31 January 2019
EMA/201148/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vizimpro

International non-proprietary name: dacomitinib

Procedure No. EMEA/H/C/004779/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE(s)	adverse event(s)
AEoSI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARF	acute renal failure
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUCinf	area under the concentration-time curve from time 0 to infinity
AUClast	area under the concentration-time curve from time 0 to the last time point
AUCtau	area under the concentration-time curve over dosing interval tau
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BSEP	bile salt export pump
CCL	chemokine (C-C motif) ligand
CCTG	Canadian Cancer Trials Group
CI	confidence interval
CL	clearance
Cavg	average concentration at steady-state
Cmax	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CQA	Critical Quality Attribute
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CXCL10	chemokine (C-X-C motif) ligand interferon gamma-inducible protein 10
CYP	cytochrome P450
DDI	drug drug interactions
DSC	Differential Scanning Calorimetry
del exon 19	EGFR-activating mutation with a deletion in exon 19
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol-5 Dimension
ERBB	erythroblastosis oncogene B
EU	European Union
F	bioavailability
f_u	fraction unbound
f_m	fractional metabolism
Fpen	Penetration factor
FRC	Functional Related Characteristics
GLP	Good laboratory practice
GMP	Good manufacturing practices
H2	histamine receptor H2
HDPE	High density polyethylene
HER	human epidermal growth factor receptor
hERG	Human ether-a-go-go-related gene

HLT	high-level term
HPLC	High performance liquid chromatography
HR	hazard ratio
HS-GC	Head space gas chromatography
IA	interim analysis
IC50	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IIR	Investigator-Initiated Research
INN	International non-proprietary name
IPC	In-process control
IR	immediate release
IR	Infrared
IRC	Independent Radiologic Central
ISS	Integrated Summary of Safety Information
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
JP	Japanese pharmacopoeia
k_a	absorption rate constant
KF	Karl Fischer titration
KRAS	Kirsten rat sarcoma viral oncogene homolog
L858R	EGFR-activating mutation with an amino acid substitution at position 858 from a leucine (L) to an arginine (R)
LC	Liquid chromatography
LDPE	Low density polyethylene
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not assessed
NCIC-CTG	National Cancer Institute of Canada-Clinical Trials Group
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No Observed Adverse Effect Level
NOR	Normal operating range
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PAR	Proven acceptable range
pcVPC	prediction-corrected visual predictive check
PBT	persistent, bioaccumulative and toxic
Pd	Palladium
PD	pharmacodynamics
PD-1	programmed cell death protein-1
PDE	Permitted Daily Exposure
PEC_{sw}	Predicted Environmental Concentration for surface water
PF-00299804	dacomitinib
PF-05199265	active O-desmethyl metabolite of dacomitinib
PFS	progression-free survival
PK	pharmacokinetics
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PO	oral(ly)
PPI	proton-pump inhibitor
PR	partial response
PRO	patient-reported outcome

PT	Preferred Term
Q	intercompartmental clearance
QbD	Quality by design
QD	once daily
QP	Qualified Person
QLQ-C30	Quality of Life Questionnaire – Core 30
QLQ-LC13	Quality of Life Questionnaire – Lung Cancer module
QoL	quality of life
QTc	QT interval corrected for heart rate
QTcB	Bazett's correction factor for QT interval
QTcF	Fridericia's correction factor for QT interval
QTcS	study-specific correction factor for QT interval
QTPP	Quality target product profile
Rac	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumours
RDI	relative dose intensity
RH	Relative Humidity
RQ	Risk Quotient
SAE(s)	serious adverse event(s)
SAWP	Scientific Advice Working Party
SCS	Summary of Clinical Safety
SFJ	SFJ Lung Cancer Ltd
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Std	standard deviation
t½	terminal phase half-life
T790M	a secondary point mutation at position 790 that substitutes methionine (M) for threonine (T)
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TKI(s)	tyrosine kinase inhibitor(s)
Tmax	time to first occurrence of Cmax
T-R	treatment-response
TRAE	treatment-related adverse event
TSE	Transmissible Spongiform Encephalopathy
TTD	time to deterioration
TTE	time to event
TTF	time to treatment failure
TYMC	Total Combined Yeasts/Moulds Count
UGT	uridine-diphosphate glucuronosyltransferase
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
V2	central volume of distribution
V3	peripheral volume of distribution
vP	very persistent
Vss	volume of distribution at steady state
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 9 February 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Vizimpro, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 March 2017.

The applicant applied for the following indication: Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance dacomitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 13 December 2012. The relevant Scientific Advice pertained to the following clinical aspects of the dossier:

- A randomised, open-label pivotal phase 3 study of dacomitinib with standard of care therapy as comparator: Acceptability of overall study design including open-label design, dose modifications, determination of EGFR mutation status, and timing and frequency of tumour assessments; choice of primary endpoint (progression-free survival) and key secondary endpoints; adequacy of proposed

statistical analysis plan, including proposed magnitude of PFS improvement, stratification factors, statistical methods, and interim analysis; choice of gefitinib as comparator therapy; sufficiency of EU patient enrolment to extrapolate to European patients; acceptability of patient reported outcome data.

- Overall registrational strategy and adequacy of clinical programme to support MAA in the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Bjorg Bolstad

The application was received by the EMA on	9 February 2018
The procedure started on	1 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	25 May 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 May 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 June 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 June 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 September 2018
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two investigator sites, one sponsor site and the site of the CRO. The outcome of the inspection carried out was issued on	11 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses	16 January 2019

to the List of Outstanding Issues to all CHMP members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vizimpro on	31 January 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Lung cancer is the leading cause of cancer-related death in men and women in developed countries, and it is the second leading cause of cancer-related death in less developed countries, representing 1.6 million cancer-related deaths worldwide annually (GLOBOCAN 2012). Lung cancer also represents more patient cancer-related deaths than breast, colon, and prostate cancers combined. Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancers, and the majority of patients present with locally advanced or metastatic disease (Haura 2001; Greenhalgh et al 2016; Reck et al 2017).

The developments in molecular testing techniques and targeted therapies have changed the diagnosis and treatment paradigms for patients with NSCLC. Research by the Lung Cancer Mutation Consortium has demonstrated that overall survival (OS) is longer for patients who have NSCLC with oncogenic driver mutations who were treated with molecularly targeted therapies in their treatment paradigm (Kris et al 2014). The discovery of mutations in the adenosine triphosphate (ATP) cleft within the epidermal growth factor receptor (EGFR) tyrosine kinase domain has better defined which patients would derive clinical benefit from the targeted treatment of these driver mutations (Lynch et al 2004). It also has furthered understanding of the development of resistance to treatment (Jamal-Hanjani et al 2017).

2.1.2. Epidemiology and risk factors

EGFR-activating mutations occur in about 10% to 20% of White patients and in about 30% to 50% in East Asian patients with NSCLC out of the approximately 1.6 million patients worldwide diagnosed with NSCLC annually (Midha et al 2015). EGFR-activating mutations are more common in tumours of non-squamous than of squamous histology, in women than in men, in Asians than in non-Asians, and in never-smokers than in prior or current smokers. The presence of EGFR-activating mutations is less well studied in some populations such as Black/African American, Hispanic/Latino, and Pacific Islanders (Sholl et al 2015).

2.1.3. Biologic features

The two most frequent sensitising mutations are Ex19del and L858R that account for 85-90% of EGFR TKI-sensitising mutations found in NSCLC (Lynch et al 2004; Paez et al 2004). Tumours harbouring these mutations are particularly sensitive towards EGFR-TKIs and undergo significant apoptosis in response to exposure to these agents (Mitsudomi and Yatabe 2010). Multiple randomised clinical studies have shown that the presence of common sensitising EGFR mutations in patients with advanced NSCLC is predictive of response and improved treatment outcome to EGFR-TKIs. Patients with less common sensitising EGFR mutations such as L861Q or G719X, while still benefitting from EGFR-TKIs, have a lesser magnitude of benefit.

In approximately 50% to 65% of the patients the resistance is due to the development of a secondsite EGFR-TKI resistance-conferring 'gatekeeper' point mutation, T790M leading to treatment failure and disease progression (Jackman et al 2009, Maemondo et al 2010, Mitsudomi et al 2010, Mok et al 2009, Oxnard et al 2011, Rosell et al 2012, Sebastian et al 2014).

2.1.4. Clinical presentation, diagnosis

Therapeutic decisions for NSCLC patients are dependent upon specific tumour histological subtype. Immunohistochemistry (IHC) is used to increase the specificity of diagnosis in the small sample setting and reduce the NSCLC-NOS (not otherwise specified) rate to fewer than 10% of cases diagnosed. Two markers only, p40 or p63 to predict squamous cell carcinoma and TTF1 to predict adenocarcinoma, are generally all that is required.

An example is the use of third-generation EGFR TKIs against T790M-mutated resistant tumours, the most common finding in EGFR-mutated tumours relapsing after first-/second generation EGFR TKI therapy (Janne et al 2015; Mok et al 2017). Pathologists should take steps to ensure that tissue handling and processing prioritises all testing required for treatment selection. Genetic alterations, which are key oncogenic events (driver mutations), have been identified in NSCLC, with two of these EGFR mutations and the anaplastic lymphoma kinase (ALK) rearrangements—determining approved, selective pathway directed systemic therapy.

Activating (sensitising) EGFR mutations are predictive for response to the EGFR TKIs. EGFR mutation testing should use validated methodology in a laboratory participating in an external quality assurance scheme in all such patient subgroups. The methodology used should provide the test sensitivity required for the tumour content of the sample and provide an adequate coverage of all clinically relevant mutations. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with specific drug resistance. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion and exon 21 L858R point mutation, including exon 20 T790M) should be determined (Planchard et al 2018).

2.1.5. Management

Early studies using small-molecule inhibitors of EGFR were performed in a generalised, all-comers population with mixed results. Gefitinib and erlotinib were initially studied in previously treated NSCLC.

Gefitinib was studied first in 2002 in 2 large Phase 2 studies that showed improved tumour response at 2 different doses. This did not translate into improvements in survival in the Phase 3 trial except in a subgroup of Asian patients. Erlotinib was studied in the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) trial BR.21 in treatment-refractory NSCLC and showed an improvement in progression-free survival (PFS) over placebo. Improved response to treatment and prolonged PFS was later noted with the identification of various mutations within EGFR that demonstrated increased sensitivity to this class of EGFR TKIs; this is especially true for the EGFR-activating mutations, deletion in exon 19 (del exon 19) and the L858R substitution mutation in exon 21 (L858R). An evaluation of gefitinib versus platinum-doublet chemotherapy in the first-line treatment of NSCLC studied in unselected patient populations and compared the results with patients whose tumours expressed EGFR mutations was performed in Asia and reported in 2009.

The patients with NSCLC with EGFR mutations had improvements in objective response rate (ORR) and PFS when treated with EGFR TKIs, while the unselected population demonstrated no difference between the treatment arms. The PFS improvement did not translate into OS improvements due to patients with EGFR-activating mutations in the chemotherapy doublet arm crossing over to receive gefitinib. Similar results were noted in other studies where patients with NSCLC with EGFR mutations were studied comparing EGFR TKIs to platinum-doublet chemotherapy, where improvements were noted in ORR and PFS, but not in OS.

Second-generation irreversible pan-human EGFR (HER)TKIs were developed to improve PFS and OS by preventing the homodimerization and heterodimerization of the HER family members and block cascade

activation involving RAS, RAF, MEK, and MAPK pathways to block cell proliferation, survival, invasion, and metastases, and also by potentially delaying the development of resistance mutations. Afatinib was approved based upon improved PFS when compared to chemotherapy doublets.

A third-generation EGFR TKI (osimertinib) has been developed targeting the primary EGFR TKI resistance mutation, a secondary point mutation at amino acid position 790 that substitutes methionine for threonine (T790M) in exon 20, occurring in approximately 60% of all patients treated with EGFR TKIs. Osimertinib showed a statistically significant response as shown by improvements in ORR (to 77% for osimertinib and 39% for platinum and pemetrexed); odds ratio 4.96%, 95%CI:2.49, 10.15; p<0.001) and PFS (mPFS of 8.2 months for osimertinib and 4.2 months for platinum and pemetrexed (HR=0.42 [95%CI:0.29, 0.61] p-value not noted) in patients with NSCLC with EGFR-activating mutations and with documented EGFR T790M mutation. Osimertinib has been approved for use in the United States (US) and the European Union (EU) for patients with EGFR T790M mutation-positive NSCLC whose disease progressed on or after EGFR TKI therapy. In the recently reported FLAURA study, osimertinib demonstrated improved PFS (target number of events for final OS analysis has not yet been reached) with acceptable safety in patients with NSCLC with EGFR-activating mutations when compared to other first-generation EGFR TKIs.

Despite these therapeutic advances, patients with NSCLC with EGFR-activating mutations continue to have disease progression within a period of 8 to 11 months after first-line EGFR TKI therapy. Current options for therapy now include first-, second-, or third generation EGFR TKIs in the first-line treatment setting, or after receiving platinum-doublet chemotherapy while mutation analysis is being determined.

About the product

Dacomitinib is a pan-human epidermal growth factor receptor (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with activity against mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21. Dacomitinib binds selectively and irreversibly to its HER family targets thereby providing prolonged inhibition.

The indication adopted by the CHMP is:

Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

Treatment with Vizimpro should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

EGFR mutation status should be established prior to initiation of dacomitinib therapy (see section 4.4).

The recommended dose of Vizimpro is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs.

Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of Vizimpro should be reduced as described in Table 1. Dose modification and management guidelines for specific adverse reactions are provided in Table 2 (see sections 4.2, 4.4 and 4.8 of the SmPC).

Table 1: Recommended dose modifications for Vizimpro adverse reactions

Dose level	Dose (once daily)
Recommended starting dose	45 mg
First dose reduction	30 mg
Second dose reduction	15 mg

Table 2: Dose modification and management for Vizimpro adverse reactions

Adverse reactions	Dose modification
Interstitial lung disease (ILD/Pneumonitis)	Withhold dacomitinib during ILD/Pneumonitis diagnostic evaluation. Permanently discontinue dacomitinib if ILD/Pneumonitis is confirmed.
Diarrhoea	• For Grade 1 diarrhoea, no dose modification is required. Initiate treatment with anti-diarrhoeal medicinal products (e.g., loperamide) at first onset of diarrhoea. Encourage adequate oral fluid intake during diarrhoea. • For Grade 2 diarrhoea, if not improved to Grade ≤ 1 within 24 hours while using anti-diarrhoeal medicinal products (e.g., loperamide) and adequate oral fluid intake, withhold dacomitinib. Upon recovery to Grade ≤ 1, resume dacomitinib at the same dose level or consider a reduction of one dose level. • For Grade ≥ 3 diarrhoea, withhold dacomitinib. Treat with anti-diarrhoeal medicinal products (e.g., loperamide), and adequate oral fluid intake or intravenous fluids or electrolytes as appropriate. Upon recovery to Grade ≤ 1, resume dacomitinib with a reduction of 1 dose level.
Skin-related adverse reactions	• For Grade 1 rash or erythematous skin conditions, no dose modification is required. Initiate treatment (e.g., antibiotics, topical steroids, and emollients). • For Grade 1 exfoliative skin conditions, no dose modification is required. Initiate treatment (e.g., oral antibiotics and topical steroids). • For Grade 2 rash, erythematous or exfoliative skin conditions, no dose modification is required. Initiate treatment or provide additional treatment (e.g., oral antibiotics and topical steroids). • If Grade 2 rash, erythematous or exfoliative skin conditions persist for 72 hours despite treatment, withhold dacomitinib. Upon recovery to Grade ≤ 1, resume dacomitinib at the same dose level or consider a reduction of 1 dose level. • For Grade ≥ 3 rash, erythematous or exfoliative skin conditions, withhold dacomitinib. Initiate or continue treatment and/or provide additional treatment (e.g., broad spectrum oral or intravenous antibiotics and topical steroids). Upon recovery to Grade ≤ 1, resume dacomitinib with a reduction of 1 dose level.
Other	• For Grade 1 or 2 toxicity, no dose modification is required. • For Grade ≥ 3 toxicity, withhold dacomitinib until symptoms resolve to Grade ≤ 2. Upon recovery, resume dacomitinib with a reduction of 1 dose level.

Type of Application and aspects on development

A summary of the discussions and outcomes of the relevant meetings with EU Health regarding the clinical development program and regulatory submission plans for dacomitinib for the proposed indication is provided below.

EMA/CHMP/SAWP/686605/2010; EMA/CHMP/SAWP/768966/2012

- Pfizer received final CHMP scientific advice related to Study 1050 study design and registration strategy on 13 December 2012. The CHMP agreed with the Study 1050 study design, endpoints, and use of gefitinib as comparator. The CHMP also agreed that the results of Study 1050, in addition to the results of Study1017, would be adequate to support approval of dacomitinib in the proposed indication.

- The CHMP recommended including patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 in Study 1050 and possibly stratifying by ECOG performance status 0 to 1 versus 2. Based on the advice of the key investigators across all regions, the applicant enrolled patients with ECOG performance status 0 to 1 in order to avoid possible inclusion of patients with poor/borderline performance or short life expectancy.

- The CHMP recommended including a sufficient number of EU patients in the pivotal study 1050 to ensure that the results observed in the total population could be safely extrapolated to EU patients. The applicant maintained their proposed approach, and the final proportion of patients enrolled in the EU (23.5%) was lower than originally planned in the SA (30%).
- The CHMP also suggested to re-biopsy patients at the time of disease progression in order to investigate mechanisms of resistance; however, tumour specimens upon disease progression were not collected per protocol, as it was not considered feasible.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 15 mg, 30 mg and 45 mg of dacomitinib as dacomitinib monohydrate.

Other ingredients are: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate and Opadry® II Blue 85F30716 (composed of polyvinyl alcohol – part hydrolysed (E1203), talc (E553b), titanium dioxide (E171), macrogol/PEG 3350 (E1521), FD&C Blue # 2/indigo carmine aluminium lake (E132)).

The product is available in the EU in aluminium/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of dacomitinib monohydrate is *(2E)-N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide monohydrate corresponding to molecular formula $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$. It has a relative molecular mass of 487.95 Daltons and the following structure:

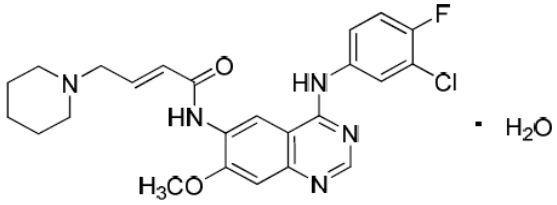


Figure 1: active substance structure

The chemical structure of dacomitinib was elucidated by a combination of elemental analysis, UV/VIS, NMR (^{1}H, ^{13}C, ^{15}N, ^{19}F, a combination of mono and bi-dimensional experiments) and IR spectroscopy, mass spectrometry, single X-ray diffraction. The thermal properties of dacomitinib were determined by Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA).

Dacomitinib is a non-hygroscopic, white to pale yellow powder that is practically insoluble in water, slightly soluble in acetone and acetonitrile and sparingly soluble in acetic acid. It is classified as BCS Class II (low solubility and high permeability) based on the Biopharmaceutical Classification System.

The active substance does not exhibit chirality. The configuration at the olefinic double bond in the structure of dacomitinib monohydrate is trans as shown in Figure 1.

The active substance shows polymorphism. Three relevant forms of dacomitinib have been identified: monohydrate Form A, monohydrate Form B and anhydrous Form C.

Dacomitinib monohydrate Form A is the solid state form selected for development and commercialization. This is the thermodynamically favoured and predominant solid state form which was identified from extensive form screening experiments and crystallization studies across a diverse range of solvents and temperatures (4 to 75°C).

The manufacturing process has been designed to ensure monohydrate Form A is produced.

Manufacture, characterisation and process controls

The active substance is manufactured by a single manufacturer in a three-step convergent synthesis with one isolated intermediate. No alternative processes, reprocessing or recoveries have been proposed.

To justify the selection of starting materials an extensive discussion on impurities arising from the synthesis of starting materials, fate, purge data and typical levels of these impurities are provided in the dossier. Spiking experiments show that all specified impurities arising from the synthesis of these starting materials are effectively removed during the GMP manufacturing process. None of these impurities or their fate products are present in the active substance above the limit for unspecified impurities. Overall, the proposed starting materials have been adequately justified in line with ICH Q11 and acceptable specifications have been set.

The batch size (i.e. quantities of raw materials) and expected yields have been stated.

The manufacturing process of the active substance has been satisfactorily described and adequate in-process controls are applied during the synthesis. Acceptable specifications and control methods for intermediate products, starting materials and reagents have been presented.

The synthetic route has been executed at laboratory, pilot and commercial scale and has been shown to produce dacomitinib meeting all specifications. The process knowledge gained through a combination of multivariate and univariate experiments, as well as scale and equipment dependency studies were used to establish the manufacturing conditions. Although not initially proposed by the applicant, a design space covering Steps 1-3 has been defined and is considered acceptable. Scientific rationale has been presented to identify the process parameters that are expected to be independent on scale, therefore verification of the design space is not needed at commercial scale. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

A genotoxic risk assessment was performed. It has been demonstrated that these impurities are purged to negligible levels during the GMP manufacturing process. Given the results obtained and the fact that dacomitinib is intended to treat patients with advanced cancer, specific limits for genotoxic impurities were not established. Actual and potential impurities were assessed using two complementary (Q)SAR methodologies, along with expert review of additional publicly available databases and internal data to identify potentially mutagenic impurities. The results from *in vitro* mutagenicity testing are provided in the non-clinical section. Briefly, several

impurities gave positive result in *in vitro* mutagenicity test, and were classified as class 2 (known mutagens with unknown carcinogenic potential.

All class 3 and class 2 impurities were further evaluated to assess the risk of being present in dacomitinib by a combination of fate and purge experimentation and/or analytical testing of pilot scale batches. This evaluation resulted in the identification of 4 genotoxic impurities that have the greatest potential of being present in dacomitinib. However, levels observed were extremely low or not detected. The batch and spiking data presented showed that the proposed commercial process purges these impurities to negligible levels.

As part of an overall risk assessment for elemental impurities, dacomitinib active substance manufactured according to the commercial process was screened for ICH Q3D Class 1 and Class 2A elements and the intentionally added elemental impurity is used as catalyst in the synthesis. The acceptable levels for the individual impurities were set based on ICH Q3D Option 1 to ensure the oral PDEs of the individual elemental impurities are not exceeded in the finished product. Available data resulting from screening several batches of dacomitinib active substance showed levels of the catalyst in all cases. Based on the data collected, the Class 1 and 2A elemental impurities and the catalyst will not be routinely monitored in dacomitinib active substance.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Two synthetic pathways were employed for the manufacture of dacomitinib active substance during development for use in clinical studies. Several synthetic routes were designed for each synthetic pathway as knowledge increased. Changes introduced have been presented in sufficient detail and have been justified. In addition, it has been demonstrated that the changes did not have a significant impact on the quality of the product. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in a container which complies with the requirements of relevant Ph. Eur. monographs or EC regulation No. 10/2011 on plastic and articles for food contact

Specification

The active substance specification includes tests for appearance, identification (IR), assay (LC), impurities (specified impurities, unspecified and total impurities) (LC), water content (KF), residual solvents (HS-GC), residue on ignition (Ph. Eur.) and particle size (laser diffraction).

The active substance specifications are based on the active substance critical quality attributes (CQA). The CQA included in the active substance specification that are specific to the dacomitinib manufacturing process are: water content, particle size distribution, specified impurity, unspecified impurities, and residual solvents.

Only one impurity is specified in dacomitinib. The proposed acceptance criterion is in accordance with ICH Q3A for an identified impurity absent of genotoxic structural concern.

Dacomitinib active substance is isolated as a monohydrate and is non-hygroscopic. The specified water content ensures the correct solid form is isolated. All dacomitinib active substance batches manufactured throughout development were isolated as monohydrate Form A, with water contents within the proposed acceptance criterion.

The dacomitinib particle size specification was established in accordance with guidance provided in ICH Q6A with due consideration given to the impact on manufacturability, dissolution and pharmacokinetics of the finished product as described in the pharmaceutical development section. Polymorphism is not included in the specification. As described above, dacomitinib (Form A) is the solid form selected for development and

commercialization. Form A is the thermodynamically favoured and predominant solid state form which was identified from extensive form screening experiments and crystallization studies across a diverse range of solvents and temperatures.

The omission of a specific control for elemental impurities, certain residual solvents, and microbiology in dacomitinib active substance specification has been adequately justified based on scientific rationale and batch analysis data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data for 31 batches of dacomitinib manufactured at both the development and commercial manufacturing sites have been presented. These batches were used for toxicology, development and stability studies and for the manufacture of finished product for clinical studies. Data from commercial scale batches manufactured by the proposed commercial manufacturing route and site have been included. Some of the batch analysis results obtained throughout development of the dacomitinib active substance and presented in the dossier were derived from analytical procedures that differ from proposed for the evaluation of commercial active substance. This is due to the evolution of analytical methodology during the development process. Each procedure was validated at the time of its use. Both the methods and specifications in place at the time of release for the respective batches were appropriate for the stage of development. The results are within the specifications and consistent from batch to batch. The batch data and stability results support the proposed specification.

Stability

Stability data from three commercial scale batches of the active substance used in clinical studies and manufactured by development synthetic route were provided. Both the development synthetic route and the commercial processes are deemed comparable since they include the same bond forming steps and similar impurity profiles. The only differences were related to reagents and minor processing conditions, which do not impact stability of the final active substance. One commercial scale batch of dacomitinib active substance manufactured by this revised process proposed for marketing and stored in the intended commercial package was added to the primary stability study. Since there are no significant differences between these synthetic routes and the active substance manufactured using these routes show comparable quality, the selection of batches for the stability studies is considered acceptable.

