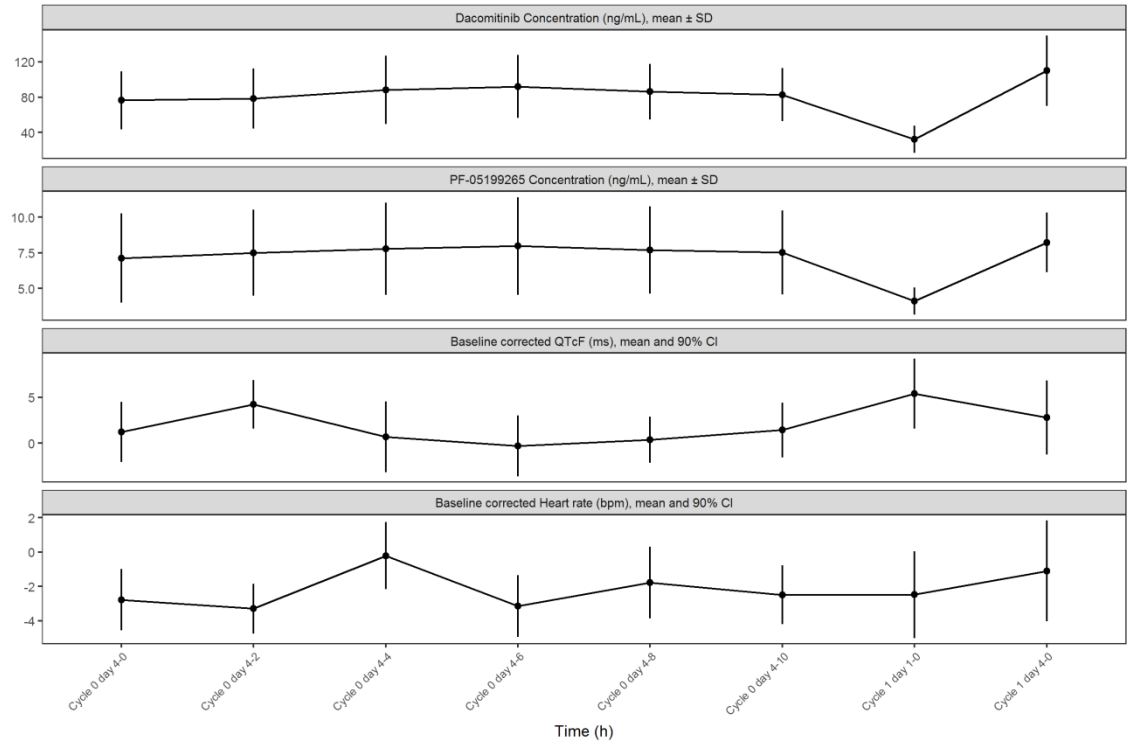
Table 11: Categorical Analysis for QRS

	Total (N)		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Cohort A	16	249	13 (81.3%)	231 (92.8%)	1 (6.3%)	13 (5.2%)	2 (12.5%)	5 (2.0%)
Cohort B	22	331	19 (86.4%)	295 (89.1%)	1 (4.5%)	4 (1.2%)	2 (9.1%)	32 (9.7%)
ALL	38	580	32 (84.2%)	526 (90.7%)	2 (5.3%)	17 (2.9%)	4 (10.5%)	37 (6.4%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Figure 6 shows the comparison of time profiles for drug and metabolite concentration, ΔQTcF and ΔHR on Cycle 0 Day 4 to evaluate presence of any time delay between concentration and QTc interval and to evaluate any heart rate effects. There does not seem to be any significant delayed effect on QTcF changes or any heart rate effects. Of note, the exposure range observed in this study is narrow, which makes the application of concentration-QTc analysis challenging.

Figure 6: Dacomitinib concentration, PF-05199265, ΔQTcF, and heart rate plotted on the same time axis (on Cycle 0 Day 4 [45 mg QD], Cycle 1 Day 1, Cycle 1 Day 4 [60 mg QD]). Error bars illustrate mean± SD for concentration and 90% CI for ΔHR and ΔQTcF



A Linear mixed effect model was used to describe C-QTc relationship for dacomitinib. The dependent variable is defined as ΔQTcF. The fixed effect parameters are intercept, slope. Subject was included as a random effect on both intercept and slope terms.