Samples were stored for up to 60 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines. The stability samples were evaluated for appearance, assay, impurities, water content, TAMC and TYMC. The batch manufactured as per the synthetic process proposed for marketing was also tested for solid form (XRPD) and particle size and conformed to the specification.

The appearance of stability samples stored under long term and accelerated conditions remained unchanged throughout the stability program and met the acceptance criteria. There were no significant changes observed in assay values under long term and accelerated conditions. Results for all impurities remained essentially unchanged for samples stored under both storage conditions. The impurity values met the acceptance criteria. All water content values for stability samples met the acceptance criteria under both storage conditions.

The real time and accelerated studies demonstrated that dacomitinib active substance manufactured by either synthetic route show equivalent stability.

A stability study was conducted under stressed conditions on the batch manufactured by the commercial route to further demonstrate the comparable stability profiles of dacomitinib active substance manufactured by the different synthetic routes. Batches of dacomitinib active substance were stored in open glass vials and exposed to various temperatures and levels of humidity. There was little detectable degradation observed in all lots during the duration of the study, showing that the compound is very stable even when exposed to stress storage conditions regardless of the manufacturing process.

A photostability study was carried out according to the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products on one batch A dark control sample was covered and placed in the light cabinet alongside the unpackaged test sample. Samples were tested for appearance, assay, impurities and water. All parameters remained unchanged versus the dark control. Therefore, it was concluded that dacomitinib active substance is not light sensitive and does not require a light restriction.

Forced degradation studies were also conducted. Samples of dacomitinib active substance were exposed to acid, base, water, hydrogen peroxide, heat, humidity and simulated sunlight. The stress conditions studied were chosen to ensure that potential degradation pathways and major degradation products are elucidated and that the assay and purity methods are appropriately stability indicating. Most degradation was observed when dacomitinib active substance was stressed at high temperature. No degradation was observed under the neutral ,oxidative or basic conditions Minor degradation was observed for acidic and photostability .In the solid state, no degradation was observed at high temperature/high humidity No significant decrease in the assay value was observed when no degradation had occurred and acceptable mass balance was achieved for all conditions. The assay and purity method for dacomitinib active substance was shown to be specific, selective, and stability-indicating.

In conclusion, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The proposed commercial formulation of dacomitinib consists of dacomitinib blue immediate release film-coated tablets available in three strengths: 15 mg, 30 mg and 45 mg. All strengths are prepared from a common blend using common pharmaceutical excipients and manufactured by a conventional direct compression process. The strengths are dose-proportionate. The range of strengths is suitable to accommodate the dosing regimen described in the SmPC, including controlled dose reduction in case of unacceptable side reactions. The tablets are differentiated by tablet size and debossing:

- The proposed commercial 15 mg tablet consists of a tablet size of 6.35 mm with de-bossing of 'Pfizer' on one side and 'DCB 15' on the opposite side. The 15 mg strength is a round, biconvex, blue film-coated tablet.
- The proposed commercial 30 mg tablet consists of a tablet size of 7.5 mm with de-bossing of 'Pfizer' on one side and 'DCB 30' on the opposite side. The 30 mg strength is a round, biconvex, blue film-coated tablet.

- The proposed commercial 45 mg tablet consists of a tablet size of 9.0 mm with de-bossing of 'Pfizer' on one side and 'DCB 45' on the opposite side. The 45 mg strength is a round, biconvex, blue film-coated tablet.

The development of Vizimpro followed an enhanced approach in accordance with ICH Q8. Attributes and parameters were categorized as either critical or non-critical based on their impact to product quality. A Quality Target Product Profile (QTPP) has been established as immediate release dosage form containing dacomitinib, that meets compendial and other relevant quality standards for appearance, identity, assay, impurities, uniformity of dosage units, dissolution and microbial limits.

Once the proposed commercial formulation and manufacturing process for Vizimpro were established, an understanding of the relationships between materials and process parameters and the quality attributes identified in the QTPP was developed. Components of the finished product, process operating parameters, and packaging components were assessed with respect to their potential to impact the quality attributes. The initial correlation to CQAs was determined based upon prior knowledge of immediate release formulation and development and scale-up of the manufacturing process.

After identifying materials and process operating parameters with potential links to CQAs, an experimental plan was developed and executed to analyse the functional relationships. The results were evaluated to (a) establish if the identified materials and parameters significantly impacted a quality attribute, (b) identify the ranges within which the process could be operated to produce dacomitinib finished product that met the defined limits and (c) determine an appropriate overall control strategy. The criticality of each operating parameter was designated, and acceptable operating ranges were established in order to assure the process and resulting finished product were appropriately controlled.

The manufacturing process is supported by a control strategy that assures each quality attribute is within the appropriate range required to deliver the desired efficacy, safety and quality of the finished product.

As indicated in the active substance section, dacomitinib Form A free-base monohydrate is the form that has been consistently isolated during the active substance manufacturing process and was selected for development and commercialization. Dacomitinib is a non-hygroscopic, white to pale yellow powder that is classified as BCS Class II (low solubility and high permeability) based on the Biopharmaceutical Classification System. Dacomitinib solubility is pH dependent, with solubility being highest under low pH gastric conditions in the fasted state. The impact of active substance particle size was an important consideration during finished product development, as dissolution of dacomitinib finished product may limit absorption. Therefore, particle size distribution was considered to be a CQA of the active substance.

A range of active substance particle distributions were used to support clinical studies. Based on the results obtained in clinical efficacy and pharmacokinetic studies, dissolution testing, content uniformity and dissolution modelling, a particle size limit was included in the active substance specification.

The proposed direct compression tablet formulation was based on a dry granulated formulation used for early clinical studies. The microcrystalline cellulose, lactose monohydrate, sodium starch glycolate and magnesium stearate used in the dry granulated formulation were maintained for the directly compressed tablet, and a non-functional aqueous film coat was applied.

The Functional Related Characteristics (FRC) of the excipients used in dacomitinib immediate release blue film-coated tablets was also reviewed. The finished product was found to have one principle degradant. Work was conducted to evaluate whether the use of different excipients had a positive effect on finished product stability. Active substance compatibility testing under accelerated conditions was carried out with blends

containing different excipients and levels of excipients to determine the impact on the formation of the main finished product degradant. Overall, substituting any of the selected excipients had no positive effect on the level of degradant, so the qualitative formulation used for the dry granulated tablet was maintained throughout development of the directly compressed tablet formulation.

The final formulation includes microcrystalline cellulose and lactose monoyhydrate (as diluents), sodium starch glycolate (as disintegrant), magnesium stearate (as lubricant) and Opadry® II Blue 85F30716 (as film-coating agent). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Different formulations, strengths and pharmaceutical forms of dacomitinib were used to support the different phases of clinical development.

Dissolution rate studies were conducted throughout development to assess the impact of the changes made on dissolution performance. Dissolution rates were found comparable using the proposed commercial dissolution method. None of the changes studied had a significant impact on dissolution. Similarity between the clinical formulation and the commercial formulation was determined using a relative bioavailability study and by dissolution rate testing. Clinical study (A7471022) was performed to determine the relative bioavailability of the white film-coated 45 mg dacomitinib tablet to 3 uncoated 15 mg tablets as a single dose following oral administration in the fasted state to healthy volunteers. Based on the results of this clinical study, acceptable equivalence between the formulations has been demonstrated.

In vitro dissolution of the dacomitinib dosage forms was evaluated across the physiological pH range to assess the impact on dissolution of the pH dependent solubility of the active substance. Drug release was fast at low pH, in line with the high solubility of dacomitinib, and slow at high pH, in line with the low solubility of dacomitinib. A number of development formulations varying the amounts of lubricant, disintegrant and tablet hardness were assessed using the dissolution test conditions. Overall the data presented demonstrate the suitability of the dissolution method for the quality control of the product.

As indicated above, dacomitinib immediate release blue film-coated 15 mg, 30 mg and 45 mg tablets are manufactured using a conventional direct compression and aqueous film coat manufacturing process using equipment commonly available in the pharmaceutical industry. Manufacturing process development demonstrated that the desired attributes of the QTPP will be met, and that the manufacturing process is robust.

Multivariate and univariate experimental studies were conducted to generate process knowledge and establish acceptable ranges for blending, lubrication and compression.

Clinical and registration stability batches have been manufactured at the proposed commercial manufacturing site using the proposed commercial manufacturing equipment.

The container closure system selected for the commercial tablets of dacomitinib 15 mg, 30 mg, and 45 mg consists of aluminum foil blisters with aluminum foil backing as stated in the SmPC.

All product contact plastic components of the packaging system comply with the requirements of EU Regulation No. 10/2011. All packaging components also comply, where applicable, with the current European Pharmacopeia.

Development stability studies showed that protective packaging is beneficial to control the formation of the shelf life limiting degradation product when exposed to high relative humidity. Overall, the choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: blending, compression, film-coating and packaging. The manufacturing process is supported by a control strategy that assures each quality attribute is within the appropriate range required to deliver the desired efficacy, safety and quality of the finished product.

The process is considered to be a standard manufacturing process. There are no critical in-process tests for manufacture of dacomitinib tablets. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The formal validation on production scale batches will be completed prior to release of the product for commercial use according to the proposed process validation scheme. This is acceptable since the manufacturing process is a standard direct compression and the proportion of the active substance in the tablet is above 2%.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and include: appearance (visual), identification (HPLC, UV), assay (HPLC), impurities (HPLC), dissolution, content uniformity (HPLC), water content (Ph. Eur.) and microbial limits (TAMC, TYMC, *E. coli*) (Ph. Eur.).The proposed specification for the product is in general acceptable for an immediate release dosage form. Limit proposed for degradation impurity at release is in accordance with ICH Q3B for a maximum daily dose of dacomitinib of 45 mg and has been qualified in safety studies.

In line with ICH Q3D, an elemental impurities risk assessment was performed on the dacomitinib finished product. The active substance, excipients, manufacturing equipment and utilities, and packaging components were evaluated as part of the risk assessment. Screening results on the active substance demonstrated that it is not a source of any Class 1 or Class 2A elemental impurities, and not a significant source of catalyst. To confirm the findings of the risk assessment, several batches of dacomitinib finished product, manufactured according to the commercial process at the commercial site and scale, were screened for elemental impurities identified during the risk assessment. Based on the data collected, no controls or acceptance criteria for individual elemental impurities are proposed for dacomitinib finished product, as the risk of elemental impurities being present at levels above their PDEs has been established to be negligible via the risk assessment, combined with supporting analytical data.

In accordance with ICH Q6A, Specifications, Decision Tree 8 (Microbiological Attributes of Non-Sterile Drug Products), the applicant proposed to eliminate routine microbiological testing. The justification was based on the following considerations; excipient controls, environmental controls and batch and stability data, and is considered acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for a total of 44 batches produced during the development, including 19 batches manufactured for clinical use and stability. All the batches comply with specification, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from commercial batches of finished product stored for up to 60 months under long term conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. All batches were manufactured and packaged at the proposed commercial site greater than 10% of commercial scale. A bracketing approach was used .

Potential stability-related quality attributes that were evaluated for the finished product within the primary (registration) stability program include appearance, assay, degradation products, dissolution, water and microbiological quality.

Two attributes were observed to trend on stability, the main degradation product and water content, but all results complied with the proposed specification. In line with these findings, protective packaging was selected for dacomitinib finished product to reduce the impact of moisture on stability. No stability trends were observed for appearance, assay, unspecified degradation products, dissolution or microbial limits and all data remained within the proposed limits.

Supportive stability data were obtained on tablets packaged in HDPE bottles containing desiccant with polypropylene closure stored for up to 60 months at 30 °C / 75% RH and 6 months at 40 °C / 75% RH. All results were within the specification.

In addition, a photostability of one batch of each strength was evaluated in accordance with ICH guideline Q1B. No significant changes were observed in any of the parameters measured, namely appearance, assay, degradation products, water content and dissolution. Therefore, it is concluded that dacomitinib tablets are stable to light and no precautionary packaging or labelling is required.

Forced degradation experiments were performed on 15 mg and 45 mg immediate release blue film-coated dacomitinib tablets from the primary registration batches and placebo mixtures to establish the extent and nature of potential degradation pathways and to confirm the suitability of the LC assay and purity method. The stress conditions included thermal, thermal/humidity and photolysis studies. No additional oxidation studies over those performed on the active substance were performed on the finished product, as no related degradation was observed during active substance purposeful degradation testing. Samples were analysed for potency and degradation products.

The studies conducted on dacomitinib tablets exposed to stress conditions showed that significant degradation was induced under thermal/humidity stress conditions and that only one significant degradation product was formed. A light degradation product was observed under strong light conditions only. No additional degradation products were observed, and mass balance was achieved. Under humidity stress conditions low levels of degradation products were formed. Under thermal stress conditions higher degradation was observed. These studies confirm that the assay and purity method is selective and stability indicating.

Based on available stability data, the proposed shelf-life of 60 months for the finished product in the proposed container (aluminium/aluminium blisters) with no special storage conditions, as stated in the SmPC (section 6.3), is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant

material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

All other components used in the dacomitinib tablets are of vegetable or synthetic origin and do not contain any material of bovine, ovine or caprine derivation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a largely satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. A design space covering all steps of the synthesis was defined.

2.2.1. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacology profile and mechanism of action of dacomitinib (PF-00299804) is presented through *in vitro* biochemical and cellular assays, as well as *in vivo* xenograft models. Pharmacokinetic profile of dacomitinib was investigated in rats and dogs, in which oral and intravenous routes of administration were evaluated. Metabolism characterisation was reported in *in vitro* studies. In the case of the non-clinical safety evaluation of dacomitinib, a conventional toxicological package, in line with ICH guideline S9. Pivotal studies were conducted in compliance with GLP regulations. Environmental Risk Assessment was conducted in line with EMEA/CHMP/SWP/4447/00 (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamic studies were conducted to show potency, selectivity and pharmacological actions of dacomitinib. The pharmacological characterisation was based on both *in vitro* and *in vivo* experimental models.

In vitro

***In vitro* inhibition of HER kinase targets and kinase non-targets**

Inhibition of HER family receptor tyrosine kinase activity: dacomitinib was initially tested towards its original target, i.e. HER kinase family. Its activity as tyrosine kinase inhibitor was measured in biochemical kinase assays based on competitive binding at the ATP binding site (study PF-00299804-Pharm-001). Accordingly,

inhibition of human catalytic domain of HER-1, HER-2 and HER-4 were evaluated. HER-3 was not tested due to it does not possess intrinsic kinase activity. The values of IC_{50} were 2.8 ng/mL (6.0 nM), 21.5 ng/mL (45.7 nM) and 34.7 ng/mL (73.7 nM), respectively for HER-1, HER-2 and HER-4.

Irreversible inhibition of EGFR kinase activity: to test the potential irreversible inhibition, purified EGFR was pre-incubated with 825 nM of dacomitinib (study PF-00299804-Pharm-001). Next, assay solution was diluted (167-fold), up to approximately 5 nM, which is below the IC_{50} value described in the previous paragraph (6.0 nM). Less than 10% of HER-1 enzyme activity was recovered after dilution.

Inactivation kinetic parameters on EGFR variants: the kinetic analysis was determined using a numerical integration approach of the differential equations describing the component processes (study PF-0299804_063846). Initial characterization of EGFR showed a K_i of 0.16 ± 0.01 nM, k_{inact} of 1.5 ± 0.1 ms^{-1}, and a k_{inact}/K_i of 9,900,000 ± 800,000 $M^{-1}s^{-1}$. Dacomitinib was less potent toward EGFR-L858R/T790M, resulting in K_i = 0.63 ± 0.04 nM, k_{inact} of 1.8 ± 0.1 ms^{-1}, k_{inact}/K_i = 2,800,000 ± 300,000 $M^{-1}s^{-1}$. The applicant mentioned that the previous assay method was not a rapid screening assay, so it decided to conduct a higher capacity kinetic method to screen different forms of EGFR. By using this new method, dacomitinib was defined as a potent inhibitor of the EGFR forms but *del19* variant. The affinity for this variant was also potent (K_i^{est} = 0.4 – 3.8 nM) and the inactivation specificity high (k_{inact} / K_i^{est} 71,500 –7,410,000 $M^{-1}s^{-1}$). The values obtained toward EGFR variants are shown in the following table (Table 3).

Table 3: Biochemical potencies of dacomitinib on EGFR variants

EGFR	Inhib. Conc.	% inhib.	$k_{obs}/[I]$ ($M^{-1}s^{-1}$)	K_i^{est} (nM)	k_{inact}/K_i^{est} ($M^{-1}s^{-1}$) (k_{obs}/I*factor)	Saturation Factor	K_m, ATP (μM)
L858R/T790M LJIC-872-G1.2	50	35±1	19100±500	2.2±0.0	789000±13000	41.2	20
T790M/Del(746-750)LJIC-933 D1.1	1000	22±2	660±50	17±1	6800±500	10.2	75.1±7.6
WT/JMLJIC-924 F1.1	50	72±2	305000±46000	0.4±0.0	7410000±1110000	24.2	34.4±3.1
L858RLJIC-921 E4.1	50	66±4	24100±700	1.0±0.1	589000±35300	24.4	68±3.7
Del (746-750)LJIC-932 E1.1	50	63±8.	7550±390	3.8±0.5	71500±9300	9.5	118±6.3

Similarly to the previously described kinetic screening method, the main metabolite PF-05199265 was also analysed. The affinity was estimated as potent (K_i^{est} = 0.14-4.4 nM) and the inactivation specificity high (k_{inact} / K_i^{est} = 323000-368000 $M^{-1}s^{-1}$).

Kinase selectivity in biochemical enzyme assays: dacomitinib was tested in two kinase panels, isolated at Pfizer and Invitrogen (study PF-00299804-Pharm-001). In the set of assays conducted with Pfizer isolated enzymes, dacomitinib showed the highest selectivity for EGFR compared with other kinases (>100-fold). A relevant inhibitory effect was also observed in LCK and SCR kinases. The IC_{50} values for these two enzymes were 94 and 110 nM, respectively, which were within 20-fold of dacomitinib concentration for the EFGR inhibition. In the Invitrogen kinase panel, dacomitinib showed to be at least 100-fold more selective for EGFR than the 90% of the kinases included in this panel. Values of IC_{50} were estimated with kinases in which dacomitinib at 1 μM showed >50% inhibitory activity. The lowest values (maximum inhibition) were obtained with EGFR (0.5 nM), HER4 (7 nM), HER2 (19 nM), BLK (81 nM), FGR (82 nM), LCK (83 nM), YES (112 nM) and SRC (130 nM) kinases.

Table 4: Estimation of IC50 values for inhibition of selected kinases in Invitrogen enzymatic assays

Kinase	IC_{50} value (nM)	Selectivity vs. HER-1
Ableson Kinase (ABL1)	670	1340X
B lymphoid tyrosine kinase (BLK)	81	162X
Bruton Tyrosine Kinase (BTK)	428	856X
Checkpoint Kinase 2 (CHK2)	>1000	>2000X
HER-1 Receptor Tyrosine Kinase	0.5	NA
HER-2 Receptor Tyrosine Kinase	19	38X
HER-4 Receptor Tyrosine Kinase	7	14X
Gardner-Rasheed feline sarcoma kinase (FGR)	82	164X
Vascular Endothelial Growth Factor Receptor-2 (VEGFR2)	769	1538X
Leukocyte-specific protein tyrosine kinase (LCK)	83	166X
LYN Kinase A (LYNA)	148	296X
p38 kinase alpha	>1000	>2000X
Rous sarcoma oncogene (SRC)	130	260X
Fyn Kinase (FYN)	375	750X
Yamaguchi sarcoma kinase (YES)	112	224X

In addition to the previous kinases panel, the selectivity of dacomitinib and its main metabolite (PF-05199265) was also assessed in a 274 kinase assay panel (study PF-00299804_063846). Only 5 (DDR1, EPHA6, LCK, DDR2, MNK1) out of 274 kinases without a cysteine residue in the hinge region of the ATP binding, were inhibited more than 50 % with dacomitinib. Accordingly, the K_i values were estimated to be 2 nM, 18 nM, 29 nM, 30 nM and 45 nM, respectively to DDR1, EPHA6, LCK, DDR2, MNK1. Only DDR1 was expected to have potency within 100-fold of wild-type EGFR. No kinases of this group were inhibited by PF-05199265.

The effect of dacomitinib and PF-05199265 on a 10-kinase group (ErbB-2 (HER2), ErbB-4 (HER4), BTK, BLK, BMX, JAK3, ITK, TEC, TXK, MAP2K7) with a similar cysteine residue (EGFR-Cys_{797}) was evaluated. In this assay, both dacomitinib and PF-05199265 showed a significant potency toward HER2 and HER4 (>50% inhibition) but not to the other related kinases.

Inhibition of EGF-stimulated EGFR and HER2 autophosphorylation in intact cells: a cell-based assay was used to test the potential inhibition by dacomitinib of EGFR and HER2 (study PF-00299804-Pharm-001). Phosphorylation levels were measured by immunoblotting from cells transfected with human HER-1 or a chimeric receptor (extracellular domain of EGFR and intracellular domain of HER2). Dacomitinib in NIH-3T3 cells resulted in IC_{50} values of 3.5 nM (1.6 ng/ml) and 41 nM (19 ng/mL) for autophosphorylation of HER-1 and chimeric receptor HER2, respectively. In A431 human squamous cell carcinoma line, the IC_{50} value was 21 nM (9.9 ng/mL).

Irreversible activity on EGFR in intact cells: dacomitinib inhibited EGFR activity in A431 cells after preliminary incubation followed by drug removal and extensive washing. The effect was observed from 1 minute to two hours (study PF-0299804-Pharm-001). The applicant compared this action with erlotinib, which was published to be rapidly reversed after washing out the inhibitor (Moyer *et al*., 1997).

***In vitro* inhibition of HER kinase target-dependent cell growth and viability**

Various human cancer cell lines and some of their mutant variants were used to assess the inhibition of growth and viability after irreversible HER inhibition (study PF-00299804-Pharm-001). Data are compared with those

obtained with gefitinib. The applicant concluded that dacomitinib showed a better potency, with lower IC_{50}, than gefitinib. The results are shown below (Table 03). In this study, KRAS and BRAF mutant cell lines were shown to be resistant to gefinitib and dacomitinib.

Table 5: Dacomitinib efficacy in EGFR, HER2 and KRAS mutant cell lines

Cell line	EGFR mutation	HER2 amplification	KRAS/BRASF mutation	Gefitinib (IC_{50})	Dacomitinib (IC_{50})
HCC827 (NSCLC)	Del746E750	wt	wt	5.4 nM	2.2 nM
HCC4006 (NSCLC)	Del746E750, A750P	wt	wt	27 nM	1.4 nM
NCI-H125 (NSCLC)	wt	wt	wt	202 nM	27 nM
HCC70 (NSCLC)	wt	wt	wt	5.9 μM	1.6 μM
A549 (NSCLC)	wt	wt	KRAS (G12V)	Not tested	>10 μM
H1666 (NSCLC)	wt	wt	BRAF (G465V)	1.9 μM	8.0 μM
HT-29 (CRC)	wt	wt	BRAF (V600E)	Not tested	>10 μM
MDA-MB-231 (Breast)	wt	wt	BRAF	>10 μM	5.5 nM
BT-474 (Breast)	wt	16xAmp	wt	466 nM	37 nM
SKOV3 (Ovarian)	wt	8xAmp	wt	1.1 μM	392 nM

Dacomitinib was also assessed in an extended panel of cancer cells (lung, breast, colorectal and gastric). In this study (study PF-00299804_134805), it is mentioned that most of the lowest IC_{50} values (maximum inhibition of cell growth and viability) corresponded with cell lines carried gene aberrations (mutations, amplifications or deletions) in HER family members.

The applicant cited an independent publication (Engelman *et al.*, 2007), in which IC_{50} values reported were in the same range that the previously shown in Pfizer studies.

In vivo

***In vivo* inhibition of HER kinase targets and effects on tumour growth**

In addition to the studies conducted by the applicant (study PF-00299804-Pharm-001) and described above, two publications are also cited with the aim of supporting the action of dacomitinib in human tumour xenograft studies (Engelman *et al.*, 2007; Gonzales *et al.*, 2008).

Inhibition of HER2 autophosphorylation: SKOV3 human ovarian xenograft model was used in this study, in which the overexpression of HER2 is known (study PF-00299804-Pharm-001). Athymic mice previously implanted into the flank with tumour fragments, received dacomitinib (oral gavage at 30 mg/Kg for two days) when the tumour reached a size of 250-400 mm^3. After the second dose, tumours were isolated and blood samples taken. The relationship between plasma levels and HER phosphorylation (Tyr 1248) was established. HER2 activity was suppressed greater than 85% at 48 hours after dosing and the steady-state average plasma concentration was estimated ($C_{SS, avg}$) at 604 ng/mL (20.6 ng/mL unbound concentration). Maximal plasma concentration was established at 3 hours. From these data, the total mouse plasma concentration for 50% of inhibition of phospho-HER2 was estimated by modelling as 88.8 ng/mL (3.0 ng/mL unbound).

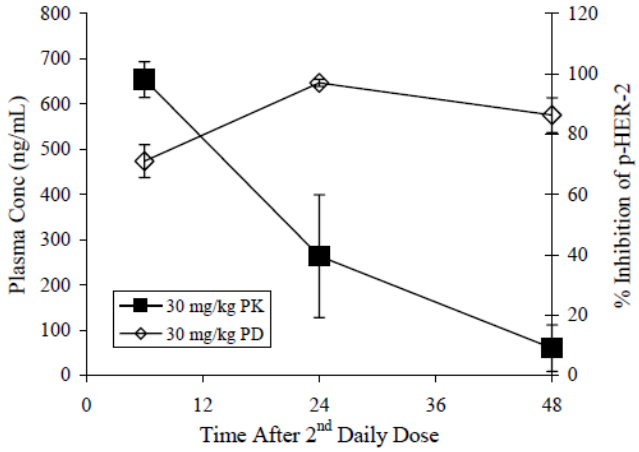


Figure 2: Relationship of PF-00299804 plasma concentration to the degree of HER-2 inhibition in SK-OV-3 ovarian carcinoma xenografts following oral administration of PF-00299804 (2 days)

Inhibition of tumour growth: four human xenograft models (H125, SKOV3, A431 or BT-474 tumours implanted) expressing/overexpressing genetic dysregulation of HER family members were tested with dacomitinib (study PF-00299804-Pharm-001). Two doses were evaluated (30 and 15 mg/kg/day) in SCID mice, with no mortality reported. Between 10% and 19% mean body weight loss from initial body weight at study start was observed. Daily administration of dacomitinib at these two doses resulted in average steady state plasma concentrations of 163 to 604 ng/mL (5.6–20.6 ng/mL, unbound concentration) for 15 and 30 mg/Kg, respectively. The efficacy parameters of the study were established as: completed response (at least 75% of volume reduction compared to the tumour mass at initial treatment); partial response (at least 50% compared to the tumour mass at initial treatment); and tumour growth delay (the difference in days, for the median treated and control tumours to reach a fixed evaluation size of 750 or 1000mm^3). The results for efficacy parameters are shown below.

Table 6: Antitumoural efficacy of dacomitinib for orally administered xenograft models

Tumour	Dose (mg/Kg)	Dosage	Complete regression	Partial regression	Tumour growth delay (day)
H125	30	QD 14days	0/8	0/8	9.1
	15		0/8	0/8	3.6
SKOV3	30	QD 14days	6/6	0/6	41.2
	15		2/6	3/6	17.1
A431	33	QD 14days	0/8	0/8	50.0
	11		1/8	2/8	45.1
BT-474	30	QD 7days	0/10	3/10	33.1
	15		0/10	0/10	34.3

The results of oral administration of dacomitinib at 30 mg/kg/day for 14 days to animals bearing advanced-stage human ovarian cancer xenograft SKOV-3 are shown in Figure 2 (left panel). It resulted in 6/6 complete tumour regressions and a tumour growth delay of 41.2 days. Phospho-HER2 (Tyr 1248) levels were measured (Figure 02, right panel) by western blotting.

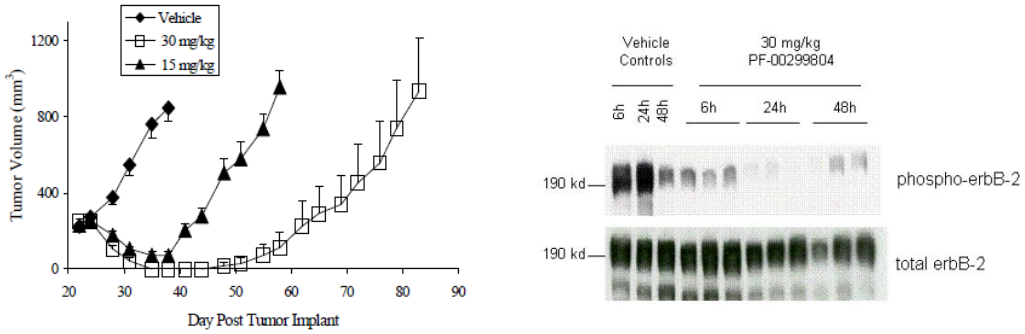


Figure 3: Effect of dacomitinib on tumour volume in SCID mice implanted with SKOV3 human tumour (left panel). Phospho-HER2 levels after dacomitinib administration (QD 14 days) in female mice implanted with SKOV3 human tumour (right panel).

The applicant cited the results obtained by Engelman (Engelman *et al.*, 2007), in which dacomitinib (10 mg/Kg daily oral administration) inhibited the tumour growth in a xenograft EGFR-mutant NSCLC model of HCC827 cells harbouring del19 mutant.

Projected efficacious plasma concentration for inhibition of xenograft growth: based on the previous study conducted in SCID mice implanted with SKOV3 cancer cells (Table 04 and Figure 02), the applicant estimated the efficacious concentration for tumour growth inhibition. The following equation was used:

$$\frac{dM}{dt} = Kg \cdot \left(1 - \frac{M}{TG_{50} + M}\right) \cdot M - Kd \cdot Cp \cdot M$$

Tumour growth rate was determined by a 1st-order growth rate constant Kg, the tumour mass M, and a negative inhibitory function of tumour mass. TG_{50} is the tumour mass associated with 50% inhibition of Kg. Tumour degradation rate is determined by a 2nd-order rate constant K_d, plasma drug concentration C_p and the tumour mass M. The predicted dacomitinib concentration (Ccs= Kg/K_d) that inhibited SKOV3 xenografts to no net growth was 250 ng/mL (8.5 ng/mL, f_u).

***In vitro* and *in vivo* studies in models harbouring EGFR T790M**

In vitro and *in vivo* effects of dacomitinib against the EGFR L858R/T790M mutation

As it was shown in Table 01, dacomitinib inhibited most of the EGFR forms (L858R and del19) *in vitro*. The activity of dacomitinib was compared with lapatinib and gefitinib in NCI-H1975 cells, harbouring primary and secondary HER-1 mutations (Figure 4). In this model, the IC_{50} value for dacomitinib was estimated at 342 nM (160 ng/mL), and it was resistant to gefinitib and lapatinib (study PF-00299804-Pharm-001).

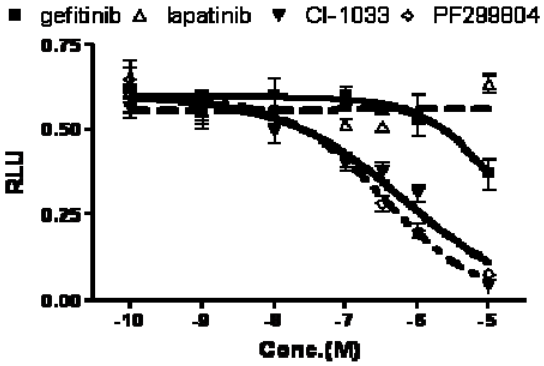


Figure 4: Dacomitinib inhibited the growth and viability of the NCI-H1975 NSCLC cell model harbouring L858R/T790M mutations

The action of dacomitinib (7.5 and 15 mg/Kg) on a xenograft model performed with the same cell line, i.e. NCI-H1975, was shown in comparison with erlotinib. No effect was observed in animals treated with erlotinib, while dacomitinib resulted in an inhibition of tumour growth of 41% and 77% (Figure 5, left panel). Inhibition of phospho-EGFR was also observed in the case of dacomitinib at both dose levels. At 7.5 mg/kg the inhibition was 69% and 78% and at 15 mg/kg it was 91% and 97% at 2 and 26 hours after dosing, respectively (Figure 5, right panel).

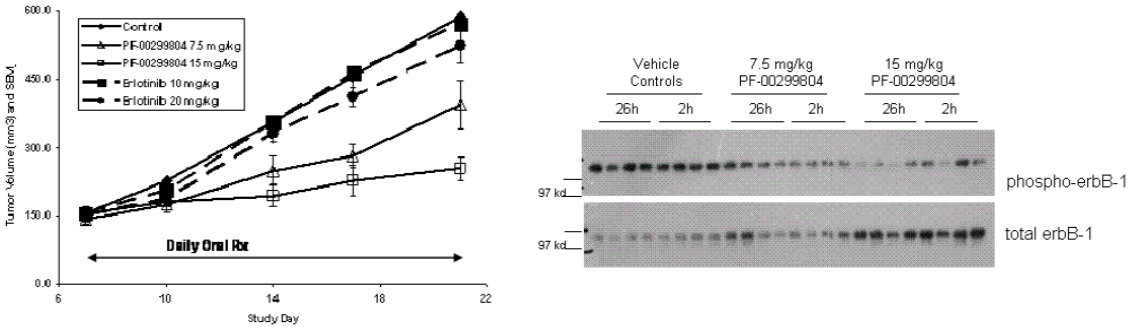


Figure 5: Effect of dacomitinib and erlotinib on a NCI-H1975 xenograft model on tumour volume (left panel) and phospho-EGFR (right panel)

Secondary pharmacodynamic studies

The results of binding, cellular and nuclear receptor functional and enzyme and uptake assays were submitted with the aim of evaluating the potential off target pharmacological activity of dacomitinib and its main metabolite PF-05199265 (studies 100014035 and 100013996). Activity was defined by a response greater than 50% of a maximal response. Based on this, dacomitinib and PF-05199265 (initial concentration of 10 μM) showed activity in some of the tested targets.

Table 7: Off target assays values obtained with dacomitinib or PF-05199265

Dacomitinib	Value
Nicotinic acetylcholine receptor (muscle type) (binding assay)	K_i = 17 μM
L-type calcium (Ca^{2+}) ion channel (dihydropyridine site) (binding assay)	K_i = 3.3 μM
L-type calcium (Ca^{2+}) ion channel (diltiazem site) (binding assay)	K_i = 2.4 μM

L-type calcium (Ca^{2+}) ion channel (verapamil site) (binding assay)	K_i = 2.2 μM
sodium (Na^{+}) ion channel (site 2) (binding assay)	K_i = 4.6 μM
norepinephrine transporter (binding assay)	K_i = 4.4 μM
dopamine transporter (binding assay)	K_i = 3.0 μM
choline transporter (binding assay)	K_i = 1.5 μM
muscarinic M1 receptor (antagonist; functional assay)	K_b = 490 nM
Abl kinase (enzyme assay)	IC_{50} = 510 nM
KDR kinase (VEGFR2) (enzyme assay)	IC_{50} = 550 nM
LCK kinase (enzyme assay)	IC_{50} = 1.7 μM
p38α MAP kinase (enzyme assay)	IC_{50} = 6.4 μM
SRC kinase (enzyme assay)	IC_{50} = 560 nM
PF-05199265 (main metabolite)	Value
GABAa benzodiazepine (BZD) receptor (binding assay)	K_i = 4.6 μM
L-type calcium (Ca2+) ion channel (diltiazem site) (binding assay)	K_i = 9.5 μM
sodium (Na+) ion channel (site 2) (binding assay)	K_i = 1.4 μM
norepinephrine transporter (binding assay)	K_i = 750 nM
dopamine transporter (binding assay)	K_i = 98 nM

The values for IC_{50}, K_i or K_b obtained in the off target pharmacological activity assays were at least 130-fold and 700-fold greater, respectively to dacomitinib (1.72 ng/mL or 3.6 nM) and PF-05199265 (0.0658 ng/mL or 0.14 nM), than the unbound C_{max} found in humans at the recommended dose of 45 mg QD.

Safety pharmacology programme

Potential exacerbated pharmacological and/or toxic effects of dacomitinib on the central nervous, cardiovascular and respiratory systems function were assessed. The parental drug and its main metabolite, PF-05199265, were also evaluated in the hERG assay, as is shown below.

Table 8: Safety pharmacology studies conducted with dacomitinib

Study	Study Number	Concentration/dose	GLP
Central Nervous System			
Neurofunctional rat	04-2730-06	0, 5, 50, 500 mg/Kg	Yes
Cardiovascular System			
hERG assay	04-2730-08	0, 0.2, 0.7, 2.3, 9.3 μM	Yes
hERG assay (PF-05199265)	131218.QHJ	0, 3, 10, 30, 100 μM	Yes
Purkinje fibres assay	PF299804/IC/001/05	0, 0.3, 1, 3, 10 μM	Yes
Cardiovascular conscious dog	04-2730-04	0, 10, 30 mg/Kg	Yes
7-day repeat-dose general toxicity dog	04-2730-03	0, 3, 10, 30 mg/Kg	No
Respiratory System			
Pulmonary rat	04-2730-07	0, 5, 50, 500 mg/Kg	Yes
7-day repeat-dose general toxicity dog	04-2730-03	0, 3, 10, 30 mg/Kg	No

Central Nervous System

Neurofunctional actions of dacomitinib were assessed in rats, dosed at 5, 50 or 500 mg/Kg (single dose oral gavage). Evaluation of the animals relied on a series of test and experimental measures, such as FOB, body temperature and locomotor activity (study 04-2790-06). The results showed no neurofunctional effects in single oral doses ≥ 500 mg/Kg (unbound C_{max} 62.2 ng/mL at 4 hours post-dose).

In the general toxicity studies (study 04-2730-03), no effects related to central nervous system were reported (clinical signs, brain weights and macroscopic/microscopic examination of brain and spinal cord).

Cardiovascular System

Established *in vitro* and *in vivo* models were used to report the effects of dacomitinib on the cardiovascular function. In the hERG assay (study 04-2730-08), dacomitinib inhibited the current amplitude. The estimation of IC_{50} on hERG potassium channel was 1.58 μM (743 ng/mL). The value for IC_{50} of the main metabolite (PF-05199265) of dacomitinib (study 131218.QHJ) was estimated at 23.8 μM (10.9 μg/mL).

The potential cardiotoxicity of dacomitinib was also tested in the Purkinje fibres assay (study PF299804/IC/001/05). No statistically significant effect was observed in any of the parameters measured (resting membrane potential (baseline), action potential amplitude, maximum rate of depolarization (V_{max}), and action potential duration at 50% and 90% repolarization).

In addition to the *in vitro* assays, *in vivo* studies were also conducted. Accordingly, instrumented conscious Beagle dogs were dosed (oral gavage) with dacomitinib at 10 or 30 mg/Kg (study 04-2730-04). At 10 mg/Kg, emesis and loose stools were observed in PK animals. At the highest dose level ocular findings (reddened conjunctiva, closed eyes and corneal changes) were also reported. A statistically significant increase in mean systolic arterial blood pressure was observed at 30 mg/Kg, although it was attributed to a secondary effect due to emesis suffered from 3 animals. The systemic exposure measured at the highest dose level, i.e. 30 mg/Kg, was 45.1 ng/mL (unbound C_{max}) which corresponds to 26x the levels found (1.72 ng/mL) at the human recommended dose (45 mg/Kg QD).

A 7-day repeat dose toxicity study (study 04-2730-03, non GLP-compliant) was performed including also cardiovascular endpoints. The results indicated no treatment-related effects on heart rate, ECG or blood pressure. Cardiovascular assessment was also incorporated to the pivotal toxicity studies, 6-month and 9-month repeat-dose in rats and dogs, respectively. No cardiovascular effects were observed in terms of heart weights and further examinations of heart tissue.

Respiratory system

Two of the general toxicity studies incorporated respiratory system-related endpoints.

A pulmonary study in rat (study 04-2730-07) was conducted by the applicant. Pulmonary function (respiratory rate and tidal volume) was measured in animals dosed at 5, 50 or 500 mg/Kg (single dose, oral gavage) of dacomitinib. A slight increase in tidal volume was observed in the case of animals treated at 5 mg/Kg in the last stage of the measurement (97-120 minute postdose). No dose-response was observed, and consequently it was considered as not adverse. In the same study, one out of six animals dosed at the highest dose level (500 mg/Kg) showed decreased activity only immediately after dosing. No additional finding was reported.

In a non-pivotal 7-day repeat-dose toxicity study conducted in dogs, no effects were reported on respiratory rate up to a dose level of 30 mg/Kg/day. During the conductance of the non-clinical pivotal studies (6- and 9-months for rats and dogs respectively), no effects were observed in terms of microscopic and macroscopic examination of lung, trachea and bronchi.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were conducted.

2.3.3. Pharmacokinetics

Validated methods were used for quantification of dacomitinib in plasma of animals included in the pivotal non-clinical studies. Metabolites were not analysed in these studies. Characterised non-GLP assays were used for plasma analysis of dacomitinib and PF-05199265 in dedicated PK studies in rat, rabbit and dog.

Pharmacokinetic profile of dacomitinib was characterised after single and repeat dose administration of dacomitinib in rats, dogs and monkeys.

Table 9: Pharmacokinetic parameters of dacomitinib in rats, dogs and monkeys after single intravenous administration

Study ID	Species	Vehicle	Dose (mg/kg)	C_{5min} (ng/mL)	$t_{1/2}$ (h)	AUC_{inf} (ng.h/mL)	Cl (mL/min/Kg)	V_{ss} (L/Kg)
764-04427	Rat	Lactic acid	5	1540±581	9.8±0.7	2060±90.7	49.1±2.2	34.2±2.8
			25	10100±10700	16.7±1.5	12900±1420	32.6±3.4	39.8±5.1
764-04419	Dog		5	1150±131	15.9±1.5	3420±131	24.4±1.0	28.0±3.4
764-04420	Monkey		5	1090±431	5.7±0.5	1900±180	44.1±4.3	17.3±1.5

After a single oral dose, the half-life was approximately 20 hours in both rat and dog.

Repeat-dose pharmacokinetic parameters were calculated in 3-day studies (non-GLP) carried out in rats, rabbits and dogs.

Table 10: Pharmacokinetic parameters of dacomitinib and PF-05199265 in rats, rabbits and dogs after oral administration of dacomitinib for 3 days

Study ID	Species	Dose (mg/kg/day)	Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (ng.h/mL)
Dacomitinib						
PF-00299804-08Mar11-140632	Rat	1.0	1	11.2±2.8	3.3±1.2	143±32
			3	22.9±7.7	7.0±0.0	365±64
PF-002990804_09May13_095344	Rabbit	4.0	1	31.1±7.3	2.3±1.5	209±17
			3	43.4±15.0	1.7±0.6	285±84
PF-002990804_08Mar11_141511	Dog	0.1	1	1.22±0.73	7.0±0.0	20.2±11.7
			3	1.45±0.51	3.3±1.2	24.8±7.9
PF-05199265						
PF-00299804-08Mar11-140632	Rat	1.0	1	2.58±0.76	2.2±1.8	37.8±13.9
			3	3.92±1.17	7.0±0.0	66.5±6.8
PF-002990804_09May13_095344	Rabbit	4.0	1	(≤1ng/mL)	(≤1ng/mL)	(≤1ng/mL)
			3	(≤1ng/mL)	(≤1ng/mL)	(≤1ng/mL)
PF-002990804_08Mar11_141511	Dog	0.1	1	1.90±1.83	7.0±0.0	31.2±27.0
			3	2.54±1.19	3.3±1.2	47.3±26.1

Permeability and efflux transporters

Dacomitinib was shown to be a weak to moderate substrate for MDR1 and BCRP, with concentration dependent saturation of efflux. It was also reported to be an inhibitor of MDR1 and BCRP. In CaCo-2 assay it exhibited moderate bidirectional permeability.

Distribution

A wide distribution of dacomitinib, and possibly of metabolites, was demonstrated in rat. It was shown an extensive distribution in 33 tissues. Of interest with respect to the proposed indication, distribution to lungs was high in rats (23x blood concentration). Furthermore, data also demonstrated distribution of dacomitinib to brain, resulting in brain exposure levels similar to plasma exposure levels in mouse. This aspect indicated that dacomitinib may cross the blood brain barrier and reach therapeutic relevant concentrations in brain. In view of that brain metastases frequently occur in NSCLC patients, this finding is of clinical interest (see questions raised in pharmacological section). The high distribution to the uvea correlates with the identification of eye tissues as target for toxicity in both rat and dog. Both dacomitinib and its metabolite PF-05199265 were reported to be highly bound to plasma protein in the in vitro studies (> 95%), which was also consistent with clinical determinations. In human plasma, dacomitinib can bind to both human serum albumin (HAS) and α1-acid glycoprotein (AAG). No differences were observed into blood cells and plasma distribution. Dacomitinib was not identified as a potential substrate for hepatic transporters, OATP1B1 and OATP1B3. No placental transfer assay was conducted with dacomitinib.

Metabolism

The primary metabolic pathways for [14C]dacomitinib after incubation with human liver microsomes were N-oxidation of the piperidine ring to form dacomitinib N-oxide (M8) and deamination of the piperidine ring with subsequent cyclization to form a hydroxy metabolite (M6). These were also observed in rat, dog, and monkey liver microsomes. In addition, in dog and monkey liver microsomes, defluorination and subsequent aromatic hydroxylation to form a hydroxylated metabolite (M3) was also observed. In cryopreserved human hepatocytes, the primary metabolic pathways were similar to those observed after incubation with liver microsomes. Additional metabolites observed included M9 (hydroxylation followed by dehydrogenation at the piperidine ring to form an oxo-metabolite), M2 (glutathione conjugation followed by subsequent cleavage to cysteine conjugate), and M3. The primary metabolic pathways and metabolites in human hepatocytes were also present in hepatocytes from rat.

The major metabolic pathways of [^{14}C]dacomitinib in humans, rats and dogs involved oxidation and glutathione conjugation. From the oxidation pathway, M18/PF-05199265 (O-desmethylation) was identified as the major metabolite. This metabolite was found in humans (>10%) and also identified in rats and dogs. The applicant characterized the metabolite toxicity by comparing exposure levels in nonclinical species to those found in humans. However, the factor selected for the conversion between dacomitinib and PF-05199265 was obtained from a non-GLP 3-day repeat-dose study. *In vitro* metabolism was evaluated in liver microsomes and hepatocytes. In this regard, isoform CYP2D6 was identified to be responsible for the formation of the main metabolite described in human species. Dacomitinib was also identified to be a strong inhibitor of CYP2D6.

Excretion

The excretion of dacomitinib has been evaluated in rats (study DM2006-0299804-039), dogs (study DM2006-0299804-038 Amendment) and humans (study PF-00299804_13Sep10_183530). Faecal route was defined as the major route of excretion, with minimal urinary excretion. Excretion in milk was not evaluated.

Pharmacokinetic drug interactions

Potential actions of dacomitinib on CYP and UGT enzymes and drug transporters were shown by the applicant. Dacomitinib did not show time-dependent inactivation against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 in human liver microsomes and it is unlikely that at clinical doses dacomitinib inhibits CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A. However, dacomitinib showed to be inhibitor of CYP2D6. The main metabolite PF-05199265 had no in vitro effect on CYPs, except CYP2D6. Dacomitinib reflected a low likelihood of interaction with other drugs involving UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15. Although it may have the potential for DDI by inhibiting UGT1A1 at clinically relevant concentrations. Induction of CYP1A2, 2B6 and 3A4 was considered to be low at concentrations clinically relevant. Regarding the potential of dacomitinib for inhibit intestinal, hepatic and renal transporters, it showed a low potential to cause DDI by inhibiting P-gp (systemically), OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and BSEP at clinically relevant concentrations. However, dacomitinib may have the potential to inhibit BCRP (systemically according to the Draft FDA Guidance only and at the GI tract), P-gp (GI tract), and OCT1.

2.3.4. Toxicology

Single dose toxicity

Single dose toxic level of dacomitinib was established by the applicant at 50 and 30 mg/Kg for rats (study 04-2730-02, non-GLP) and dogs (study 04-2730-01, non-GLP), respectively. Animals given with higher dose levels showed adverse findings, such as emesis, skin lesions, loose/liquid stools, dehydration, corneal damage and decreases in body weight and food consumption.