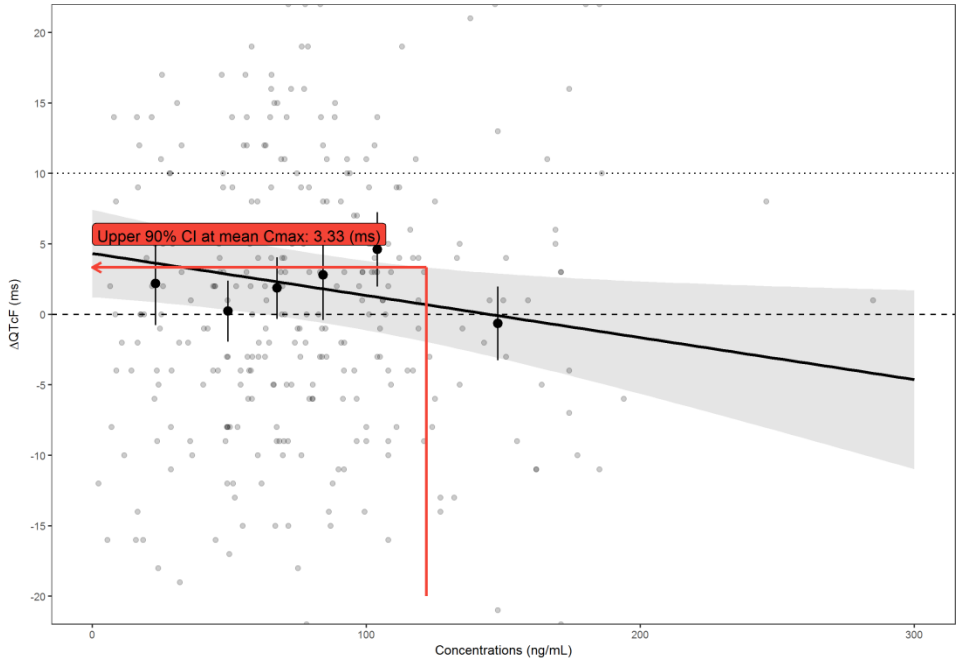
$$\Delta QTc_{ik} = (\mu + \eta_{\mu,i}) + (\theta_1 + \eta_{C,i})C_{ik} + \varepsilon_{ik}$$

The final fixed effect parameters for the linear mixed effect models are listed in Table 12. Based on the output of the model, dacomitinib concentration-ΔQTcF relationship was not statistically significant (p=0.06), with a slope estimate of -0.03 (95% CI: [-0.06; -0.00]) ms/(ng/mL). Observed and model estimated ΔQTcF versus the observed dacomitinib concentrations are visualized in
Figure 7. Due to the relatively narrow dacomitinib exposure range in this study, no conclusion should be made solely based on the Concentration-QT analysis results.

Table 12: Concentration-ΔQTcF Relationship Fixed Effects Parameter Estimates and Their Associated Precision

Fixed effect Parameter	Estimate	Lower 95% CI	Upper 95% CI	Relative standard error (%)	p-value
(Intercept)	4.33	0.76	7.89	41.38	0.02
Concentration	-0.03	-0.06	0.00	45.26	0.06

Figure 7: Observed and Estimated ΔQTcF vs. Dacomitinib concentration. The points and bars represent ΔQTcF mean and 90% CI at the median concentration in a bin. Black line represents predictions from the prespecified Concentration-ΔQTcF model. The shaded area represents the 90% CI of the prediction.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, significant ventricular arrhythmias or sudden cardiac death) did not occur in this study. One patient (Patien [redacted] (b) (6)) experienced a non-serious AE of seizure (Grade 2). This subject did not experience QTcF prolongation during the study (post-treatment QTcF values ranged from 399-428 ms).