Repeat dose toxicity

Table 11: Repeat dose toxicity studies with dacomitinib

Species/ strain/ Study ID (GLP)	Dose (mg/kg/day) Route (Vehicle)	n/sex /group	Duration	Major findings
Rat/Sprague Dawley Study number 04-2730-02 Non-GLP	0, 5, 50, 500 Oral (gavage) (0.5% methylcellulose in 0.1%) polysorbate 80/Solution)	5	13 days (low dose). 8 days (mid dose) 5 days (high dose).	Mortality: 4 males and 5 females died in the 500 mg/kg/day dose group. 1 male rat died in the 50 mg/kg/day dose group. ≥ 5 mg/kg/day: loose/liquid stools, stained fur, chromorhinorrhea, partially closed eyes, hunched stance, ↓ activity; ↑ WBC, neutrophils, monocytes, and/or platelets, ↓ haematocrit and haemoglobin (F), ↑ eosinophils (F), and/or reticulocytes; ↓total protein, albumin and globulin; enteropathy of small/large intestines, cecal changes; 1 female advanced renal papillary necrosis. ≥ 50 mg/kg/day: mortality, alopecia, ↓ food consumption, ↓ body weight, ↑ ALT, AST, BUN, and/or GGT; renal papillary necrosis, cortical and medullary tubular degeneration/dilation, squamous epithelial atrophy (vagina, oesophagus and forestomach), gastric ulcers of forestomach, hepatocellular vacuolation;

				Abnormal cecal contents, hepatic necrosis/vacuolation and enteropathy. Microscopic changes occurred in the gastrointestinal tract (oesophagus, stomach, small and large intestines), vagina, kidney, liver, bone marrow, and possibly lung. Myeloid hyperplasia. ↑ foamy alveolar macrophages <u>500 mg/kg/day</u>: pale liver, dehydration, hepatocellular necrosis **NOAEL: could not be established, < 5 mg/kg.**
Rat/Sprague Dawley Study number 04-2730-11 GLP	0, 0.5, 5, 20/10 Oral gavage, QD, 10 mL/kg 0.5% Methylcellulose (w/v) in deionized water / Solution	15 10 (0.5 dose group) 5 (reversibility) 6 (TK)	1 month 1-month recovery period.	<u>Mortality:</u> In the 20 mg/kg/day group, one main study male was euthanized moribund, one TK male died on day 14, the remainder of the main study males were euthanized on day 16, the remaining TK males group were euthanized on day 17. Two female rats in the main study 20/10 mg/kg/day group died on day 25 during the administration of the reduced dose of 10 mg/kg/day. The remaining females in the main study and TK groups were then euthanized on day 25. Of the two females from the 20/10 mg/kg/day dose group retained for the recovery phase, one died on Day 3 of the recovery phase while the other survived until the end of the recovery phase. In the 5 mg/kg/day group, two males were euthanized in moribund condition on day 22, and one TK female died at the end of the treatment phase on day 31. <u>0.5 mg/kg/day</u>**:** skin reddening (minimal). <u>≥ 5 mg/kg/day:</u> Microscopic findings in skin (8/11 males and 9/10 females); alopecia with serocellular crusting and pinpoint scabs most prominent around the nose and mouth, eyes, ventral neck, forelimbs, hind limbs, and over the dorsum of the back, reddened and oedematous skin; macroscopic changes in kidneys characterized by unilateral dilation of the renal pelvis, were associated with papillary necrosis . loose/liquid stools; ↑ platelets, neutrophils; ↓ RBC, haematocrit and haemoglobin; ↑reticulocytes, red blood cell distribution width; ↑neutrophils, monocytes, eosinophils, basophils and platelets ↑ ALT, AST, GGT, BUN, creatinine, and phosphorous; ↓ total protein, albumin, calcium, sodium, and chloride; ↑ phosphorous.: ↑ ratio of urine-specific enzymes, glucose, urinary white and/or red blood cells, and epithelial cells. ↑ urinary N-acetyl-β-D-glucosaminidase (NAG) and total protein ratios; ↑ specific gravity; ↓ white and/or red blood cells and (occasional) epithelial cells in the urine; changes in mean absolute and relative (to brain) weight ratios; ↑ mean absolute and relative kidney weights (1.1x control mean values), ↓ thymus weights (F) associated with lymphoid depletion; epithelial atrophy of multiples organs (oesophagus,

				forestomach, and cornea in both sexes; mammary gland in males; cervix and vagina in females), renal papillary necrosis, and skin inflammation. Myeloid hyperplasia with expansion of bone marrow myeloid precursor cells. Lymphoid depletion in the spleen, thymus and lymph nodes. <u>20/10 mg/kg/day:</u> ↓body weight, ↓food consumption, the left kidney of a single recovery male at 20 mg/kg/day had an abnormally shaped cortex that was depressed and shrunken; a change that was microscopically associated with fibrosis. **NOAEL: 0.5 mg/kg/day.**
Rat/Sprague Dawley Study number 6348-474 GLP	0, 0.2, 0.5, 2 Oral gavage, QD, 10 mL/kg 0.5% Methylcellulose (w/v) in reverse osmosis water / Solution	20 6 (toxicokinetics) 5 (recovery group)	26 weeks 1-month recovery period.	<u>All doses:</u> Skin effects: rough haircoat, skin sore/scab, scaly tail with open sores. This dermal toxicity was less severe in the lower dose groups, compared to that observed in animals in the 2 mg/kg/day group. <u>≥ 0.2 mg/kg/day:</u> ↑aspartate and alanine aminotransferase (F only, M from 0.5 mg/kg/day). <u>≥ 0.5 mg/kg/day:</u> Sporadic mean body weight changes. ↓kidney weight (mean, absolute and relative to body/brain weight) (M). ↓ mean corpuscular volume and absolute reticulocyte count. Microscopic findings were noted in the skin, kidney, tongue, esophagus, eye, cervix, vagina, and inguinal and mandibular lymph nodes. <u>≥ 2 mg/kg/day:</u> Two rats were killed (day 82) due to moribund condition with skin lesions and weight loss. All remaining toxicity and TK males except the recovery males were sacrificed on Day 90 due to severe dermal lesions. One female rat was sacrificed (day 96) of the dermal toxicity reasons. Four additional females (2 toxicity and 2 TK) in the 2 mg/kg/day group were sacrificed in a moribund condition (day 121 -127) due to similar skin lesions. Due to skin lesions (that did not respond to triple antibiotic with hydrocortisone) and body weight loss, all remaining toxicity females (except the recovery females), were sacrificed early on Day 131 of the dosing phase, while the recovery females completed a 12-week (85 days) recovery phase. Two control females died of accidental causes unrelated to dacomitinib administration. All other animals survived to their dosing phase or recovery phase scheduled sacrifice. ↓ body weight, ↓ RBC, haemoglobin, haematocrit; ↑ reticulocytes, platelet, white blood cell count, neutrophils, monocytes, eosinophils, basophils and platelets**,** fibrinogen and red blood cell distribution width. ↑ urea nitrogen, creatinine and inorganic phosphorus; ↓ total protein, albumin and albumin-to-globulin ratio; ↑ globulin; ↓ glucose,

				cholesterol, alkaline phosphatase, calcium and sodium. ↑ urine occult blood, urine sediment red blood cells, urine protein (reagent strip method; F), and urine protein-to-urine creatinine ratio (F) and decreased incidence of urine ketones (M). Crusted skin/subcutis, scaly skin/subcutis, large mandibular lymph nodes, and large renal pelvis (1 F). Microscopic observations were made in the skin, kidney, liver, tongue, esophagus, nonglandular stomach, eye, cervix, vagina, prostate, duodenum, ileum, mandibular and inguinal lymph nodes, and sternal and femoral bone marrow. **NOAEL: 0.2 mg/kg/day**
Dogs/Beagle Study number 04-2730-03 Non-GLP	0, 3, 10, 30 Oral (gavage) (0.5% methylcellulose in 0.1%) polysorbate 80/Solution)	2	7 days	≥ 3 mg/kg/day: salivation, loose and/or liquid stool, nasal discharge, decreased activity,emesis conjuctival reddening and hyperemia, partially closed eyes; ↑ neutrophils, monocytes and fibrinogen, ↓ albumin, total protein, calcium; erosions/ulcerations of cornea, oral mucosa, and renal pelvic epithelium; enterophathy. ≥ 10 mg/kg/day: reddening of oral mucosa and tongue, mouth malodour, multi-coloured stool; ↓ body weight, ↓ food consumption, ↑ red blood cell parameters, lesions of the paw, nose or hind limb 30 mg/kg/day: skin reddening **NOAEL: could not be established, < 3 mg/kg/day**
Dogs/beagle Study number 04-2730-05 GLP	0, 0.3, 1, 3 Oral gavage, QD, 1 mL/kg 0.5% Methylcellulose (w/v) in deionized water / Solution	3-5 2 (recovery group)	1 month 1-month recovery period.	≥ 0.3 mg/kg/day: Loose stools, Reddened mucous membrane and/or conjunctiva(e) ≥ 1 mg/kg/day: liquid stools, ophthalmic effects (corneal dye uptake and corneal oedema). Microscopic changes in the eye. ≥ 3 mg/kg/day: Reddened conjunctivae were accompanied by partially closed eyes, ocular discharge or opacity, and/or lacrimation (in some animals), skin reddening (1M), alopecia/fur thinning. Mouth malodour. Haematology findings ↑ neutrophils, monocytes, fibrinogen. Clinical chemistry findings: ↓ albumin and ↑ globulin. Macroscopic changes in the skin and large intestine. Microscopic changes in the skin and liver. **NOAEL**: **0.3 mg/kg/day**
Dogs/beagle Study number 6348-475 GLP	0, 0.03, 0.1, 1 Oral gavage, QD, 2 mL/kg 0.5% Methylcellulose (w/v) in reserve	6	9 months 3-month recovery period.	≥ 0.03 mg/kg/day: Liquid and nonformed faeces, clear eye discharge (F), red skin of the gums, muzzle, ears, and/or paws, excessive shedding, erythema (M) ≥ 0.1 mg/kg/day: clear eye discharge (M), alopecia (1F), red skin inside and/or on the ears (M), red gums and muzzle, erythema (F),

	osmosis water / Solution			minimal to slight vacuolation of the zona reticularis of the adrenal cortex (F) (non adverse). ≥ 1 mg/kg/day: squinting and red/swollen conjunctivae, elevated third eyelids; cloudy eye discharge, corneal deposits (F), corneal dystrophy (F) ↓ albumin and albumin to globulin ratio, ↑ fibrinogen (F). ↑ absolute and relative (to body and brain weights) adrenal weights (F); ↑ mean absolute and relative adrenal gland weights correlated with the dacomitinib-related microscopic observation of vacuolation of the zona reticularis of the adrenal gland. Minimal to slight attenuation of the corneal epithelium, central corneal ulceration (1F), minimal to slight atrophy of the mandibular salivary glands, minimal erosion/ulceration of the mucosa of the tongue (M) **NOAEL: 0.1 mg/kg/day**

Based on the clinical findings described in the repeated dose toxicity studies, NOAEL values were established at 0.2 mg/Kg/day for rats and 0.3 mg/Kg/day for dogs.

Genotoxicity

The complete battery of test for genotoxicity (GLP compliant) were conducted with dacomitinib (Table 15). It included a bacterial reverse mutation assay (study number 04-2730-10), a chromosomal aberration assay (study number 04-2730-09) and a micronucleus assay in rats (study number 06GR304).

Table 12: Genotoxicity studies conducted with dacomitinib

Study	Species	Doses (mg/Kg/day)	GLP	Study number
Bacterial mutation	Salmonella typhimurium (TA1535, TA1537, TA98) and Escherichia coli (WP2uvrA pKM101)	0.005-5 mg/plate	Yes	04-2730-10
Chromosome aberration	Human lymphocytes	0.64-2.0 µg/mL 1.0-4.0 µg/mL	Yes	04-2730-09
Micronucleus assay	Rat/Sprague-Dawley	0, 5, 250, 2000	Yes	06GR304

In the bacterial reverse mutation assay, performed in the presence and absence of metabolic activation, and taking into consideration cytotoxicity and insoluble limitations. No mutagenicity was observed.

DNA damage was evaluated in human peripheral lymphocytes extracted from healthy donors and cultured. The results indicated that dacomitinib was weakly clastogenic in the *in vitro* human lymphocyte chromosome aberration assay.

The *in vivo* potential chromosomal damage of dacomitinib was evaluated in the micronucleus assay in rats. Dacomitinib did not induce chromosome damage as evidenced by the absence of micronucleus formation in the bone marrow cells of male or female rats when tested up to a maximum tolerated dose of 2000 mg/kg/day.

Carcinogenicity

No carcinogenicity studies were conducted with dacomitinib.

Reproduction Toxicity

No fertility and early embryonic development studies were conducted with dacomitinib.

In repeat-dose toxicity studies with dacomitinib, effects on reproductive organs were observed in female rats given approximately 0.3 times the unbound AUC at the recommended human dose (for 6 months) and were limited to reversible epithelial atrophy in the cervix and vagina. There was no effect on reproductive organs in male rats given ≤ 2 mg/kg/day for 6 months (approximately 1.1 times the unbound AUC at the recommended human dose), or in dogs given ≤ 1 mg/kg/day for 9 months (approximately 0.3 times the unbound AUC at the recommended human dose) (see section 5.3 of the SmPC).

Pregnant female rats were dosed with dacomitinib from gestation day 6 to 17 (study 08GR326). Selected doses were 0.2, 1 and 5 mg/Kg/day. A toxicokinetic group with similar dosing regimen was also included in the study (results are shown in Table 10). Maternal toxicity (clinical findings, reduced body weight, body weight gain and food consumption) was confirmed at 5 mg/Kg/day. The applicant reported no significant foetal external, visceral or skeletal malformations at 0.2 and 1 mg/Kg/day dose levels. It established the maternal and developmental NOAEL at 1 mg/Kg/day (unbound AUC_{24} and C_{max} of 9.55 ng.h/mL and 0.66 ng/mL, respectively on gestation day 17).

In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses up to approximately 2.4 times and 0.3 times, respectively, the unbound AUC at the recommended human dose during the period of organogenesis. Maternal body weight gain and food intake were lower in pregnant rats and rabbits. The maternally toxic dose was foetotoxic in rats, resulting in reduced foetal body weights and higher incidence of unossified metatarsals (see section 5.3 of the SmPC).

Maternal toxicity was demonstrated at 4.0 mg/kg/day by a reduction in body weight gain and food consumption. There were no treatment-related effects on caesarean section observations or foetal body weights, external, visceral, or skeletal malformations or variations. The NOAEL for maternal toxicity was 1.5 mg/kg (C_{max} and $AUC_{[0-24]}$ of 11.8 ng/mL and 139 ng.h/mL, respectively). Based on the absence of treatment-related effects on embryo-foetal viability, growth, or morphological development, the NOAEL for developmental toxicity was 4.0 mg/kg (C_{max} and $AUC_{[0-24]}$ of 26.6 ng/mL and 352 ng·h/mL, respectively).

No pre- and postnatal development studies were conducted with dacomitinib.

Toxicokinetic data

Toxicokinetic data were obtained from repeated dose and pivotal toxicity studies performed in rats and dogs, reprotoxicity studies in rats and rabbits; and in a rat micronucleus assay. Phototoxicity study also incorporated a toxicokinetic evaluation.

When compared plasma concentration at the last day of the study in rats, i.e. day 30 or 180, with the values obtained at day 1 postdose, it was observed accumulation in plasma after repeat dose administration. However, this effect was not observed when comparison is done between days 90 and 180 in the chronic repeat dose.

Only one toxicokinetic study in rabbits is shown (study 08GR498), which corresponded to reprotoxicity assessment of dacomitinib. In this study, a dose proportional increase of systemic exposure, at gestation day 19, was observed.

Three toxicokinetic studies performed in Beagle dogs were reported by theapplicant, related to the absorption process of dacomitinib. It was formulated with 0.5% methylcellulose. It is noted that a slight accumulation was observed after comparison of C_{max} and AUC values of day 1 to day 30 in the 1-month toxicity study (study

04-2730-05); and day 1 vs. day 90 or day 272 (study 6348-475) in the 9-month toxicity study. As described in the chronic toxicity conducted in rats, no accumulation was observed between days 90 and 272 in dogs.

Local Tolerance

Intravenous and perivenous routes of administration were analysed (study 12LJ047) in rabbits. Dacomitinib (0.2 or 1 mg/mL) was well-tolerated by both routes. Redness and discoloration was observed 4 days after dosing, although no difference was reported with saline, vehicle or treated groups.

Other toxicity studies

The applicant reported twenty-four impurities identified from the drug substance. They were evaluated for potential mutagenicity *in vitro*. One degradation product occurred after storage of the drug product was also identified (PF-03702008).

Impurities PF-00818977-01, PF-01458762, PF-01678282, PF-05188294, PF-05201372 and PF-05226216 were tested in a bacterial mutagenicity plate assay. The results of these studies indicated that PF-00818977, PF-01458762, PF-05201372 and PF-05226216 were not considered to be bacterial mutagens, while PF-01678282 and PF-05188294 were considered to be bacterial mutagens.

Other impurities, PF-01038584, PF-05198214, PF-06238417, PF-06243812 and PF-06675793 were evaluated in an exploratory bacterial mutagenicity plate assay. PF-01395646, PF-01421674, PF-01731369 and PF-03949619 were tested for mutagenic potential using only *S. typhimurium* strains TA98 and TA100. PF-01731369, PF-03949619 and PF-06675793 were not considered to be bacterial mutagens. PF-01038584, PF-01395646, PF-01421674, PF-05198214, PF-06238417 and PF-06243812 were considered to be bacterial mutagens.

The last group of impurities (PF-00219077, PF-02432182, PF-05188291, PF-05234782, PF-06239789, PF-06239795, PF-06272982, PF-06466351 and PF-06470418) was tested for mutagenic potential using *S. typhimurium* strains TA98lux and TA100lux. PF-00219077 and PF-06466351 were not considered to be bacterial mutagens with TA98lux or TA100lux. PF-02432182, PF-05188291, PF-05234782, PF-06239789, PF-06239795, PF-06272982 and PF-06470418 were considered to be bacterial mutagens.

The metabolite M6 (PF-03702008) was detected both in rat and dog after dacomitinib administration. On the contrary, it was not formed in humans.

Complementary to other toxicity studies, the applicant reported the potential haemolytic and phototoxicity effects of dacomitinib. After the analysis of the results, it resulted that dacomitinib did not cause haemolysis at a concentration of 0.2 mg/mL neither phototoxicity up to a single dose level of 100 mg/mL.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant submitted an Environmental Risk Assessment for dacomitinib, in accordance with CHMP guidance EMEA/CHMP/SWP/4447/00 (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use).

Table 13: Summary of main study results

Substance (INN/Invented Name): Dacomitinib/Vizimpro					
CAS-number (if available): 1110813-31-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	pH 4 log D_{ow} = 0.524 pH 7 log D_{ow} = 3.92 pH 9 log D_{ow} = 5.04			Potential PBT **(Y)**
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	5.04 (pH 9)			**B (>4.5)**
	BCF (OECD305)	2051 (whole fish) 3162 (lipid, growth corrected)			**B (>2000)**
Persistence	DT_{50}	>120 days in soil			**P**
Toxicity	NOEC	0.0012 mg/L, in the most sensitive species (fish)			**T (<0.01mg/L)**
PBT-statement :	**The compound is considered as a PBT substance**				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (prevalence)	0.0068	μg/L			< 0.01 threshold No
Other concerns (e.g. chemical class)	NA	NA			NA
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	**Sludge Sorption Coefficient** Activated sludge, Denton WWTF: **Kd** 4861; **Log K_{oc}** 4.11 Activated sludge, Cambridge WWTF: **Kd** 5229; **Log K_{oc}** 4.22 Geometric mean: **Kd** 5042; **Log K_{oc}** 4.17 **Soil Sorption Coefficient** Clay Loam TB-PF Soil: **Kd** 9142; **Log K_{oc}** 5.34 Sandy Soil (Speyer#2.1): **Kd** 1556; **Log K_{oc}** 5.31 Geometric mean: **Kd** 3772; **Log K_{oc}** 5.33 **Sediment Sorption Coefficient** Silt Loam Sediment: **Kd** 11471; **Log K_{oc}** 5.51 Sandy Sediment (direct): **Kd** 3082; **Log K_{oc}** 6.19 Sandy Sediment (indirect): **Kd** 5014; **Log K_{oc}** 6.40 Geometric mean: **Kd** 5617; **Log K_{oc}** 6.03			Based on the sludge K_d of 5042, the fraction removed onto sludge solids was **0.454 or 45.4%** It calculated as follows: [0.165(Kd)]/[(0.165)(Kd) + (1000)] where 0.165 represents the grams of sludge wasted per 1000 grams of WWTF aqueous effluent.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Brandywine Creek/Choptank River $DT_{50,\ water}$ = 1.5-1.6 days $DT_{50,\ test\ system}$ = 22.2-102 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (72h)	OECD 201	NOEC (biomass)	0.022	mg/L	*Pseudokirchneriella subcapitata*
		NOEC (growth)	0.054		
		LEC50 (biomass)	0.079		
		LEC50 (growth)	0.219		
Daphnia sp. Reproduction Test (21 days)	OECD 211	NOEC	0.275	mg/L	
		LOEC	0.565		

Fish, Early Life Stage Toxicity Test (early lifecycle)	OECD 210	NOEC LOEC	0.0012 0.003	mg/L	Fathead Minnow (*Pimephales promelas*)
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT_{50}	>120 >120 >120 >120	Days	Loamy sand Sandy loam Clay loam Clay loam
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	% inhibition	-7.0 % -0.6 % -4.3 % -1.0 %	1 mg/kg 10 mg/kg 1 mg/kg 10 mg/kg	Day 14 Day 28
Terrestrial Plants, Growth Test	OECD 208	NOEC LOEC NOEC LOEC NOEC LOEC NOEC LOEC NOEC LOEC NOEC LOEC	10 >10 10 >10 10 >10 10 >10 10 >10 4 >4	mg/kg	Onion (*Allium cepa*) Ryegrass (*Lolium perenne*) Turnip (*Brassica rapa*) Cucumber (*Cucumis sativa*) Lettuce (*Latuca sativa*) Tomato (*Lycopersi. esculentum*)
Earthworm, Acute Toxicity Tests (14 days)	OECD 207	NOEC LOEC	10 >10	mg/kg	
Collembola, Reproduction Test (28 days)	ISO 11267/ OECD232	NOEC LOEC	2.4 11	mg/kg	
Sediment dwelling organism	OECD 218	NOEC LOEC	110 211	mg/kg	*Chironomus riparius*
Sludge die away – 28 day sludge biodegradation	OECD 314B	Ultimate biodegradation (CO_2 evolution) 0.49% in 28 days 52.49% remaining with solids at Day 28 Loss of parent DT50 is 407.7 hours (17 days)			

2.3.6. Discussion on non-clinical aspects

Dacomitinib non-clinical development was performed in accordance with current guidelines and scientific requirements.

The non-clinical aspects of dacomitinib were assessed in *in vitro* biochemical and cellular assays and *in vivo* xenograft, safety pharmacology, pharmacokinetic, and toxicity models. *In vitro* studies showed that dacomitinib inhibited the activity of HER family members and mutant variants. *In vivo* studies presented an antitumour activity of dacomitinib in xenograft models. According to the *in vitro* data provided (Cross *et al.*, 2014; Schwartz *et al.*, 2014), dacomitinib showed a very similar profile to afatinib (a second generation TKI), having a more potent effect than gefinitib and erlotinib (first generation TKI) in terms of EGFR phosphorylation. Differences with osimertinib (third generation TKI) were also observed on proliferative efficacy, although potency was dependent on the EGFR cell line analysed (Cross et al., 2014 and Schwartz et al., 2014). In these studies, information on exposure levels in the xenograft models was however only presented for one model (SKOV3) and the study designs hampered the possibility to evaluate the effective dacomitinib exposure level in vivo. Thus, evaluation of the optimal biological exposure should be based on clinical data. Although the applicant has described the pharmacological actions of dacomitinib, it should be considered that other EGFR-TKIs develop resistance after regular use, and understanding the resistance mechanisms to dacomitinib is currently limited. Besides, NSCLC is commonly associated to brain metastases. In this regard, it was reported (Endersby *et al.*, 2015 and Zahonero *et al.*, 2015) potential pharmacological actions of dacomitinib on preclinical models of glioblastoma, medulloblastoma and pineoblastoma.

The secondary and safety pharmacology studies conducted with dacomitinib, reported no relevant concerns. No separate *in vivo* safety pharmacology study has been performed with the human main metabolite PF-05199265. This is acceptable since the metabolite is formed by both rats and dogs and can be evaluated in repeat dose toxicity studies, although the method used for estimation of exposure of PF-05199265 has been questioned. However and taking into consideration that dacomitinib falls under the scope of ICH S9, the evidence that the metabolite has been detected in animal species used for toxicity testing is sufficient.

The nonclinical PK profile of dacomitinib was evaluated mainly in rats and dogs. The characterisation included ADME properties, as well as correspondent metabolism (plasma protein binding properties, partitioning into red blood cells, hepatocyte uptake properties and drug metabolism). Results showed that while the accumulation ratios in dogs in most cases actually were in line with the estimated value based on half-life and dose interval, the accumulation ratios in rats were in general greater than what was predicted. A possibility of saturable clearance process(es) in rats following repeat dose administration cannot be excluded. It is however noted that although toxicokinetic data from the 6 month repeat dose toxicity study in rat (6348-474) indicated drug accumulation during the first 90 days of the dosing phase, exposure on Day 180 was similar to that on Day 90. This indicated that the Day 180 exposure levels used for interspecies comparison were representative of a steady state condition. Quantifiable concentrations of the main metabolite M18/PF-05199265 (O-desmethylation) were obtained in rats and dogs, indicating that this metabolic pathway was present in both species. It is also observed that the dacomitinib exposure levels determined after 11 days of treatment in the EFD-study in rats (6348-475) support the assumption that much of the parent drug accumulation in rat may have occurred after only a few days of dacomitinib dose administration. Toxicokinetic data from repeat dose toxicity studies in dogs indicate a stable accumulation ratio for the parent compound over time. Taken together, the lack of information on exposure to important human metabolite(s) in pivotal repeat dose toxicity studies is considered a deficiency in the dossier. However, and given that this MAA is considered to fall under the scope of ICH S9; the evidence that the M18 metabolite (PF-05199265) indeed has been detected in animal species used for toxicity testing is sufficient.

General toxicity, genotoxicity, embryo-foetal development, potential haemolysis, and phototoxicity studies were conducted.

In oral repeated-dose toxicity studies for up to 6 months in rats and 9 months in dogs, the primary toxicities were identified in the skin/hair (dermal changes in rats and dogs, atrophy/dysplasia of hair follicles in rats), kidney (papillary necrosis often accompanied by tubular degeneration, regeneration, dilatation and/or atrophy and changes in urinary markers indicative of renal injury in rats, erosion or ulceration of the pelvic epithelium with associated inflammation without changes indicative of renal dysfunction in dogs), eye (cornea epithelial atrophy in rats and dogs, corneal ulcers/erosions with red/swollen conjunctiva(e), conjunctivitis, elevated third eyelid, increased squinting, partially closed eyes, lacrimation, and/or ocular discharge in dogs), and digestive system (enteropathy in rats and dogs, erosions/ulcers of the mouth with reddened mucous membranes in dogs), and atrophy of epithelial cells of other organs in rats. In addition, hepatocellular necrosis with transaminase increases and hepatocellular vacuolation were observed in rats only. These effects were reversible with the exception of hair follicles and kidney changes. All effects occurred at systemic exposure below that in humans at the recommended dose of 45 mg QD (see section 5.3 of the SmPC and RMP).

Dacomitinib was tested using a series of genetic toxicology assays. Dacomitinib was not mutagenic in a bacterial reverse mutation (Ames) assay, and not clastogenic or aneugenic in the *in vivo* bone marrow micronucleus assay in male and female rats. Dacomitinib was clastogenic in the *in vitro* human lymphocyte chromosome aberration assay at cytotoxic concentrations. Dacomitinib is not directly reactive toward DNA as evidenced by the negative response in the bacterial reverse mutation assay and did not induce chromosome damage in a bone

marrow micronucleus assay at concentrations up to approximately 60-70 times the unbound AUC or C_{max} at the recommended human dose. Dacomitinib is not expected to be genotoxic at clinically relevant exposure concentrations.

Carcinogenicity studies have not been performed with dacomitinib which is considered acceptable in accordance with ICH S9.

Fertility studies have not been performed with dacomitinib. In repeat-dose toxicity studies with dacomitinib, effects on reproductive organs were observed in female rats given approximately 0.3 times the unbound AUC at the recommended human dose (for 6 months) and were limited to reversible epithelial atrophy in the cervix and vagina.

There was no effect on reproductive organs in male rats given ≤ 2 mg/kg/day for 6 months (approximately 1.1 times the unbound AUC at the recommended human dose), or in dogs given ≤ 1 mg/kg/day for 9 months (approximately 0.3 times the unbound AUC at the recommended human dose).

Developmental toxicity effects were reported. In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses up to approximately 2.4 times and 0.3 times, respectively, the unbound AUC at the recommended human dose during the period of organogenesis. Maternal body weight gain and food intake were lower in pregnant rats and rabbits. The maternally toxic dose was foetotoxic in rats, resulting in reduced foetal body weights and higher incidence of unossified metatarsals (see sections 4.6 and 5.3 of the SmPC).

A phototoxicity study with dacomitinib in pigmented rats showed no phototoxicity potential.

Environmental risk assessment studies have shown that dacomitinib has the potential to be very persistent, bioaccumulative and toxic to the environment (see sections 5.3 and 6.6 of the SmPC).

2.3.7. Conclusion on the non-clinical aspects

The non-clinical pharmacodynamics, pharmacokinetic and toxicological aspects of dacomitinib have been assessed. From a non-clinical point of view, data submitted support the use of dacomitinib for the treatment of adult patients with locally advanced or metastatic NSCLC with epidermal growth factor receptor-activating mutations.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 14: Summary of included studies

Protocol	Phase	Subjects	N	PK Sampling
A7471001	1	Patients with solid tumors	121	Serial and Sparse
A7471002	2	Patients with advanced NSCLC	66	Serial and Sparse
A7471003	1/2	Patients with advanced NSCLC	55	Serial and Sparse
A7471005	1	Patients with solid tumors	13	Serial and Sparse
A7471009	3	Patients with NSCLC	878 Total (439 dacomitinib Arm)	Sparse
A7471014	1	Patients with solid tumors	16	Serial
A7471015	1	HVs	24	Serial
A7471017	2	Patients with NSCLC	89	Sparse
A7471018	1	HVs with or without normal hepatic function	8	Serial
A7471020	1	HVs	6	Serial
A7471021	1	HVs	14	Serial
A7471022	1	HVs	32	Serial
A7471027	2	Patients with metastatic squamous cell cancer of the head and neck	69	Serial and Sparse
A7471028	2	Patients with NSCLC	188 Total (94 dacomitinib Arm)	Sparse
A7471031	1b	Patients with NSCLC	22	Sparse
A7471039	1	HVs	14	Serial
A7471042	2	Patients with NSCLC	236	Serial and Sparse
A7471046	1	HVs	14	Serial
A7471047	2	Patients with NSCLC	41	Serial and Sparse
A7471050	3	Patients with NSCLC	452 Total (227 dacomitinib Arm)	Serial and Sparse
A7471051	1	HVs	14	Serial

HVs=healthy volunteers; N=number of subjects enrolled; NSCLC=non-small cell lung cancer; PK=pharmacokinetic.

Table 15: Summary of dacomitinib studies to support the proposed indication

Study methods	Pivotal Study	Key Supportive Study	Supportive Studies		
	A7471050	A7471017 Cohort A[a]	A7471009	A7471028	A7471011
Development Phase	Phase 3	Phase 2	Phase 3	Phase 2	Phase 3
Design	Open-label, randomized active-controlled	Open-label, single-arm	Double-blind, randomized active-controlled	Open-label, randomized active-controlled	Double-blind, randomized placebo-controlled

Study methods	Pivotal Study	Key Supportive Study	Supportive Studies		
	A7471050	A7471017 Cohort A[a]	A7471009	A7471028	A7471011
Characteristics of advanced NSCLC (including prior treatment, if applicable)	• Newly diagnosed Stage IIIB/IV or recurrent disease • EGFR-activating mutations • No prior systemic chemo-therapy for advanced disease	• Stage IIIB-IV • EGFR-activating mutations, or patients who were pheno-typically likely to have tumours with EGFR-activating mutations • No prior systemic chemo-therapy for advanced disease	• Locally advanced or metastatic (Stage III-IV) • At least 1 prior chemo-therapy	• Stage IIIB-IV • 1 or 2 prior chemo-therapy regimens	• Stage IIIB-IV • Up to 3 prior chemo-therapy regimens and at least 1 therapy with erlotinib or gefitinib
Dacomitinib Starting Dose QD	45 mg	45 mg or 30 mg [b]	45 mg	45 mg	45 mg
Comparator Dose QD	Gefitinib 250 mg	None	Erlotinib 150 mg	Erlotinib 150 mg	Placebo
Study Dates (FPFV-LPLV)	09 May 2013-Not reached yet[c]	11 March 2009-30 April 2015	16 June 2011-14 September 2015	10 November 2008-15 August 2014	23 December 2009-18 June 2015
Number of Patients in ITT population[d]	Dacomitinib 227 Gefitinib 225	Dacomitinib 89[b]	Dacomitinib 439 Erlotinib 439	Dacomitinib 94 Erlotinib 94	Dacomitinib 480 Placebo 240
Number of patients with NSCLC with EGFR-activating mutations in ITT population	Dacomitinib 227 Gefitinib 225	Dacomitinib 45[e]	Dacomitinib 37 Erlotinib 39	Dacomitinib 16 Erlotinib 9	Dacomitinib 83 Placebo 52

Abbreviations: CSR=clinical study report; EGFR=epidermal growth factor receptor; FPFV=date of first patient first visit; HER=human epidermal growth factor receptor; ITT=intent-to-treat; LPLV=date of last patient last visit; NSCLC=non-small cell lung cancer; QD=once daily; sCSR=supplemental clinical study report.

a. Cohort B explored the utility of dacomitinib in HER2-amplified or HER2-mutated NSCLC in any line of therapy, and thus the results for this cohort are not summarized in this SCE, as they are not relevant to the proposed indication.

b. Study 1017 Cohort A had two dose groups: (1) dacomitinib at a starting dose of 45 mg (N=59) and (2) dacomitinib at a starting dose of 30 mg, increased to 45 mg after 2 cycles if the 30-mg dose was tolerated (N=30). Numbers of patients shown in this table are for both dose groups combined.

c. Study 1050 is completed, ie, the final analysis of the primary endpoint has been completed and a CSRs is available. At the time of this submission, it is anticipated that some patients in pivotal Study 1050 will still be receiving treatment and/or be in follow-up for secondary endpoints including overall survival (OS) or safety.

d. Number enrolled or randomized.

e. Of the 45 patients with NSCLC with EGFR-activating mutations in Study 1017 Cohort A, 16 were in the 30-mg starting dose group and 29 were in the 45-mg starting dose group.

2.4.2. Pharmacokinetics

Clinical pharmacokinetic data were obtained from 21 clinical studies in 143 healthy volunteers and 1238 patients with various solid tumours. In addition, 25 *in vitro* studies were conducted on human biomaterials to characterize the pharmacokinetics of dacomitinib. Dacomitinib and the main metabolite PF-05199265 were determined in plasma and urine samples using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS).

Absorption

The drug substance, dacomitinib monohydrate, is classified as a BCS class II drug, which means it is highly permeable and poorly soluble. *In vitro* studies indicate that dacomitinib is passively absorbed and is a weak to

moderate substrate of the intestinal efflux transporters P-glycoprotein (P-gp) and BCRP. Concentration dependent efflux was observed over the studied concentration range (0.29-10.42 µM).

In vivo, absorption was slow. Following the administration of a single 45 mg dose of dacomitinib tablets, the mean oral bioavailability of dacomitinib is 80% (90% CI: 74.9, 85.5) compared to intravenous administration, with C_{max} occurring 5 to 6 hours after oral dosing. Following dacomitinib 45 mg daily dosing, steady-state was reached within 14 days (see section 5.2 of the SmPC).

In a formal food effect study (Study 1015), after administration of dacomitinib to healthy subjects who had consumed a high-fat, high-calorie breakfast, the ratios of adjusted geometric means for AUCinf and Cmax were 1.14 and 1.24, respectively, compared to the fasted state. The 90% CI for AUCinf was within established bioequivalence criteria (80% to 125%).

Distribution

In plasma, dacomitinib binds to albumin and α_1-acid glycoprotein and the fraction unbound is approximately 2% *in vitro* and *ex vivo* in healthy volunteers. *In vitro* data suggest approximately equal partitioning between human plasma and blood cells (blood:plasma ratio of 1.08).

Dacomitinib distributes extensively outside plasma with a mean steady state volume of distribution of 1889 L (18% CV) following intravenous administration. The distribution to specific tissues in humans is not known. Dacomitinib appears not to be a substrate of the cellular transport proteins OATP1B1 and OATP1B3 *in vitro*. It is not known whether dacomitinib is a substrate of other transporters involved in distribution.

Elimination

- **Excretion**

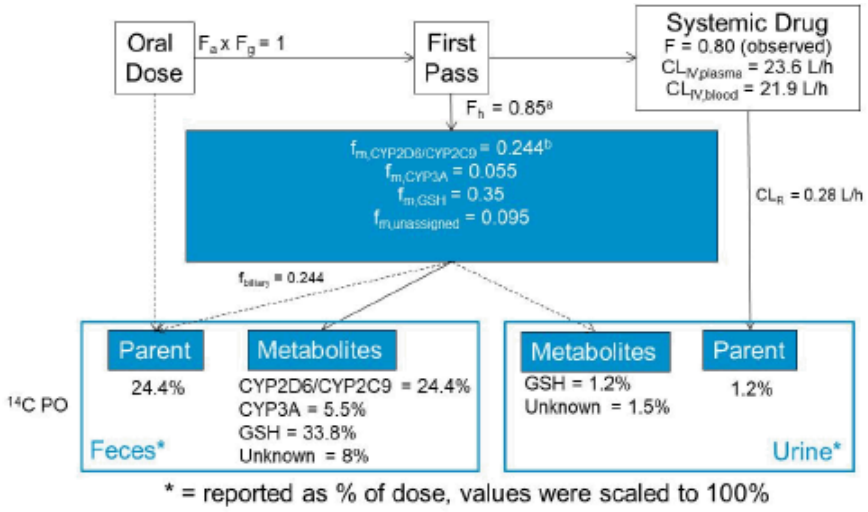
In a mass balance study (A7471020) in 6 healthy male subjects given a single-oral dose of [^{14}C] radiolabeled dacomitinib, a median of 82% of the total administered radioactivity was recovered in 552 hours; faeces (79% of dose) was the major route of excretion, with 3% of the dose recovered in urine, of which <1% of the administered dose was unchanged dacomitinib (see section 5.2 of the SmPC). The extent of biliary excretion has not been studied.

- **Metabolism**

Dacomitinib undergoes oxidation and glutathione conjugation as the major metabolic pathways. Following oral administration of a single 45-mg dose of [^{14}C] dacomitinib (study A7471020), the most abundant circulating metabolite was O-desmethyl dacomitinib. This metabolite exhibited *in vitro* pharmacologic activity that was similar to that of dacomitinib in the *in vitro* biochemical assays. In faeces, dacomitinib, O-desmethyl dacomitinib, a cysteine conjugate of dacomitinib, and a mono-oxygenated metabolite of dacomitinib were the major drug-related components. *In vitro* studies indicated that CYP2D6 was the major CYP isozyme involved in the formation of O-desmethyl dacomitinib, while CYP3A4 contributed to the formation of other minor oxidative metabolites. O-desmethyl dacomitinib accounted for 16% of human plasma radioactivity and is formed mainly by CYP2D6 and to a lesser extent CYP2C9 (see section 5.2 of the SmPC).

The quantitative relative contributions of the elimination pathways to the total clearance of dacomitinib is not known.

Based on the available *in vitro* data, single dose *in vivo* data and a PBPK model (submitted during the procedure), the following quantitative relative contribution of involved enzymes/pathways to the total clearance of dacomitinib (scaled to 100%, based on 82% recovery in the mass balance study) has been proposed:



$CL_{IV,blood}$ = IV blood clearance; $CL_{IV,plasma}$ = IV plasma clearance; CL_R = Renal clearance; CYP = Cytochrome P450; F = Bioavailability; F_a = Fraction of dose absorbed into enterocytes from intestinal lumen; F_g = Fraction of drug absorbed into enterocytes that escapes intestinal metabolism; F_h = Fraction hepatic metabolism; $f_{biliary}$ = Fraction excreted in bile; f_m = Fraction metabolized; GSH = Glutathione; IV = Intravenous; PO = Oral.
a. Assumes GSH component is extrahepatic (see Section 3.1.1.2).
b. See Section 3.1.1.2 and Section 3.1.1.5 for estimation of individual f_m for CYP2C9 and CYP2D6.

Figure 6: Dacomitinib metabolism and disposition

The PBPK model results indicated that following oral administration of dacomitinib (45 mg QD), the Day 1 dynamic (time-variant) fm for CYP2D6 and CYP3A to dacomitinib clearance were 20% and 6.5%, respectively, in CYP2D6 EM subjects, and were 0% and 8.3%, respectively, in CYP2D6 PM subjects. The dynamic fm for CYP2D6 and CYP3A4 attributed to dacomitinib clearance at steady state were 13.9% and 7%, respectively, in CYP2D6 EM subjects, and 0% and 8.3%, respectively, in CYP2D6 PM subjects. The elimination half-life in patients ranged from 54 to 80 hours. Dacomitinib showed a clearance of around 20.0 L/hr with a 32% inter-individual variability (CV).

PF-05199265 has inhibitory and selectivity profile similar to dacomitinib. However, the contribution of PF-05199265 to overall efficacy and safety after multiple dosing is expected to be minimal as the ratio to dacomitinib is low and the plasma fraction unbound is <0.01. The remaining metabolites were present in low contributions and are not expected to contribute to the pharmacological activity.

In CYP2D6 poor metabolizers (n=6), dacomitinib exposure (AUC_{tau}) was 52% higher than in extensive metabolizers (n=33). In ultra-rapid metabolizers (n=3), exposure was 23% lower than in extensive metabolizers.

- **Pharmacokinetics of metabolites**

The PK analysis of PF-05199265 was based on pooled data (N=963) from 6 clinical trials in patients with advanced NSCLC and 8 clinical pharmacology studies in healthy subjects.

The population PK analysis of PF-05199265 was characterized using a 1-compartment PK model with the input rate of PF-05199265 formation as the individual post-hoc estimates of dacomitinib elimination rate.

The final PF-05199265 PK model included a parameter to account for a decrease on the input rate of formation when dacomitinib was given in combination with a CYP2D6 inhibitor. The addition of this parameter indicated that in the presence of a CYP2D6 inhibitor the formation of metabolite is reduced 84% relative to the absence of concomitant use of CYP2D6 inhibitors, this observation is in agreement with the conclusions derived from Study A7471021. Furthermore, when a covariate on apparent metabolite clearance (CLm/F) after multiple dacomitinib dose administration was incorporated into the model indicating that after multiple daily doses of dacomitinib, the apparent clearance of PF-05199265 is increased by 106%.

Table 16: PF-05199265 Final model PK parameters summary

Parameter	Estimate	RSE (%)	Shrinkage (%)
$\theta_{CL_m/F}$ (L/hr)	80.360	8.346	6.14
$\sigma_{prop.error}$	0.533	3.570	9.67
$\theta_{F_m \text{ on input rate}}$	0.156	10.919	-
$\theta_{MD \text{ on } CL_m}$	1.057	17.321	-
IIV	Value	CV(%)	
$\omega^2_{CL_m/F}$	0.749	86.562	-
OFV_{IMP}	913.862	-	-

ePharmacology artifact ID RA13747584. Line 1 substituted.
IIV=inter-individual variability; CLm=metabolite clearance; F_m=fraction of dacomitinib converted to PF-05199265; MD=multiple dose; PK=pharmacokinetic; h=hour; L=liter; OFV=objective function value; RSE= relative standard error; ω^2=variance of the IIV.

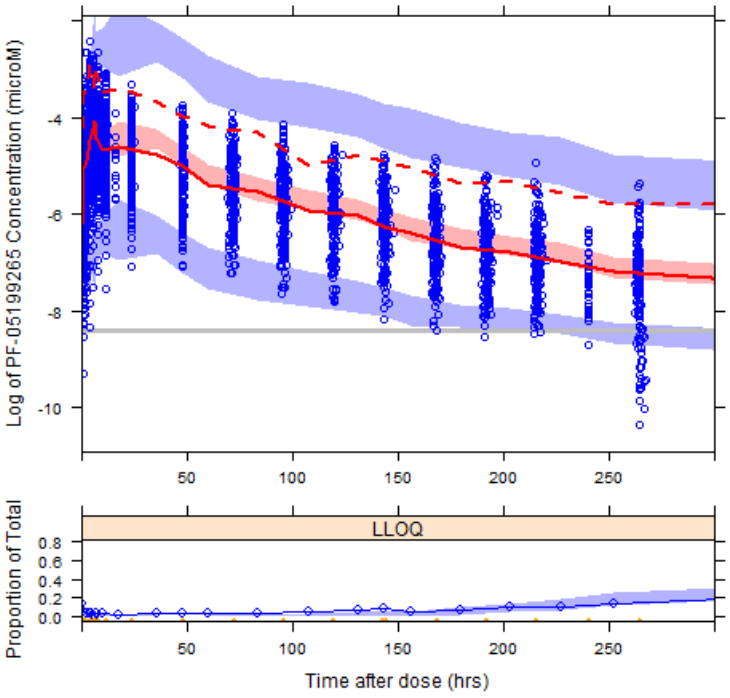


Figure 7: Visual Predictive Check for PF-05199265 Observations in Subjects After Dacomitinib Single Dose Administration

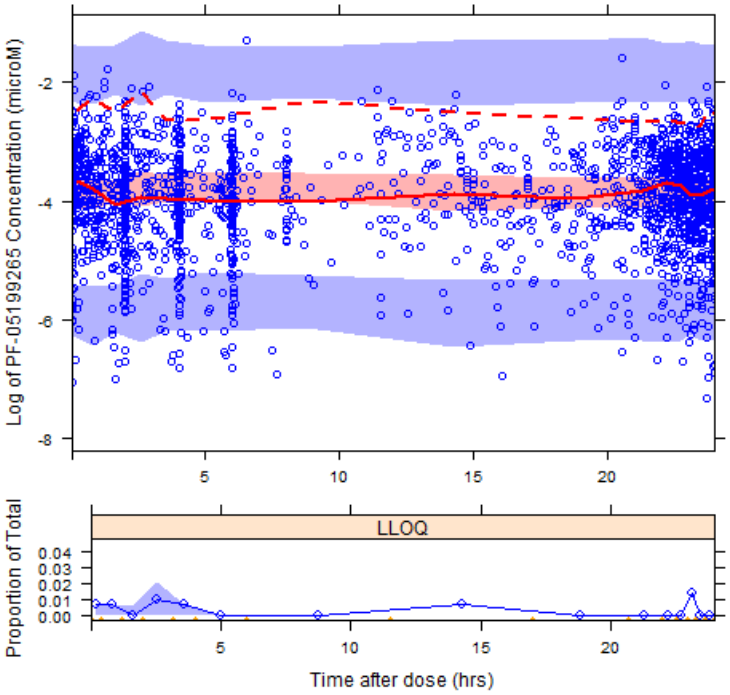


Figure 8: Visual Predictive Check for PF-05199265 Observations After Dacomitinib Multiple Dose Administration Under Once Daily Dose Schedule

Dose proportionality and time dependencies

C_{max} and AUC_{24} versus dose data (2-60 mg) were analysed by log-log regression. After multiple dosing, the slope of C_{max} versus dose was 1.083 (90% CI: 1.001, 1.166). The slope of AUC_{tau} versus dose was 1.104 (90% CI: 1.015, 1.192). Thus, there was a tendency to a greater than proportional increase in systemic exposure with increasing dose. Although the slope of the C_{max} and AUC_{tau} regressions were slightly greater than 1, PK generally appeared to be dose proportional.

Following repeated dosing (once daily), steady state was reached within 14 days with exposure 5-6.4 times higher compared with single dose exposure. There was a marked difference in the ratio of PF-05199265 to dacomitinib in plasma after single dose (0.23-0.52) and at steady state (0.08). Graphical data indicated a modest, but systematic decrease in dacomitinib exposure (C_{trough}) over time (first six cycles).

Inter- and intra-individual variability

Based on non-compartmental analysis, inter-individual variability (CV%) after a 45 mg dose in patients ranged from 51% to 70% in C_{max} and from 31% to 45% in AUC_{inf}.

In the population pharmacokinetic analysis, total inter-individual variability was estimated to be 35% in clearance, 33% in central volume of distribution, 47% in the peripheral volume of distribution and 121% in the absorption rate constant (prior to inclusion of covariates partly explaining total variability).

Special populations

A population PK analysis was conducted by the use of nonlinear mixed effects modelling (NONMEM v. 7.3) to characterise the PK of dacomitinib and to evaluate the effect of intrinsic and extrinsic factors on the PK. The analysis included data from eight studies in healthy subjects and 13 studies in patients with different solid tumours, in total 1,435 subjects (11,751 observations; of which 13.5% were dropped for various and not fully justified reasons).

The PK of dacomitinib were described by a two-compartment disposition model with first order absorption and elimination. Covariates associated with a significant increase in clearance included increasing body weight (as a predefined covariate using a power function with an allometric exponent of 0.75), male gender, Asian race, baseline aspartate aminotransferase, baseline serum albumin, EGFR activating mutations and not using a CYP2D6 inhibitor. Age, healthy subject vs. patient, smoking history, ECOG status (0/1), creatinine clearance, baseline bilirubin, baseline tumour type and baseline hepatic impairment grade did not significantly impact on the clearance of dacomitinib. Food intake was a significant covariate increasing the absorption rate. No covariates were identified to influence the volume of distribution. An effect of body weight on CL and volume of distribution was predefined in the modelling analysis plan, and included in the final model.

Table 17: Dacomitinib final model PK parameters summary

	Final Model Analysis			Bootstrap Results	
Parameter	Estimate	RSE (%)	Shrinkage (%)	Median	95 % CI
θ_{CL} (L/hr)	19.952	2.088	17.05	19.350	(17.993 - 20.395)
θ_{V_2} (L)	899.371	4.901	71.08	913.673	(813.519 - 1125.298)
θ_{k_a} (hr^{-1})	0.067	8.024	44.99	0.070	(0.060 - 0.086)
θ_Q (L/hr)	17.320	4.019	92.29	16.780	(14.809 - 18.382)
θ_{V_3} (L)	908.308	5.764	70.83	879.509	(742.831 - 1327.960)
θ_F	0.848	1.661	86.00	0.844	(0.838 - 0.850)
$\sigma_{prop.error.oral}$	0.355	2.712	2.75	0.356	(0.338 - 0.377)
$\sigma_{prop.error.iv}$	0.502	6.051	15.99	0.506	(0.433 - 0.564)
$\theta_{BALB\ on\ CL}$	0.543	15.045	-	0.547	(0.380 - 0.757)
$\theta_{EGFR\ mutant\ on\ CL}$	0.093	31.720	-	0.098	(0.039 - 0.174)
$\theta_{EGFR\ wild\ type\ on\ CL}$	-0.046	57.786	-	-0.044	(-0.097 - 0.013)
$\theta_{CYP2D6\ inhibition\ on\ CL}$	-0.330	30.207	-	-0.335	(-1.000 - -0.082)
$\theta_{Asian\ on\ CL}$	0.085	30.755	-	0.090	(0.038 - 0.148)
$\theta_{Female\ on\ CL}$	-0.115	17.103	-	-0.118	(-0.158 - -0.080)
$\theta_{Food\ on\ k_a}$	0.227	131.807	-	0.151	(-0.260 - 1.675)
$\theta_{BAST\ on\ CL}$	0.002	37.429	-	0.002	(0.000 - 0.004)
IIV	Value	CV(%)		Median	95% CI
ω^2_{CL}	0.103	32.078	-	0.107	(0.090 - 0.769)
$\omega^2_{V_2}$	0.096	30.958	-	0.116	(0.063 - 0.205)
$\omega^2_{k_a}$	1.466	121.091	-	1.369	(0.849 - 1.973)
ω^2_Q (Fixed)	0.025	15.811	-	0.025	(0.025 - 0.025)
$\omega^2_{V_3}$	0.178	42.159	-	0.208	(0.066 - 1.553)
ω^2_F (Fixed)	0.025	15.811	-	0.025	(0.025 - 0.025)
OFV_{IMP}	-5159.952	-	-	-4959.625	-

ePharmacology artifact ID RA13722111. Line 1 substituted.
The bioavailability parameter (F) was calculated as the logit. This table shows the value of F after backtransformation.
CI=confidence interval; IIV=inter-individual variability; CL=clearance; F= absolute bioavailability; k_a= first order absorption rate constant; PK=pharmacokinetic; Q=intercompartmental clearance; V_2=central volume of distribution; V_3=peripheral volume of distribution; h=hour; L=liter; OFV=objective function value; RSE= relative standard error; ω^2=variance of the IIV.