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically meaningful increases in the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Maximum proposed clinical dosing regimen: 45 mg QD Single Dose PK after administration of an oral 45 mg dose in patients: • Geometric Mean C_{max} (Geometric %CV): 17.6 (70) to 23.2 (51) ng/mL • Geometric Mean AUC_{inf} (Geometric %CV): 1348 (45) to 1810 (35) ng·h/mL Steady-State PK after administration of 45 mg QD in patients: • Geometric Mean C_{max} (Geometric %CV): 74.2 (68) to 105 (42) ng/mL • Geometric Mean AUC_{tau} (Geometric %CV): 1505 (67) to 2166 (41) ng·h/mL	
Maximum tolerated dose	45 mg QD	
Principal adverse events	• In Study 1050, the most commonly reported (≥40%) all-causality AEs included Diarrhoea (87.2%), Paronychia (61.7%), Dermatitis acneiform (48.9%), Stomatitis (43.6%). • The maximum tolerated dose of dacomitinib was established as 45 mg daily in Study 1001, a Phase 1 dose escalating study in 121 patients with advanced solid tumors, which included 57 patients with NSCLC, with dose limiting toxicities of Stomatitis, skin toxicities and Dehydration.	
Maximum dose tested	Single Dose	60 mg
	Multiple Dose	60 mg QD
Exposures Achieved at Maximum Tested Dose	Single Dose	Geometric Mean C_{max} (Geometric %CV): 34.1 (37) ng/mL Geometric Mean AUC_{inf} (Geometric %CV): 3296 (64) ng·h/mL
	Multiple Dose	Geometric Mean C_{max} (Geometric %CV): 108 (57) ng/mL Geometric Mean AUC_{tau} (Geometric %CV): 1720 (70) ng·h/mL
Range of linear PK	2 - 60 mg	
Accumulation at steady state	Following repeated oral administration of 45 mg QD doses, mean accumulation ratio (CV%): 5.7 (45) to 6.4 (32)	
Metabolites	PF-05199265: the most abundant circulating metabolite in plasma (steady-state exposure <20% of the parent exposure), with inhibitory and selectivity profile similar to dacomitinib	
Absorption	Absolute Bioavailability	80% (90% CI: 74.9, 85.5)
	T_{max}	Median (range): 5 to 6 hours (2 to 25.7 for dacomitinib Median (range): 4 to 6 hours (4 to 24) for PF-05199265
Distribution	Vd	Geometric Mean (Geometric %CV): 1889 (18) L
	% bound	98% protein binding in human plasma
Elimination	Route	• Dacomitinib undergoes oxidative metabolism and glutathione conjugation. Following oral administration of a single dose of [14C]dacomitinib to healthy subjects, approximately 79% and 3% of

		the administered radioactive dose was recovered in feces and in urine, respectively. • None of the drug-related components in urine, individually, accounted for >1% of the administered dose.
	Terminal t½	• 54 to 80 hours for dacomitinib • 67 to 75 hours for PF-05199265
	CL	Geometric mean (Geometric%CV): 23.6 (25) L/h
Intrinsic Factors	Age Sex Race	Population PK analysis indicates that there is no statistically significant effect of age and no clinically relevant effects of sex, and race on dacomitinib PK.
	Hepatic & Renal Impairment	Mild or moderate hepatic impairment (defined as Child-Pugh class A and B, respectively) have no clinically relevant effect on the exposure of dacomitinib subjects (Study A7471018). Population PK analysis indicates that mild, moderate or severe renal impairment has no impact on the exposure of dacomitinib.
Extrinsic Factors	Drug interactions	• Coadministration of multiple doses of paroxetine, a strong inhibitor of CYP2D6, with a single 45 mg dose of dacomitinib in healthy subjects, who were extensive CYP2D6 metabolizers, increases dacomitinib AUC_{inf} and C_{max} by approximately 37% and 10%, respectively, relative to when dacomitinib is given alone. • Coadministration of a single dose of dacomitinib 45 mg with a single dose of dextromethorphan in healthy subjects, who were extensive CYP2D6 metabolizers, increases dextromethorphan AUC_{last} and C_{max} by approximately 855% and 874%, respectively, relative to when dextromethorphan is given alone. • Coadministration of multiple doses of rabeprazole, a proton pump inhibitor (PPI), with a single 45 mg dose of dacomitinib in healthy subjects decreases dacomitinib AUC_{inf} and C_{max} by 29% and 51%, respectively, relative to when dacomitinib is given alone.
	Food Effects	Mean C_{max} was increased by 24% and AUC_{inf} was increased by 14% when dacomitinib was administered with a high-fat, high calorie meal. Dacomitinib can be given with or without food.
Expected High Clinical Exposure Scenario	Dacomitinib is a substrate of CYP2D6. Coadministration of a strong inhibitor of CYP2D6 increases dacomitinib AUC_{inf} and C_{max} by approximately 37% and 10%, respectively, relative to when dacomitinib is given alone. Based on this information, the "worst case scenario" for high dacomitinib exposures would be the steady-state exposure after multiple doses of 45 mg QD when co-administered with	