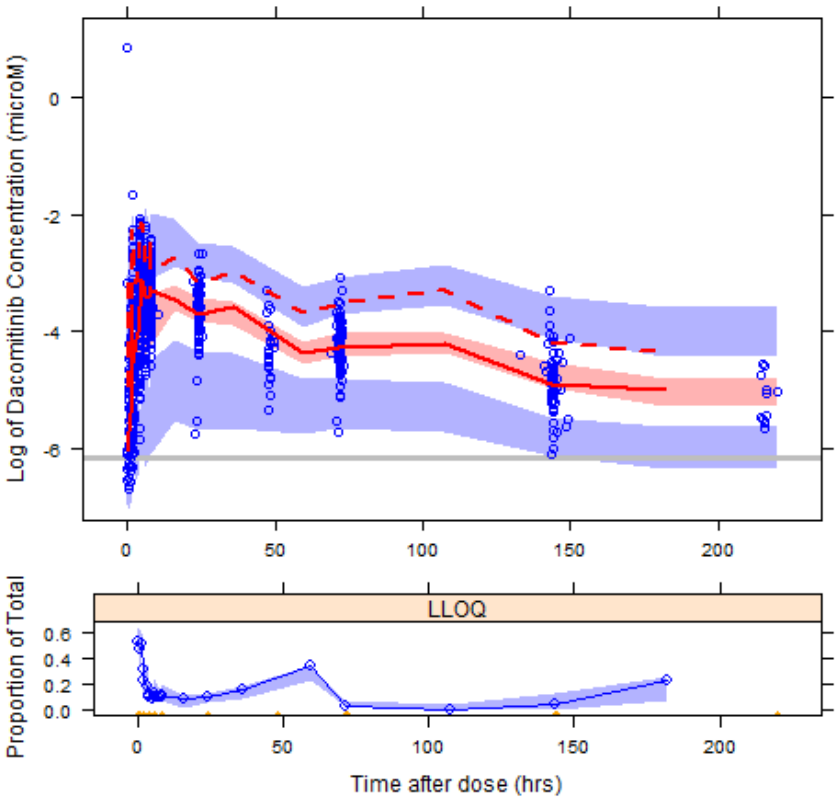
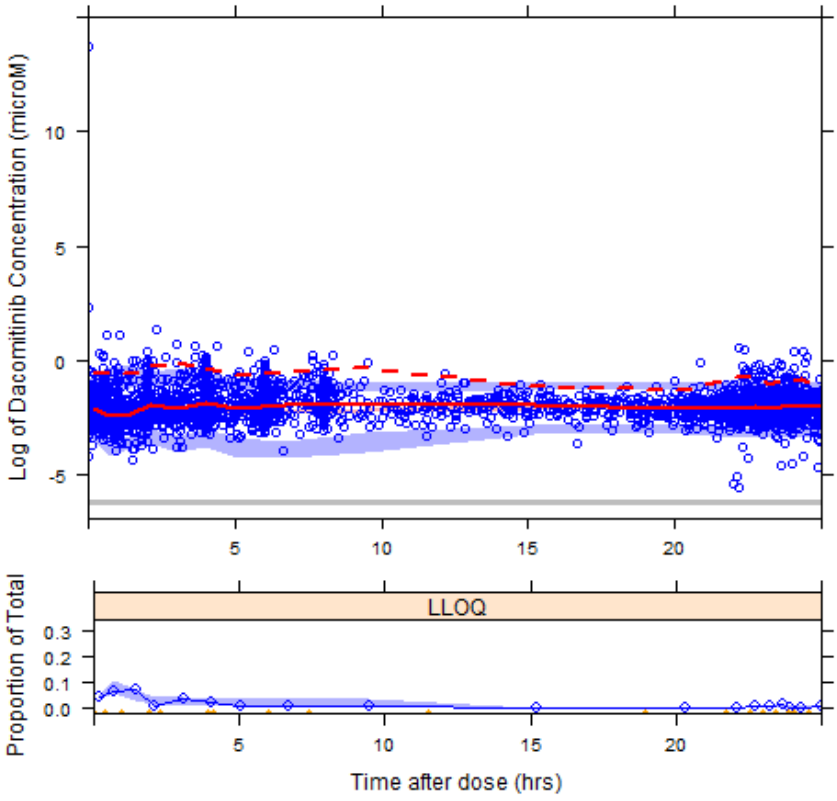


Figure 9: Visual Predictive Check for Dacomitinib Observations After Multiple Dose Administration Under Once Daily Dose Schedule



Renal impairment

No clinical studies have been conducted in patients with impaired renal function.

Hepatic impairment

In a dedicated hepatic impairment trial (A7471018), following a single-oral dose of 30 mg Vizimpro, dacomitinib exposure (AUC_{inf} and C_{max}) was unchanged in mild hepatic impairment (Child-Pugh A; N=8) and decreased by 15% and 20%, respectively in moderate hepatic impairment (Child-Pugh B; N=9) when compared to subjects with normal hepatic function (N=8). Dacomitinib pharmacokinetics has not been studied in subjects with severe hepatic impairment (Child-Pugh class C). In addition, based on a population pharmacokinetic analysis using data from 1381 patients, that included 158 patients with mild hepatic impairment defined by National Cancer Institute (NCI) criteria [total bilirubin ≤ Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) > ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST; N=158], mild hepatic impairment had no effect on the pharmacokinetics of dacomitinib. From the small number of patients in the moderate group [total bilirubin > 1.5 to 3 × ULN and any AST; N=5], there is no evidence for a change in dacomitinib pharmacokinetics (see section 5.2 of the SmPC).

Body weight, gender, race, and age

The effects of body weight, gender, race and age was evaluated using population PK analysis. The data supported the predefined inclusion of body weight as a covariate on clearance. The allometric scaling model predicted 55% higher clearance in 90 kg subjects compared with 50 kg subjects. Female subjects were estimated to have 11.5% lower clearance than males, and Asian subjects were estimated to have 8.5% higher clearance than White subjects. There was no significant effect of age on dacomitinib clearance. Approximately 9.5% of the population included in the dacomitinib PK dataset were aged ≥75 years.

Table 18: Elderly patients investigated for PK data

Variable	Age (years)	Total
N		1379
Age Group	<65	868 (62.94%)
	65-74	379 (27.48%)
	75-84	124 (8.99%)
	>84	8 (0.58%)

Dacomitinib has not been studied in children.

Pharmacokinetic interaction studies

Effects of other substances on dacomitinib exposure

The absorption of dacomitinib decreases with increasing pH. *In vivo*, co-administration of a single 45 mg dacomitinib dose with the PPI rabeprazole 40 mg once daily for 7 days decreased dacomitinib C_{max}, AUC_{0-96h} (area under the concentration-time curve from time 0 to 96 hours), and AUC_{inf} (AUC from time 0 to infinity) (n=14) by approximately 51%, 39%, and 29%, respectively, when compared to a single 45 mg dose of dacomitinib administered alone. (see section 4.5 of the SmPC).

Dacomitinib has been shown to be a substrate of P-gp, BCRP, CYP3A4 and CYP2D6 *in vitro*. One *in vivo* interaction study was performed to assess the effect of the strong CYP2D6 inhibitor paroxetine on dacomitinib PK. Daily dosing of paroxetine 30 mg led to a 37% increase in dacomitinib AUC_{inf} and a 10% increase in dacomitinib C_{max}. Therefore, no dose adjustment is recommended for dacomitinib upon concomitant administration with a CYP2D6 inhibitor.

Based on data from observations in 8 patients in Study A7471001, there was no apparent effect of local antacid administration on C_{max} and AUC_{inf} of dacomitinib. Based on pooled data in patients, there was no apparent effect of histamine-2 (H2) receptor antagonists on steady-state trough concentration of dacomitinib (geometric mean ratio of 86% (90% CI: 73; 101).

Effects of dacomitinib on other substances

In vivo, co-administration of single 45 mg oral dose of dacomitinib increased the mean exposure (AUC_{last} and C_{max}) of dextromethorphan, a probe CYP2D6 substrate, 855% and 874%, respectively, compared with administration of dextromethorphan alone.

Among the studied transporters *in vitro*, dacomitinib showed a low potential to inhibit P-gp (systemically), OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and BSEP at clinically relevant concentrations. However, dacomitinib may have the potential to inhibit OCT1 (K_i 0.25 µM), systemic BCRP (K_i 0.25 µM), intestinal BCRP (K_i 0.25 µM) and intestinal P-gp (K_i 3.87 µM).

In human hepatocytes, dacomitinib did not induce CYP3A4, 2B6 or 1A2 mRNA or enzymatic activity at concentrations up to 3 µM (>50x of the unbound C_{max} at steady state 45 mg QD).

In vitro direct inhibition and time-dependent inhibition studies were performed in human liver microsomes. There was no relevant inhibition of CYP 1A2, 2B6, 2C8, 2C9, 2C19 and 3A or UGT 1A1, 1A4, 1A6, 1A9, 2B7 and 2B15. For CYP2D6, a potentially clinically relevant direct inhibition was observed (unbound C_{max}/K_i ratio was >0.02 [based on The "Basic Model" from the *EMA Guideline on drug interactions* to assess the risk of *in vivo* DDIs]).

The main metabolite PF-05199265 was not found to be a potential inhibitor of CYP enzymes *in vitro* except for potential CYP2D6 inhibition. The interaction potential with PF-05199265 was not further tested because its ratio to dacomitinib at steady state was <25%.

Exposure relevant for safety evaluation

After multiple 45 mg dose administration and steady state achievement (14 days) the geometric mean exposure ranged from 1505 to 2166 ng•h/mL for AUC_{tau} and from 74.2 to 105.1 ng/mL for C_{max}. Maximum exposure observed after this regimen was approximately 240 ng/mL and 4700 ng•h/mL, respectively (according to graphical presentations of exposure, Figures 8 and 9 in Module 2.7.2).

For the main metabolite PF-05199265, the geometric mean C_{max} was 6.58 ng/mL and the geometric mean AUC_{tau} was 141 ng•h/mL on Cycle 2 Day 1 after 45 mg QD dosing.

2.4.3. Pharmacodynamics

Mechanism of action

Dacomitinib is a selective, adenosine triphosphate (ATP)-competitive, irreversible, small-molecule inhibitor of the human epidermal receptor, also called ERBB (HER) family of receptor tyrosine kinases (RTKs), including epidermal growth factor receptor, also called HER1 or ERBB1 (EGFR), human epidermal receptor 2, also called ERBB2 (HER2), human epidermal receptor 4, also called ERBB4 (HER4), and their oncogenic variants (ie, EGFR with exon 19 deletions or exon 21 L858R mutation). Dacomitinib inhibited the activity of HER1, HER2, and HER4 in biochemical kinase assays, demonstrated dose-dependent inhibition of the HER1 and HER2 RTK phosphorylation in tumour xenografts expressing these RTK targets in vivo, and demonstrated inhibition of tumour growth or tumour regression in experimental models of cancer. The irreversible mode of action leads to prolonged inhibition of EGFR kinase activity.

The O-desmethyl metabolite (PF-05199265) is also a potent inhibitor of the EGFR kinase family *in vitro*.

Primary and Secondary pharmacology

Primary pharmacology

The relationships between dacomitinib exposure and efficacy endpoints were explored, ie, E-R analyses; the E-R analyses included only the dacomitinib-treated patients. Similarly, this E-R analysis explored intrinsic and extrinsic factors as potential predictors of response and intended to characterize, if any, the relationship between dacomitinib exposure and the efficacy measurements.

Secondary pharmacology

To evaluate the effect of dacomitinib on QT interval prolongation, a pharmacokinetic/pharmacodynamic relationship between dacomitinib or PF-05199265 concentrations and electrocardiogram (ECG) data was developed based on data collected from Study 1047. In this analysis, dacomitinib was found to have an effect on RR intervals with 90% CI for the slope excluding the null values. However, the 95% CI for the slope estimate included the null value suggesting that the relationship between dacomitinib plasma concentrations and the RR interval is negligible. PF-05199265 was not found to affect RR intervals. Therefore, the formulas that would generate QTc values that were independent of the underlying heart rate were selected for the analysis. The correction factors QTcF, QTcB and QTcS were investigated. Of these, QTcS was determined to be the most appropriate correction factor. Based on the results of these analyses, an exposure-dependent increase in mean QTc was not observed at concentrations of dacomitinib and PF-05199265 achieved in this study, which were representative of expected concentrations with 45 mg QD dosing.

All data available concerning the mechanism of action are from nonclinical studies, and no specific clinical pharmacology studies have been performed to qualify the suggested mechanism of action. PD was investigated as a secondary, mostly exploratory objective in several studies. The phase II studies **A7471017** (proof-of-concept) and **A7471047** investigated the efficacy of dacomitinib in EGFR activation mutation-positive NSCLC and T790M positive NSCLC, respectively. QT prolongation was investigated in study **A7471047**. A PKPD modelling approach was used to further investigate the effect of dacomitinib on the QT interval in NSCLC patients (**PMAR-EQDD-A747f-DP4-617**).

Exposure-response analyses

Exposure-efficacy relationship

The exposure-efficacy relationship was investigated based on data from 268 patients in Study 1050 (pivotal Phase III) and Study 1017 (Phase II), where the majority (94%) were started on 45 mg dacomitinib daily and 93% had only predose PK sampling. The data were analysed with logistic regression modelling and time-to-event modelling. No clear relationships between dacomitinib exposure (as estimated based on the individual PK parameter estimates in the population PK analysis) and objective response (OR) or progression-free survival (PFS) were established over the exposure range studied. The final time-to-event model identified *decreasing* average concentration (C_{avg}) of dacomitinib, increasing albumin, decreasing lactate dehydrogenase and increasing maximum grade of the adverse events rash/dermatitis acneiform and other skin toxicities as significant predictors of increasing PFS.

In a sub-analysis including patients who did not change dacomitinib dose levels during treatment (88 subjects on 45 mg QD and 8 on 30 mg), dacomitinib exposure was not a significant predictor of PFS. Importantly, in a similar analysis based on only patients continuing on 45 mg QD in Study 1050, and which included the gefitinib arm, choice of treatment (dacomitinib vs. gefitinib) was not a significant predictor of PFS, and the HR between the arms was close to 1 (0.97; 95% CI 0.81-1.19).

Exposure-safety relationship

The relationship between dacomitinib exposure and selected cluster safety endpoints were evaluated using logistic regression and time-to-event modelling. Only the logistic regression modelling results are presented here, as the results were generally similar. Simulations based on these models indicated that increasing exposure to dacomitinib increased the probability of experiencing Grade ≥3 skin toxicities and diarrhoea and Grade ≥1 stomatitis (Table 19).

Table 19: Summary of exposure-safety models

Safety cluster	Most predictive dacomitinib exposure parameter	Other significant covariates	Simulated probability of experiencing AE at	
			45 mg QD	30 mg QD
RASH/DERMATITIS ACNEIFORM (Grade ≥3)	C_{avg} on the day of the adverse event	Increasing body weight	32 %	15 %
OTHER SKIN TOXICITIES (Grade ≥3)	C_{avg} on the day of the adverse event	-	11 %	6 %
DIARRHOEA (Grade ≥3)	C_{avg} on the day of the adverse event	-	11 %	5 %
STOMATITIS (Grade ≥1)	C_{max} on the day of the adverse event	Increasing body weight, Study (1050 or 1017)	33 %	17 %

C_{avg} Average concentration, C_{max} Maximum concentration

Logistic regression models were used to evaluate the potential effect of Race and/or EGFR mutation subtype on the probability of experiencing each of the safety endpoints evaluated. Race was a covariate considered in the initial stepwise covariate modelling and it did not result in a statistically significant improvement to the model fit [measured using deviance (Agresti, 2003)]. This indicates that Race is not a significant covariate and does not have any effect on the probability of each of the AE endpoints. EGFR mutation subtype was evaluated by dichotomising the exon 19 deletion and exon 21 mutation. Mutation subtype (ref=exon 19 deletion, test=exon 21 mutation) was added to each of the final logistic regression models (using dacomitinib exposure) and the

model was re-estimated. In every model, the mutation subtype was not statistically significant at a p=0.05 significance level.

2.4.4. Discussion on clinical pharmacology

In the *in vitro* absorption studies (see section 2.3.3), dacomitinib showed to be a weak to moderate substrate for MDR1 and BCRP, with concentration dependent saturation of efflux (at concentrations >2 µM). Due to high bioavailability (see below) no major clinical implications of increased bioavailability due to genetically determined reduced BCRP activity or inhibition of P-gp/BCRP are expected.

The mean oral bioavailability was estimated to be 80%, ranging the dose-normalised AUCinf of test/reference from 65.3% to 100%. Food does not alter bioavailability to a clinically meaningful extent. Dacomitinib is a substrate for the membrane transport proteins P-gp and BCRP. However, based on the oral bioavailability of 80%, these membrane transport proteins are unlikely to have any impact on dacomitinib absorption (see section 5.2 of the SmPC).

There was large inter-individual variability in the absorption rate and t_{max}. However, individual differences in absorption rate are not expected to be clinically relevant as long as the bioavailability fraction remains unchanged and C_{max} is not the primary driver of clinical efficacy or adverse event probability (which was indicated by the exposure-response analyses).

Proton pump inhibitors reduced exposure to dacomitinib by 50% on Cmax and 30% on AUC, and the applicant suggests that co-administration with these agents should not be recommended. Although there is no apparent exposure-response relationship, a clinically relevant impact of a reduced exposure cannot be ruled out. The effect of H2 receptor antagonists on dacomitinib exposure has not been studied. Based on physiology and knowledge from other molecular targeted agents with pH-dependent absorption (*e.g.* erlotinib), a staggered dosing approach (administration of dacomitinib at least 2 hours before or 10 hours after H2 receptor antagonist administration) would allow dacomitinib absorption at the time of lowest gastric pH and thereby minimize the extent of this potential interaction.

The potential distribution of dacomitinib to the CNS is relevant to predict the potential effect of dacomitinib on CNS metastases, considering the dacomitinib properties (moderate permeability, weak substrate of P-gp and BCRP). However, there is limited information available on dacomitinib PK in brain tissue as well as the impact of genetic polymorphism of the main CNS efflux transporters. Evaluation of clinical impact is thus limited to clinical empirical evidence.

In the mass-balance study, only 82% of the administered dose was recovered, which is relatively low. Although the elimination pathways have not been fully elucidated, the main routes of elimination following dacomitinib administration have been adequately characterised. The available PK data in CYP2D6 poor and ultra-rapid metabolizers were very limited. However, they do indicate only modest differences between these subpopulations and CYP2D6 extensive metabolizers. The drug interaction study of co-administration with the strong CYP2D6 inhibitor paroxetine indicated no clinically relevant effects on dacomitinib, which may be viewed as an estimation of expected exposure in CYP2D6 poor metabolizers. Together, these data indicate that the fractional metabolism by CYP2D6 is relatively low (<50%) and that no clinical consequences are expected from standard dosing across genotype subgroups to an extent that justifies pre-treatment genotyping. No dose adjustment is recommended for dacomitinib upon concomitant administration with a CYP2D6 inhibitor.

There was a tendency to a greater than proportional increase in exposure with increasing dose. The underlying mechanism may be that higher dacomitinib exposure leads to CYP2D6, P-gp and/or BCRP (proteins that

dacomitinib both inhibit and is a substrate of). Since the coefficients for the slopes were only slightly above 1 (AUC point estimates of 1.21 and 1.10 after single and multiple dosing, respectively), the potential nonlinearity may not be clinically relevant over the dose range studied.

Based on the marked time-dependent changes in the dacomitinib-to-PF-05199265 ratio, it appears that the CYP2D6 f_m values are time-dependent, possibly due to concentration-dependent CYP2D6 auto-inhibition. This has implications for the interpretation of metabolism and interaction studies performed after single dose administration, but is likely not to have important clinical consequences.

The graphical data suggested a modest, but systematic decrease in C_{trough} values but the statistical analysis did not conclude on any time-related trend.

Findings from the population PK justifies not performing a dedicated renal impairment study which is acceptable.

The applied methods for population pharmacokinetic modelling were overall adequate and standard model building techniques were applied. The exclusion of the majority (74.2%) of observations was either prespecified in the analysis plan, or due to incomplete information or abnormally high or low observations.

The final model was validated using prediction-corrected visual predictive checks (pcVPCs). All pcVPCs were generated using 1000 simulations, which is considered adequate.

The population pharmacokinetic approach is generally an acceptable method to assess the effect of renal function and it is accepted that a dedicated study is not performed. Based on population pharmacokinetic analyses, mild (60 mL/min ≤ CrCl < 90 mL/min; N=590) and moderate (30 mL/min ≤ CrCl < 60 mL/min; N=218) renal impairment, did not alter dacomitinib pharmacokinetics, relative to subjects with normal (CrCl ≥ 90 mL/min; N=567) renal function. The pharmacokinetics in patients with severe renal impairment (creatinine clearance < 30 mL/min) or requiring haemodialysis have not been studied. No dose adjustments are needed for patients with mild and moderate renal impairment (see section 4.2 and 5.2 of the SmPC)..

A dedicated hepatic impairment clinical study of dacomitinib showed no change in AUC in subjects with mild hepatic impairment and a 15% decrease in moderate hepatic impaired patients. Thus, the administration of dacomitinib did not show any clinically relevant impact on dacomitinib exposure in mild or moderate hepatic impaired patients and no starting dose adjustments are required (see section 4.2 of the SmPC). The applicant has committed to submit the results of a new clinical study investigating the impact on severely impaired hepatic function on dacomitinib and metabolite (PF-05199265) PK within Q1 2022. Only subjects identified as extensive metabolisers or intermediate metabolisers of CYP2D6 will be included in the primary statistical analysis of the study (see RMP). Treatment in this population is not recommended.

Based on population pharmacokinetic analyses, patient age, race (Asian and non-Asian), gender, and body weight do not have a clinically relevant effect on predicted steady-state exposure of dacomitinib. Approximately 90% of patients included in this analysis were Asian or White. No starting dose adjustment of dacomitinib is needed in these patient populations.

The safety and efficacy of Vizimpro in the paediatric population (< 18 years of age) have not been established. No data are available.

Dacomitinib was a substrate of the intestinal efflux transporters P-gp and BCRP. Inhibition of these transporters *in vivo* may result in increased dacomitinib exposure. However, since the mean bioavailability of dacomitinib was 80%, the potential increase in absorption extent is limited (~ 1/4 higher exposure may be expected in case of complete inhibition in an average patient), and it is supported that this finding was not pursued by *in vivo* studies.

Co-administration of dacomitinib with PPI rabeprazole significantly decreased dacomitinib C_{max} and $AUC_{0\text{-}96h}$. Concomitant use of proton pump inhibitors (PPIs) with dacomitinib should be avoided (see sections 4.4 and 4.5 of the SmPC). Local antacids and H2 receptor antagonists may be used if needed. Dacomitinib should be administered 2 hours before or at least 10 hours after taking H2 receptor antagonists.

Dacomitinib is a strong CYP2D6 inhibitor and may increase exposure (or decrease exposure of active metabolites) of other medicinal products metabolised by CYP2D6. Concomitant use of medicinal products predominantly metabolised by CYP2D6 should be avoided unless such products are considered necessary (see sections 4.4 and 4.5 of the SmPC). H2 receptor antagonists should be administered 2 hours before or at least 10 hours after taking dacomitinib. *D*acomitinib may increase exposure of other medicinal products (or decrease exposure to active metabolites) primarily metabolised by CYP2D6. Concomitant use of proton pump inhibitors (PPIs) with dacomitinib should be avoided

Based on *in vitro* data, dacomitinib may have the potential to inhibit the activity of P-glycoprotein (P-gp) (in the gastrointestinal [GI] tract), Breast Cancer Resistance Protein (BCRP) (systemically and GI tract), and organic cation transporter (OCT)1 at clinically relevant concentrations (see sections 4.5 and 5.2 of the SmPC).

Efficacy in NSCLC EGFR activating mutations has been demonstrated in the pivotal study (A7471050) where dacomitinib was shown to be superior to gefitinib in prolonging PFS in the overall target population. Considering that most NSCLC patients with EGFR activating mutations who initially respond to first generation TKIs relapse, the presumed activity of dacomitinib towards the acquired T790M mutation is of particular interest. The results from studies A7471047 and A7471002 indicate that the benefit in patients with T790M mutations in EGFR might be limited. In several clinical studies, secondary objectives have included exploratory investigations of biomarkers/pharmacogenomics. The knowledge on molecular mechanisms underlying resistance to first- and second-line EGFR TKI therapy are evolving. Molecular alterations triggering resistance may alter the drug target itself or activate alternate signal transduction pathways. However, the potential benefit of dacomitinib in the treatment of T790M-mediated EGFR TKI resistant NSCLC has not been sufficiently investigated in the clinical setting. Clinical data for dacomitinib activity in patients with EGFR T790M are not currently available.

Overall, based on the available nonclinical and clinical data the risk of QT prolongation is considered low.

The PK data indicate that the clinical activity of the O-desmethyl metabolite (PF-05199265) is negligible.

Exposure-response relationships

No clear relationship between dacomitinib exposure and efficacy could be characterized over the exposure range studied. Increasing exposure to dacomitinib ($C_{avg,\ overall}$) was significantly associated with shorter PFS, which is opposite of what is theoretically expected. Furthermore, although there was a clear difference in median PFS for Asian (18.2 months) and Non-Asian (10.9 months) patients in the raw data subgroup analyses for Study 1050, race was not identified as a significant covariate in the modelling analysis based on mostly the same data. The covariate skin toxicity, which is correlated with both race and exposure, was not shown to have confounded the underlying relationship between dacomitinib exposure and efficacy and between race and efficacy.

Significant exposure-safety relationship was defined for Grade ≥3 rash/dermatitis acneiform, other skin toxicities, diarrhoea and Grade ≥1 stomatitis.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of dacomitinib has been comprehensively characterised and all relevant information has been included in the PI.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The applicant will submit the results from a new clinical study investigating the impact on severely impaired hepatic function on dacomitinib and metabolite (PF-05199265) PK by Q1 2022 (see RMP).

2.5. Clinical efficacy

The efficacy of dacomitinib in the proposed indication is primarily supported by the outcome of the pivotal Study A7471050 (1050), a randomized, open-label, Phase 3 pivotal study of dacomitinib versus gefitinib as first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations. In addition, there was 1 key supportive study (A7471017 Cohort A) of dacomitinib as first-line treatment and 3 other supportive studies (A7471009, A7471028, and A7471011 [also known as Study BR.26]) in later lines of therapy.

All 5 studies have been completed (the final analysis of the primary endpoint has been completed).

2.5.1. Dose response study

No formal Phase 2 dose finding studies were performed and no dose/exposure-response modelling was conducted prior to Phase 3. In Study 1001, dacomitinib was administered to patients at doses ranging from 0.5 to 60 mg. Dacomitinib 45 mg QD was determined as the maximum tolerated dose (MTD) in Study 1001, and confirmed in Study 1003 and Study 1005. Dacomitinib at a dose of 45 mg QD in NSCLC has been further investigated and confirmed in Phase 2 (Studies 1002, 1017, 1028, and 1042) and Phase 3 (Studies 1009, 1011, and 1050) clinical studies of efficacy and safety.

2.5.2. Main study

ARCHER 1050: A Randomized, Open-Label, Phase 3, efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s)

Methods

Table 20: Flow Chart of Study A7471050 Design

Eligible subjects with:	Stratification:		Open label:	Treatment until:	All Patients should be followed for:
Newly diagnosed stage IIIB/IV or recurrent NSCLC ECOG PS 0-1 Adequate renal, hepatic and hematologic function Tumor specimen available for EGFR activating mutation and pathologic confirmation	Race (Japanese vs. mainland Chinese vs. other East Asian vs. non-East Asian) EGFR mutation status (exon 19 deletion vs. the L858R mutation in exon 21)	Randomize	Dacomitinib 45 mg or Gefitinib 250 mg Both administered orally once daily	Progressive Disease as determined by RECIST v1.1 and/or New systemic anticancer therapy instituted or Unacceptable Toxicity or Patient Withdrawal or Patient dies	Progression if no evidence of progressive disease at the time of treatment discontinuation regardless of the start of subsequent new cancer therapy and Subsequent new cancer therapy and Overall Survival

Source: Study A7471050 protocol
ECOG=Eastern Cooperative Oncology Group; EGFR=Epidermal Growth Factor Receptor; NSCLC=Non-small cell lung cancer; PS=Performance status; RECIST=Response Evaluation Criteria in Solid Tumors.

Study Participants

Inclusion Criteria

Eligible patients were expected to meet the following criteria:

1. Provision of a voluntarily given, personally signed and dated, written ICD.

2. Age ≥20 years in Japan and Korea, and ≥18 years in other countries, male or female.

3. In all countries except China: The presence of an EGFR-activating mutation (exon 19 deletion or the L858R mutation in exon 21) in tumour specimens was determined by the local laboratory using the Qiagen *therascreen*

EGFR Mutation Detection Kit RGQ (Scorpions ARMS), or 1 of standardized and commercially-available test assays. In China, the presence of an EGFR-activating mutation (exon 19 deletion or the L858R mutation in exon 21) was determined in tumour specimens by the central laboratory based on either the Qiagen *therascreen* EGFR assay or the AmoyDx EGFR Mutations Detection Kit. It was acceptable for patients with the presence of the T790M mutation in exon 20 together with either EGFR-activating mutation (exon 19 deletion or the L858R mutation in exon 21) to be included in this study.

4. Evidence of newly diagnosed Stage IIIB/IV (based on Union for International Cancer Control staging system v7)or recurrent (minimum 12-month disease-free interval between completion of systemic therapy and recurrence of NSCLC required) NSCLC of adenocarcinoma histo- and/or cytopathology or its pathologically accepted variants using tumour specimen (assessed according to accepted standards by a local laboratory).

5. Tumour specimen with adequate tumour cell content either from tissue or cell block for cytologic specimen, preferably from the same source as used for the local testing, must have been available for central laboratory confirmation of adenocarcinoma histo- and/or cytopathology and presence of EGFR-activating mutation. In the situation of recurrent NSCLC after receiving neoadjuvant/adjuvant chemotherapy, the tumour specimen was to be obtained at the time of recurrence after completion of neo/adjuvant therapy.

6. ECOG PS of 0 or 1.

7. No prior treatment with systemic therapy for locally advanced or metastatic NSCLC. Prior treatment with an EGFR TKI or other TKIs was not allowed.

8. Radiologically measurable disease by RECIST v1.1 criteria;

9. Adequate organ function, including:

a. Estimated creatinine clearance ≥30 mL/min (as determined by Cockcroft-Gault formula or the study site's standard formula);

b. Urinary protein <3+ by urine dipstick. If urine protein by dipstick was ≥3+, then a urine protein:creatinine ratio (UPCR) was to be obtained. The patients could enter only if the UPCR was <2.0;

c. Absolute neutrophil count (ANC) ≥1500 cells/mm3;

d. Platelets ≥100,000 cells/mm3;

e. Hemoglobin ≥10.0 g/dL;

f. Bilirubin ≤1.5 x upper limit of normal (ULN);

g. Aspartate aminotransferase (AST; also known as serum glutamic oxaloacetic transaminase) and alanine aminotransferase (ALT; also known as serum glutamic pyruvic transaminase) ≤2.5 x ULN (≤5.0 x ULN if hepatic metastases).

10. Female patients must have been postmenopausal (defined as 12 months of amenorrhea following last menses), or they or their partners must have been surgically sterile, or must have agreed to use effective contraception while receiving study treatment and for at least 3 months thereafter.

11. All female patients with reproductive potential must have had a negative pregnancy test (serum or urine) prior to starting study treatment.

12. Male patients or their female partners must have been surgically sterile or must have agreed to use effective contraception while receiving study treatment and for at least 3 months thereafter.

13. Willing and able to comply with study scheduled visits, treatment plans, laboratory tests, and other study procedures.

Exclusion Criteria

Patients were ineligible to participate in this study if any of the following criteria were met:

1. Any evidence of mixed histo- and/or cytology that included elements of small cell or carcinoid lung cancer.

2. Any other mutation other than exon 19 deletion or the L858R mutation in exon 21, with or without the presence of the T790M mutation in exon 20.

3. Any history or evidence of brain metastases or leptomeningeal metastases, even if treated with radiation or surgery in the past and now stable.

4. Any previous anti-cancer systemic treatment of locally advanced, or metastatic NSCLC including but not limited to chemotherapy, targeted therapies, small molecules, EGFR-TKIs and other TKIs, monoclonal antibodies, anti-cancer vaccines, radiotherapy (other than palliative radiotherapy to lesions that will not be followed for tumor assessment on this study, i.e., non-target lesions). Completed neoadjuvant/adjuvant chemo-therapy and/or combined modality chemo-therapy/radiation therapy permitted only in cases in which there is a minimum of 12 months disease free interval between completion of systemic therapy and recurrence of NSCLC. Prior treatment with a EGFR-TKI or other TKIs is not allowed

5. Any surgery (not including minor procedures such as lymph node biopsy), palliative radiotherapy, or pleurodesis within 2 weeks of baseline assessments.

6. Any clinically significant gastrointestinal abnormalities that may have impaired intake, transit, or absorption of the study drug, such as the inability to take oral medication.

7. Current enrollment in another therapeutic clinical study.

8. Any psychiatric or cognitive disorder that would have limited the understanding or rendering of informed consent and/or compromise compliance with the requirements of this study; or known drug abuse/alcohol abuse.

9. History of, or currently suspected, diffuse non-infectious pneumonitis or interstitial lung disease (ILD);

10. Any history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

11. Uncontrolled or significant cardiovascular disease;

12. Severely impaired (defined as Child-Pugh class C) hepatic dysfunction;

13. Prior malignancy: Patients were not eligible if they have history of, or evidence of another concurrent malignancy. Exception would be effectively-treated past history of non-melanoma skin cancer or in-situ cervical cancer with no evidence of active disease.

14. Other severe acute or chronic medical condition that may have increased the risk associated with study participation or investigational drug administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

15. Use of narrow therapeutic index drugs that were CYP2D6 substrates (procainamide, pimozide, thioridazine, etc.) from screening to randomization.

Treatments

Patients received open-label study treatment and were randomized in a 1:1 ratio to 1 of the following 2 treatment arms:

Investigational treatment: dacomitinib 45 mg PO once daily;

Comparator treatment: gefitinib 250 mg PO once daily.

Treatment was administered until disease progression, institution of new anticancer therapy, intolerable toxicity, withdrawal of consent, death, or investigator decision dictated by protocol compliance, whichever occurred first. Study treatment was administered for up to 48 months.

At the time of progression and termination of study treatment, the patients could receive any regulatory approved therapy (i.e. not another EGFR-TKI) at the judgment of the investigator. Patients who had progressive disease (PD) (per RECIST v1.1, by IRC review) 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, with or without local therapy (eg, surgical removal and/or radiation of a single lesion), at the discretion of the investigator and in agreement with the Sponsor, until any alternate or additional systemic anti-cancer therapy regimen was implemented.

Crossover of patients from one treatment arm to the other after disease progression was not allowed.

Objectives

Primary Objective:

To demonstrate that dacomitinib treatment was superior to gefitinib treatment with respect to progression-free survival (PFS), as determined by blinded Independent Radiologic Central (IRC) review, in the study population.

Key Secondary Objective:

- To compare OS, and objective response rate (ORR) as determined by blinded IRC review and investigator assessment (INV), between the 2treatment arms.
- To compare the patient-reported outcomes (PROs) of health-related quality of life (HRQoL) and disease/treatment-related symptoms between the 2 treatment arms;
- To compare the PRO of health status between the 2 treatment arms;
- To evaluate the safety and tolerability between the 2 treatment arms;
- To compare PFS as determined by INV, and duration of response (DoR) both as determined by blinded IRC review and INV between the 2 treatment arms;

Outcomes/endpoints

The primary efficacy endpoint was PFS by RECIST v1.1 as determined by blinded IRC review. PFS was defined as the time from randomization to the date of disease progression by RECIST v1.1.

Secondary endpoints included:

- OS

- ORR, as determined by both IRC and INV per RECIST v1.1.
- PFS per investigator
- DoR, as determined by both IRC review and INV.
- Time to treatment failure (TTF) as determined by both IRC review and INV.
- Patient-reported outcome (PRO).

Sample size

The primary endpoint of the study was PFS as determined by blinded IRC review. It was estimated that approximately 440 randomized patients and a minimum of 256 PFS events would be required to achieve a 90% power to detect a ≥50% improvement in PFS (ie, this translated to an improvement in median PFS from 9.5 to at least 14.3 months) in patients randomized to receive dacomitinib versus those randomized to receive gefitinib in the intent-to-treat (ITT) Population (ie, HR ≤0.667, using a stratified log-rank test at 1-sided α=0.025, a 1:1 randomization and a censoring rate of approximately 42%). At the end of the study, the primary analysis tested the HR (dacomitinib/gefitinib) ≥1 versus <1 using a 1-sided stratified log-rank test. The study was to be considered a positive study if the 1-sided stratified log-rank test for PFS was significant at the 0.025 level at the time of the final PFS analysis.

Randomisation

Patients were randomly assigned in a 1:1 ratio to either the dacomitinib arm or the gefitinib arm. Randomization was stratified by 2 factors: race (Japanese vs mainland Chinese vs other East Asian vs non-East Asian, as reported by the patient) and EGFR-activating mutation status (exon 19 deletion versus the L858R mutation in exon 21). Of note, all Asian patients enrolled in Study 1050 were East Asian; therefore the non-East Asian patient subgroup in Study 1050 was equivalent to a non-Asian population. Japanese and mainland Chinese were selected as stratification factors due to local regulatory requirements.

A central Interactive Web Response System (IWRS) was used for patient enrollment at the time of informed consent and randomization, as well as for drug management.

Blinding (masking)

The study was open-label.

Statistical methods

Table 21: Statistical analysis methods for primary and secondary efficacy endpoints including patient-reported outcomes in pivotal study A7471050

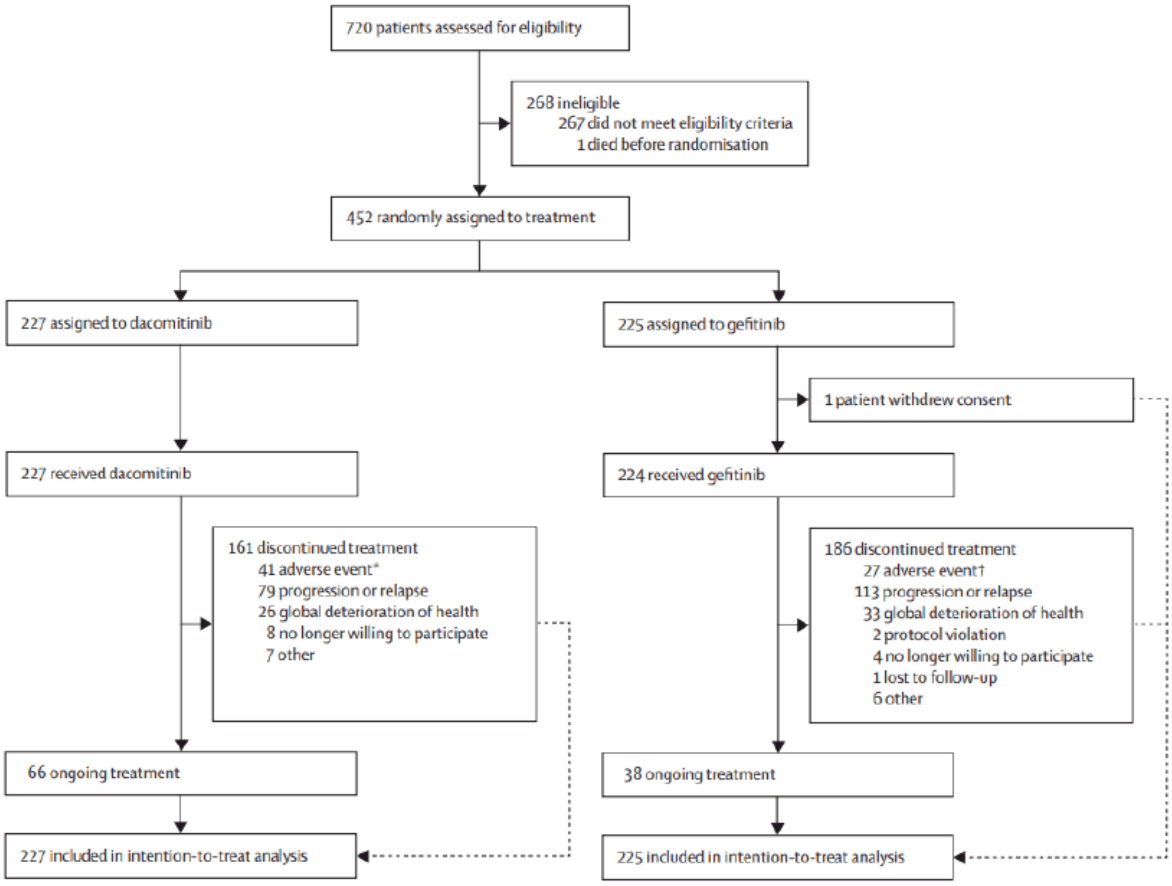
Endpoint	Statistical Analysis Method
Primary	
PFS (IRC Review)	K-M method (median and 95% CI); Stratified Cox Regression model (HR and 95% CI); Stratified log-rank test; Unstratified Cox Regression model (HR and 95% CI); Unstratified log-rank test
Secondary	
ORR	Exact method based on Binomial distribution (95% CI); Stratified CMH test; Pearson Chi-squared test; Differences between response rates (95% CI)
OS	K-M method (median and 95% CI); Stratified Cox Regression model (HR and 95% CI); Stratified log-rank test; Unstratified Cox Regression model (HR and 95% CI); Unstratified log-rank test
PFS (Investigator Assessment)	K-M method (median and 95% CI); Stratified Cox Regression model (HR and 95% CI); Stratified log-rank test; Unstratified Cox Regression model (HR and 95% CI); Unstratified log-rank test
DoR	K-M method (median and 95% CI); Stratified Cox proportional hazards model (HR and 95% CI); Stratified log-rank test; Unstratified Cox Regression model (HR and 95% CI); Unstratified log-rank test
TTF	K-M method (median and 95% CI); Stratified Cox proportional hazards model (HR and 95% CI); Stratified log-rank test; Unstratified Cox Regression model (HR and 95% CI); Unstratified log-rank test
PROs	Descriptive statistics for absolute scores and change from baseline of the QLQ-C30, QLQ-LC13, and EQ-5D/VAS at each cycle; Chi-squared test for difference in the distribution of the share of patients who improved, deteriorated or remained stable; Longitudinal analysis using repeated measures mixed-effects modeling to assess overall actual scores and change from baseline; K-M method (median and 95% CI) for TTD, Hochberg adjusted p-value

Source: Module 5.3.5.1 A7471050 CSR Sections 9.7.4; 16.1.9.1
Abbreviations: CI=confidence interval; CMH=Cochran–Mantel–Haenszel; CSR=clinical study report; DoR=duration of response; K-M=Kaplan-Meier; HR=hazard ratio; IRC=Independent Radiologic Central; ORR=objective response rate; OS_{30m}=overall survival at 30 months; PFS=progression-free survival; PRO=patient-reported outcome; QLQ-C30=quality of life questionnaire-core 30; QLQ-LC13=quality-of-life questionnaire lung cancer module (13); TTD=time to deterioration; TTF=time to treatment failure; VAS=visual analog scale.

There was an Interim analysis of OS at the time of final analysis for PFS for futility only. A gatekeeping procedure was used for hypotheses testing in a hierarchical approach to control the family-wise error rate for the analyses of primary endpoint, and key secondary endpoints of ORR per IRC review and OS. The null hypothesis for the primary endpoint was rejected. However, the null hypothesis for ORR was not rejected, and formal hypothesis testing for OS was therefore not to be conducted and the null hypothesis of equal OS is therefore not rejected.

Results

Participant flow



Source: Figure 1 in Wu et al, 2017
* 22 treatment-emergent adverse events related to study drug, 18 treatment-emergent adverse events not related to study drug, and one non-treatment-emergent adverse event.
† 15 treatment-emergent adverse events related to study drug and 12 treatment-emergent adverse events not related to study drug.

Figure 10: Chart of participant flow

The study completed its enrolment on 25 March 2015 with 452 patients randomized (ITT Population). Of these, 227 (100%) patients in the dacomitinib arm and 224 (99.6%) patients in the gefitinib arm received at least 1 dose of study treatment (AT Population). One (1) patient in the gefitinib arm was randomized but did not receive study treatment.

In the ITT Population, by the data cutoff date of 29 July 2016 the majority of patients in each treatment arm had permanently discontinued from treatment (70.9% in the dacomitinib arm and 82.7% in the gefitinib arm) and 40.1% of patients in the dacomitinib arm and 46.7% of patients in the gefitinib arm had discontinued from the study.

The most common reasons for permanent discontinuation were objective progression or relapse (34.8% dacomitinib vs. 50.4% gefitinib), global deterioration of health (11.5% dacomitinib vs. 14.7%), and TEAEs (17.6%

dacomitinib vs. 12.1% gefitinib).

Recruitment

The study was conducted at 90 study sites worldwide. Countries with study sites that randomized patients into the study were China (21 sites), Hong Kong (2 sites), Italy (13 sites), Japan (10 sites), Poland (3 sites), Republic of Korea (5 sites), and Spain (17 sites).

Conduct of the study

Several amendments to the original protocol were implemented. The amendments are not considered to have affected the outcome of the study.

A summary of major/critical protocol deviations is reported in the Table below.

The major/critical protocol deviations identified in the study fell into 3 categories:

- Patients who entered the study even though they did not strictly meet eligibility criteria.
- Patients who received incorrect treatment or dose of the study drug(s).
- Patients who did not participate in study assessments as required by the protocol.

Table 22: Post-Enrolment Major/Critical Post Deviations Summary- ITT Population

Number (%) of Patients	Dacomitinib (N=227) n (%)	Gefitinib (N=225) n (%)	Total (N=452) n (%)
Patients with any major/critical protocol deviation	120 (52.9)	102 (45.3)	222 (49.1)
Inclusion/exclusion criteria	49 (21.6)	43 (19.1)	92 (20.4)
Informed consent deviations	21 (9.3)	24 (10.7)	45 (10.0)
Study treatment	39 (17.2)	32 (14.2)	71 (15.7)
Labs	5 (2.2)	9 (4.0)	14 (3.1)
Procedure/tests	5 (2.2)	1 (0.4)	6 (1.3)
Safety reporting	10 (4.4)	9 (4.0)	19 (4.2)
Study procedure criteria	50 (22.0)	43 (19.1)	93 (20.6)

Source: Table 14.1.1.2 (see Errata).
ITT=intent-to-treat; N=number of patients; n=number of patients meeting prespecified criteria.

Baseline data

Table 23: Summary of demographic and baseline characteristics of patients with NSCLC with EGFR-activating mutations – Pivotal study A7471050 and Key supportive study A7471017 Cohort A – ITT population

Parameter Characteristic Statistic	A7471050 Dacomitinib (N=227)	 Gefitinib (N=225)[a]	A7471017 Cohort A Dacomitinib (N=45)
Age (years)			
Median, (Range)	62.0 (28-87)	61.0 (33-86)	62.0 (39-84)
<65 years	133 (58.6)	140 (62.2)	26 (57.8)
≥65 years	94 (41.4)	85 (37.8)	19 (42.2)
Gender, n, (%)			
Male	81 (35.7)	100 (44.4)	14 (31.1)
Female	146 (64.3)	125 (55.6)	31 (68.9)
Race, n (%)			
Asian	170 (74.9)	176 (78.2)	25 (55.6)
Non-Asian	57 (25.1)	49 (21.8)	20 (44.4)
White	56 (24.7)	49 (21.8)	18 (40.0)
Black	1 (0.4)	0	1 (2.2)
Other	0	0	1 (2.2)
Smoking Status, n (%)			
Non-Smoker	147 (64.8)	144 (64.0)	36 (80.0)
Ex-Smoker	65 (28.6)	62 (27.6)	9 (20.0)
Smoker	15 (6.6)	19 (8.4)	0

Source: Module 2.7.3.3.1.1, Table 5.
Abbreviations: n=number of patients in each category; N=number of patients.
a. One (1) patient in the gefitinib arm was randomized but did not receive study treatment.

Table 24: Summary of Biomarker Status at Randomization, ITT Population

	Dacomitinib (N=227) n (%)	Gefitinib (N=225) n (%)	Total (N=452) n (%)
EGFR Mutation (at Randomization)	227 (100.0)	225 (100.0)	452 (100.0)
Exon 19 deletion	134 (59.0)	133 (59.1)	267 (59.1)
With T790M	0 (0.0)	2 (0.9)	2 (0.4)
Without T790M	134 (59.0)	131 (58.2)	265 (58.6)
L858R mutation in exon 21	93 (41.0)	92 (40.9)	185 (40.9)
With T790M	2 (0.9)	0 (0.0)	2 (0.4)
Without T790M	91 (40.1)	92 (40.9)	183 (40.5)

Patients in study 1050 had Stage III/IV NSCLC at study entry (either newly diagnosed or recurrent disease) . Most patients in the dacomitinib arm and the gefitinib arm had an initial disease stage of Stage IV (181 patients [79.7%] and 183 patients [81.3%], respectively) and a current disease stage of Stage IV (184 patients [81.1%] and 183 patients [81.3%], respectively).

All patients had a histological status of adenocarcinoma. Most patients were randomised into the study within a month after initial diagnosis.

Four (4) patients in the dacomitinib arm and 1 patient in the gefitinib arm did not have a biopsy prior to study entry provided for EGFR mutation evaluation, as a deviation to the protocol.

In Study 1050, a total of 4 patients (0.9%; 2 in each treatment arm) had received prior systemic treatment; each of these patients received 1 platinum-based chemotherapy regimen.

Of these 4 patients, 2 (1 patient in each treatment arm) had received adjuvant systemic treatment for an earlier stage of NSCLC as permitted by the protocol, and 2 (1 patient in each treatment arm) were initially treated for Stage IV NSCLC with disease recurrence prior to entering the study and, according to the protocol, would have been ineligible for enrollment and treatment. Few patients in Study 1050 had previously undergone surgery (9.3% in the dacomitinib arm and 8.4% in the gefitinib arm) or radiation treatment (3.1% in the dacomitinib arm and 2.7% in the gefitinib arm).

The vast majority of patients reported concomitant drug use (224 [98.7%] in the dacomitinib arm and 213 [95.1%] in the gefitinib arm). The 3 most frequently reported concomitant drug treatments in the dacomitinib arm were loperamide (111 patients [48.9%]), herbal preparation/Traditional Chinese Medicine (64 patients [28.2%]), and dexamethasone (62 patients [27.3%]). The 3 most frequently reported concomitant drug treatments in the gefitinib arm were herbal preparation/Traditional Chinese Medicine (66 patients [29.5%]), dexamethasone (50 patients [22.3%]), and paracetamol (49 patients [21.9%]).

In relation to subsequent systemic therapy (SST), 113 (49.8%) patients in the dacomitinib arm and 140 (62.2%) in the gefitinib arm received SST. The median SST was 2 (range: 1 to 7) in the dacomitinib group and 1 (range: 1 to 8) in the gefitinib group. Pemetrexed, cisplatin and carboplatin were the most frequent SST in both treatment arms. Osimertinib was the EGFR-TKI most commonly used as SST (14.1% dacomitinib vs. 20.9% gefitinib).