	strong CYP2D6 inhibitors, i.e. there would be 1.37-fold and 1.10-fold increases in steady-state AUC_{tau} and C_{max}, respectively, compared with administration of 45 mg QD dacomitinib alone. The maximal administered clinical dose of dacomitinib was 60 mg QD, which is expected to achieve a similar AUC_{tau} and a higher C_{max} than those for the "worst case scenario".
Preclinical Cardiac Safety	• Off-target pharmacological activity – Dacomitinib L-type Ca2+ channel (dihydropyridine site) Ki = 3.3 µM L-type Ca2+ channel (diltiazem site) Ki = 2.4 µM L-type Ca2+ channel (verapamil site) Ki = 2.2 µM Na+ channel (site 2) Ki = 4.6 µM • Off-target pharmacological activity – PF-05199265 L-type Ca2+ channel (diltiazem site) Ki = 9.5 µM Na+ channel (site 2) Ki = 1.4 µM • Safety pharmacology studies conducted in rats and dogs did not reveal a potential for dacomitinib to cause any effect on the cardiovascular system. In cardiovascular in vitro studies, dacomitinib was identified as an inhibitor of hERG potassium ion channels (IC50 1.58 µM; 743 ng/mL), but had no effects on cardiac action potentials in vitro or on heart rate, ECG parameters (including QTc) and arterial blood pressure of conscious, telemetered dogs at systemic exposure (unbound C_{max}) 26x that in humans at the recommended dose of 45 mg QD (1.72 ng/mL). In addition, PF-05199265, the dacomitinib metabolite, inhibited hERG potassium ion channels (IC50 23.8 µM; 10.9 µg/mL).In repeat-dose toxicity studies, the oral administration of dacomitinib to dogs at doses up to 30 mg/kg/day for 7 consecutive days did not have any effect on heart rate, ECG parameters (including QTc) and mean arterial blood pressure. Systemic exposure at the 30 mg/kg dose (unbound C_{max} of 20.3 ng/mL) corresponds to approximately 11x that in human at the recommended dose of 45 mg QD. In addition, no dacomitinib-related effects on the cardiovascular system (as evaluated via heart weights, and macroscopic and microscopic examination of heart tissue) were noted in repeat-dose toxicity studies in rats for up to 6 months and dogs for up to 9 months in duration, at systemic exposures up to 1.1x and 0.3x, respectively, that in human at the recommended dose of 45 mg QD (based on unbound C_{max}).
Clinical Cardiac Safety	• There are 26 clinical studies (24 completed, 2 ongoing) as of the data cutoff date of 29 July 2016. • Patient exposure to dacomitinib includes clinical trials (1975 patients single agent, 173 patients combination therapy), clinical pharmacology studies (143 patients/healthy volunteers), Investigator-initiated studies (382), compassionate use (28 patients). • The majority of the clinical experience with dacomitinib has utilized the 45 mg QD dosing regimen. A pool of 1473 patients with NSCLC irrespective of line of therapy or EGFR mutation status, treated with single-agent dacomitinib at 45 mg daily has been analyzed (Pool B). A complete list of dosing regimens is found in the attached table: 5.3.5.3 Integrated Summary of Safety Table 1. • In the pool of 1473 patients with NSCLC treated with single-agent

	dacomitinib at 45 mg daily (Pool B), the following E14 PT terms were reported: Syncope (9 patients, 0.6%, all Grade 3 severity[a]), Seizure (6 patients, 0.4%; 1 Grade 1, 4 Grade 2, 1 Grade 3, no Grade 4-5), Sudden death (1 patient, <0.1%, Grade 5), Ventricular tachycardia (1 patient, <0.1%, Grade 2). There were no reports of Torsade de pointes, Ventricular fibrillation or Ventricular flutter. • Of the 1473 patients treated in Pool B, 1 (0.2%) patient had postbaseline QTcF of ≥ 500 msec, and in the pivotal Study 1050, there were no reports of QTcF ≥ 500 msec.

[a] Three of the 9 AEs of Syncope were reported within the respective CSRs as Grade 1 events. However, given the CTCAE Version 4.03 criteria for Syncope, these 3 events are considered to be Grade 3 in severity.

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