Table 25: Summary of Subsequent Systemic Therapy (SST), ITT Population

	Dacomitinib (N=227)	Gefitinib (N=225)
Number (%) of subjects who received		
3rd generation agents [a]	22 (9.7)	25 (11.1)
Immunotherapies [b]	1 (0.4)	2 (0.9)
Chemotherapies [c]	63 (27.8)	80 (35.6)
EGFR TKIs [d]	20 (8.8)	19 (8.4)
Small Molecules [e]	1 (0.4)	1 (0.4)
Surgery [f]	0 (0.0)	3 (1.3)
Other [g]	6 (2.6)	12 (5.3)

a: Includes osimertinib (AZD9291), olmutinib (HM61713), rociletinib (CO-1686), avitinib (AC0010), TAS-121, and "EGFR TKI inbihitor".
b: Includes nivolumab, atezolizumab, durvalumab, investigational drug (immunotherapy), and human IgG1 monoclonal antibody.
c: Includes pemetrexed, cisplatin, carboplatin, paclitaxel, bevacizumab (given with chemotherapy), nedaplatin, gimeracil with oteracil/tegafur, vinorelbine, bleomycin, carboplatin/pemetrexed, carboplatin/gemcitabine, capecitabine, cisplatin/paclitaxel, cisplatin/pemetrexed, cis-DDP, custerirsen (antisense molecule given with chemotherapy), etoposide, lobaplatin, paclitaxel/carboplatin, temozolomide, thalidomide, methotrexate, "chemotherapeutics", cisplatin/gemcitabine, docetaxel, gemcitabine, TAS-102 (oral thymidine-based nucleic acid analogue and a thymidine phosphorylase inhibitor) and irinotecan hydrochloride hydrate.
d: Includes gefitinib, erlotinib, icotinib, afatinib, and "EGFR TKI".
e: Includes apatinib, giltertinib, capmatinib, famitinib, S49076 NFI, JNJ-42756493, MSC 2156119J, cabozantinib, volitinib and orantinib.
f: Includes excision of cervical lymph node, exeresis, lung lobectomy, lymphadenectomy, and pleural cavity drainage.
g: Includes nintedanib, denosumab, zoledronic acid, herbal preparation, ozone, IgG1 monoclonal antibodies, investigational product, herbal preparation ingredients unknown, custersen (monotherapy), cytokine-induced killer cells, dendritic cells cytokine-induced killer cells, avastin, "curative intent", docetaxel + cis-pratinum, cisplatin and pemetrexed, carboplatin + paclitaxel, PF299804 and ramucirumab.
Source Data: 16.2.5.2.4.3

Numbers analysed

Table 26: Summary of populations – ITT population

	Dacomitinib (N=227) n (%)	Gefitinib (N=225) n (%)
ITT population	227 (100)	225 (100)
AT population	227 (100)	224 (99.6)
PRO analysis set (QLQ-C30 and QLQ-LC13)	226 (99.6)	222 (98.7)
PRO analysis set (EQ-5D)	224 (98.7)	221 (98.2)
BM analysis set	227 (100)	224 (99.6)
PK analysis set	212 (93.4)	5 (2.2)[a]
PK analysis set (China only)	20 (8.8)	0

Source: Table 14.1.1.1.4.
AT=as-treated; BM=biomarker; EQ-5D=EuroQol-5 Dimensions; ITT=intent-to-treat; N=number of patients; n=number of patients meeting prespecified criteria; PK=pharmacokinetics; PRO=patient-reported outcome; QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30 (items); QLQ-LC13=European Organisation for Research and Treatment of Cancer Lung Cancer Module of the Quality of Life Questionnaire-13 (items).
a. Five (5) patients in the gefitinib arm had plasma specimens for PK collected in error. PK results from these patients are not analyzed or presented in this report.

Outcomes and estimation

Primary efficacy analysis

The median duration of PFS follow-up using reverse Kaplan-Meier method in the ITT Population based on IRC review was 22.1 months.

Table 27: Summary of Progression-Free Survival based on Independent Radiologic Central Review in Pivotal Study A7471050 –ITT population

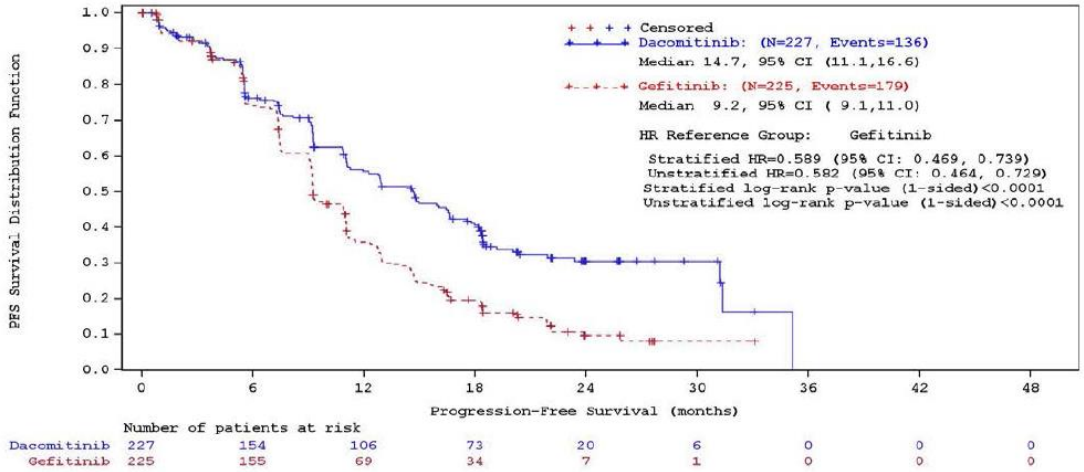
Response Parameter	Dacomitinib N=227	Gefitinib N=225
Number (proportion) with event, n (%)	136 (59.9)	179 (79.6)
Type of event, n (%)		
Objective progression	124 (54.6)	173 (76.9)
Death without objective progression	12 (5.3)	6 (2.7)
Number (proportion) censored, n (%)	91 (40.1)	46 (20.4)
Reason for censorship, n (%)		
No adequate baseline assessment	1 (0.4)	2 (0.9)
No on-study disease assessments	4 (1.8)	3 (1.3)
Given new anti-cancer treatment prior to tumor progression	23 (10.1)	18 (8.0)
Withdrew consent for follow-up	5 (2.2)	0
Lost to follow-up	0	0
Unacceptable gap (>16 weeks) between PD or death to the most recent prior adequate assessment	2 (0.9)	1 (0.4)
Discontinued without PD/death and no longer in follow-up for tumor progression	0	0
In follow-up for tumor progression	56 (24.7)	22 (9.8)
Probability of being event free at Month 12[a], % (95% CI)[b]	55.7 (48.5, 62.3)	35.9 (29.3, 42.4)
Probability of being event free at Month 18[a], % (95% CI)[b]	40.7 (33.7, 47.5)	19.6 (14.4, 25.5)
Probability of being event free at Month 24[a], % (95% CI)[b]	30.6 (23.8, 37.5)	9.6 (5.6, 15.0)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	7.3 (5.6, 9.1)	5.6 (5.5, 7.4)
50%	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
75%	31.2 (21.9, 35.1)	14.7 (13.0, 18.3)

Versus Gefitinib	
Stratified hazard ratio[d] [95% CI]	0.589 (0.469, 0.739)
Stratified log-rank test p-value, 1-sided[d]	<0.0001
Unstratified hazard ratio[e] [95% CI]	0.582 (0.464, 0.729)
Unstratified log-rank test p-value, 1-sided[e]	<0.0001

Source: Module 5.3.5.1 A7471050 CSR Table 14.2.5.3.1.1

Abbreviations: CI=confidence interval; CSR=clinical study report; EGFR=epidermal growth factor receptor; HR=hazard ratio; IWRS=Interactive Web Response System; ITT=intent to treat; N=number of patients; n=number of patients meeting prespecified criteria; PD=progressive disease; vs=versus.

a. Estimated from the Kaplan-Meier method.
b. Calculated based on Greenwood methods.
c. Based on the Brookmeyer and Crowley method.
d. HR and its CI are obtained from the stratified Cox regression and other p-values are based on the stratified log-rank test with race (Japanese vs mainland Chinese and other East Asian vs non-East Asian) and EGFR mutation status (del exon 19 vs the L858R mutation in exon 21) at randomization as the stratification factors. Both stratification factors race and EGFR mutation status were per IWRS at randomization.
e: HR and its CIs are obtained from the unstratified Cox regression and other p-values are based on the unstratified log-rank test.



Source: Figure 14.2.5.3.1.

Stratified HR and its CI were obtained from the stratified Cox Regression and stratified p-value was based on the stratified Log-rank test with race (Japanese vs mainland Chinese and other East Asian vs non-Asian) and EGFR mutation status at randomization as the stratification factors per IWRS.

CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; ITT=intent-to-treat; IWRS=Interactive Web Response System; N=number of patients; PFS=progression-free survival.

Figure 11: Kaplan-Meier plot of progression-free survival based on independent review – ITT population

Supportive Analyses of the Primary Endpoint

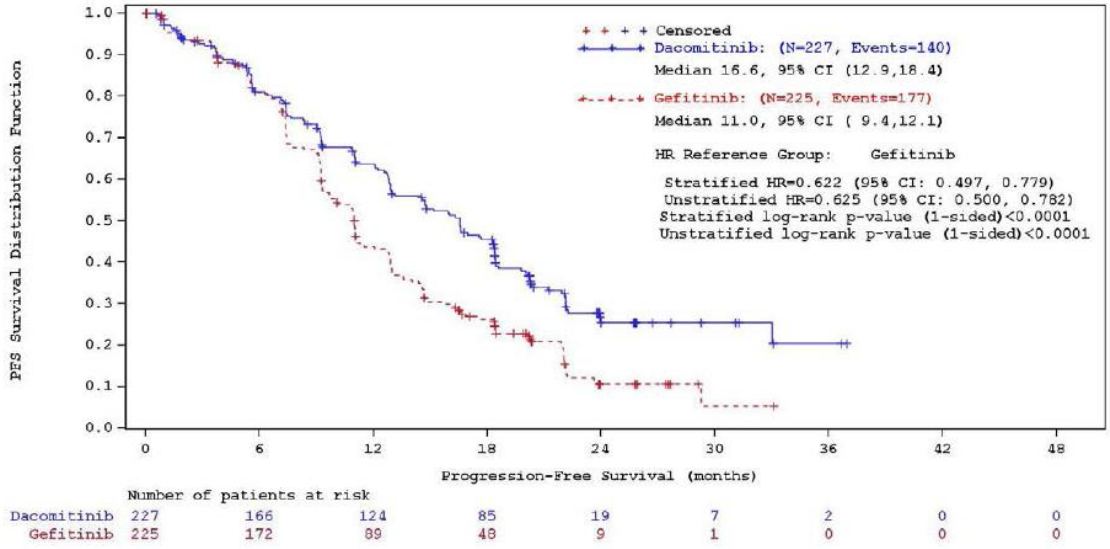
The robustness and consistency of the primary efficacy results were investigated in various sensitivity analyses. Overall, the results of these analyses were consistent with the primary analysis.

Analysis of the Primary Endpoint Not Censoring New Anti-Cancer Treatment.

Twenty-three (23) patients (10.1%) in the dacomitinib arm and 18 patients (8.0%) in the gefitinib arm were censored in the primary analysis for new anti-cancer treatment given prior to tumour progression. Overall, 137 patients (60.4%) in the dacomitinib arm and 181 patients (80.4%) in the gefitinib arm had a PFS event as of the data cutoff date. The HR of dacomitinib versus gefitinib not censoring new anti-cancer treatment was 0.582 (95% CI: 0.464, 0.729; 1-sided p<0.0001) based on the stratified analysis. The HR of dacomitinib versus gefitinib was 0.573 (95% CI: 0.458, 0.718; 1-sided p<0.0001) based on the unstratified analysis. The estimated median PFS was 14.7 months (95% CI: 11.3, 17.5) for the dacomitinib arm and 9.3 months (95% CI: 9.2, 11.0) for the gefitinib arm.

Secondary efficacy endpoints

- Progression-free survival per investigator assessment



HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and wilcoxon test with Race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomization as the stratification factors.
Source Data: Table 14.2.5.3.2.1
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Figure 12: Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment, ITT Population

Table 28: Disagreement between PFS results per INV versus PFS results per IRC- ITT population

Parameter and Disagreement Type[a]	Dacomitinib		Gefitinib		Differential Disagreement (%)
	N	n (%)	N	n (%)	
Censoring status disagreement rate (c + b)/N	227	36 (15.9)	225	30 (13.3)	2.6
Early disagreement rate (EDR) (b + a3)/(a1 + a2 + a3 + b)	140	28 (20.0)	177	25 (14.1)	5.9
Late disagreement rate (LDR) (c + a2)/(a1 + a2 + a3 + c)	136	74 (54.4)	179	99 (55.3)	-0.9
Overall disagreement rate (a2 + a3 + b + c)/N	227	102 (44.9)	225	124 (55.1)	-10.2

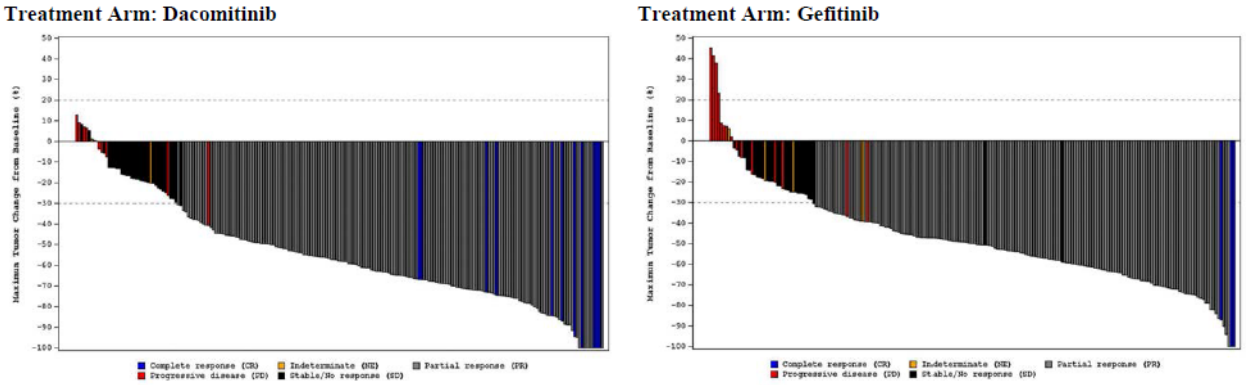
Source: Table 14.2.1.2.
INV=investigator assessment; IRC=Independent Radiologic Central; ITT=intent-to-treat; N=number of patients; n=number of patients meeting prespecified criteria; PFS=progression-free survival.
a. Parameters are defined as:
a1: number of agreements on both timing (difference ≤7 days) and occurrence of PFS event by IRC and INV review.
a2: number of agreements on occurrence of PFS event between IRC and INV for which INV declares PFS event later than IRC (>7 days).
a3: number of agreements on occurrence of PFS event between IRC and INV for which INV declares PFS event earlier than IRC (>7 days).
b: number of subjects for whom INV declares PFS event but IRC does not.
c: number of subjects for whom IRC declares PFS event but INV does not.

- Objective response rate (ORR)

Table 29: Objective response rate and best overall response based on IRC review in pivotal study A7471050 – ITT population

	Dacomitinib N=227	Gefitinib N=225
Objective response rate (CR plus PR), n (%)	170 (74.9)	161 (71.6)
95% exact CI[a]	(68.7, 80.4)	(65.2, 77.4)
Vs gefitinib		
1-sided p-value (stratified)[b]	0.1942	
1-sided p-value (unstratified)[c]	0.2117	
Best overall response, n (%)		
Complete response	12 (5.3)	4 (1.8)
Partial response	158 (69.6)	157 (69.8)
Stable disease	30 (13.2)	27 (12.0)
Progressive disease	12 (5.3)	15 (6.7)
Indeterminate	15 (6.6)	22 (9.8)

Source: Module 5.3.5.1 A7471050 CSR Table 14.2.2.1.
Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; CSR=clinical study report; EGFR=epidermal growth factor receptor; ITT=intent-to-treat; N=number of patients; n=number of patients meeting prespecified criteria; PR=partial response.
a. Using exact method based on binomial distribution.
b. p-value is from the CMH test stratified by EGFR mutation status (del exon 19 vs the L858R mutation in exon 21) based on their values at randomization and by race (Japanese vs mainland Chinese and other East Asian vs non-East Asian).
c. p-value is from a Pearson chi-squared test. When the number in at least 1 cell is too small (<5), an exact test is used.



Source: Module 5.3.5.1 A7471050 CSR Figure 14.2.12.1.1
Based on RECIST v1.1.
Abbreviations: CSR=clinical study report; ITT=intent-to-treat; RECIST=Response Evaluation Criteria in Solid Tumors.

Figure 13: Waterfall plot of maximum tumour change from baseline based on Independent Review by best overall response – ITT population

The ORRs per investigator assessment for patients in the dacomitinib and gefitinib arms were similar to those per IRC review: 75.3% (95% CI: 69.2, 80.8) and 70.2% (95% CI: 63.8, 76.1), respectively; stratified 1-sided p-value=0.0924 based on the CMH test stratified by EGFR mutation status (based on values at randomisation) and by race.

- Duration of response

Table 30: Duration of response in responders based on IRC review in pivotal study A7471050 – ITT population

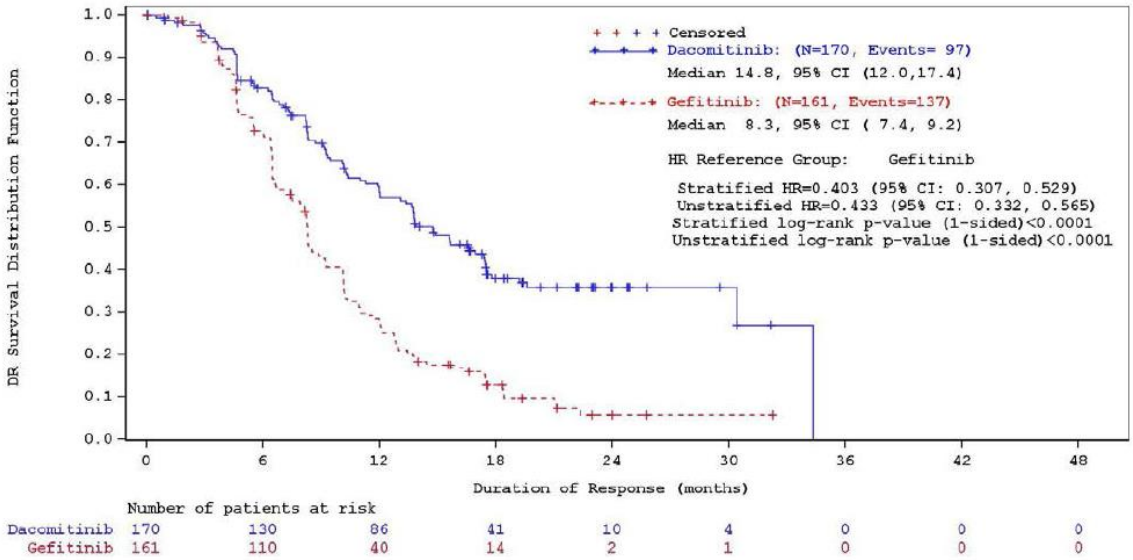
Response Parameter	Dacomitinib N=227	Gefitinib N=225
Patients with a response (CR or PR), n (%)	170 (74.9)	161 (71.6)
Type of response		
Patients with a response (CR or PR) and subsequent progression or death due to any cause while on study	97 (42.7)	137 (60.9)
Patients with a response (CR or PR) who have not progressed or died due to any cause while on study	73 (32.2)	24 (10.7)
Number censored, n (%)	73 (32.2)	24 (10.7)
Reason for censorship, n (%)		
No progression or death after response (CR or PR)	73 (32.2)	24 (10.7)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[a]		
50%	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)
Descriptive Summary of Response Duration (months)		
N	170	161
Mean	12.78	9.17
Median (Range)	12.02 (0.0-34.3)	8.11 (0.0-32.2)
Vs gefitinib		
Stratified hazard ratio (95% CI)[b]	0.403 (0.307, 0.529)	
Stratified log-rank test p-value, 2-sided[b]	<0.0001	

Source: Module 5.3.5.1 A7471050 CSR Table 14.2.7.1.1

Abbreviations: CI=confidence interval; CR=complete response; CSR=clinical study report; HR=hazard ratio; ITT=intent to treat; N=number of patients; n=number of patients meeting prespecified criteria; PR=partial response; vs=versus.

a. Based on the Brookmeyer-Crowley method.

b. HR and its CI and p-value are obtained from the stratified Cox regression and other p-values are based on the stratified log-rank test with race (Japanese vs mainland Chinese and other East Asian vs non-East Asian) and EGFR mutation status at randomization as the stratification factors.



HR and its CIs are obtained from the stratified Cox Regression and other p-values are based on the stratified log-rank and wilcoxon test with Race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomization as the stratification factors.
Source Data: Table 14.2.7.1.1
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Figure 14: Kaplan-Meier Plot of Duration of Response for Responders Based on Independent Review, ITT Population

The DoR HR for responders per investigator review for dacomitinib versus gefitinib was 0.545 (95% CI: 0.418, 0.711; 1-sided p-value<0.0001) based on the stratified analysis.

- Overall survival

A pre-specified interim analysis (IA) of OS was conducted at the time of final PFS analysis (29 July 2016) as specified in the Statistical Analysis Plan. The study passed the IA of OS for futility with 167 (36.9%) OS observed events with a HR of 0.759 (95% CI: 0.559, 1.031; 1-sided p-value=0.0381). Neither treatment arm had reached the median due to immature data by the data cut-off date.

The final analysis of OS in Study 1050 was conducted based on 220 (48.7%) deaths among 452 patients as of the 17 February 2017 data cutoff date. The median follow-up time for all 452 randomised patients in Study 1050 was 31.3 months (95% CI: 30.9, 31.9).

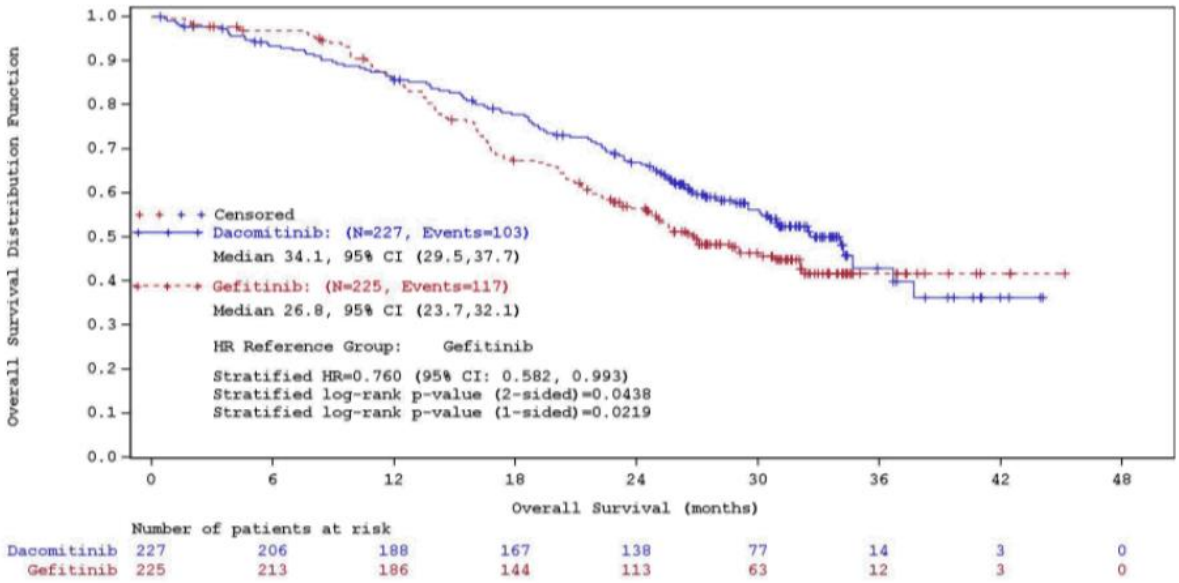
While the final readout of OS was statistically significant when assessed on its own, since the gate-keeping procedure stopped at the testing of ORR (per IRC review) as ORR was not statistically significant, the final readout of OS was not considered to be statistically significant.

Table 31: Summary of OS (stratified by race [merging Mainland Chinese and Other East Asian] and EGFR mutation status at randomization) – ITT population

	Dacomitinib N=227 n (%)	Gefitinib N=225 n (%)
Number of patients	227 (100)	225 (100)
Number of deaths	103 (45.4)	117 (52.0)
Cause of death		
Disease under study	93 (41.0)	108 (48.0)
Study treatment toxicity	2 (0.9)	1 (0.4)
Unknown	3 (1.3)	5 (2.2)
Other	5 (2.2)	3 (1.3)
Number of censored	124 (54.6)	108 (48.0)
Reason for censorship		
Alive	102 (44.9)	85 (37.8)
Patient no longer willing to participate	17 (7.5)	12 (5.3)
Lost to follow-up	4 (1.8)	6 (2.7)
Discontinued study for not meeting eligibility criteria	0	3 (1.3)
Other	1 (0.4)	2 (0.9)
Number of patients with last contact date >1 year prior to data cutoff date	158 (69.6)	137 (60.9)
Survival probability at month 12[a] (95% CI)[b]	85.6 (80.2, 89.6)	85.8 (80.5, 89.8)
Survival probability at month 18[a] (95% CI)[b]	77.7 (71.6, 82.7)	67.3 (60.6, 73.1)
Survival probability at month 24[a] (95% CI)[b]	66.9 (60.2, 72.8)	56.4 (49.5, 62.8)
Survival probability at month 30[a] (95% CI)[b]	56.2 (49.0, 62.8)	46.3 (39.3, 53.1)
Survival probability at month 36[a] (95% CI)[b]	43.0 (32.9, 52.7)	41.7 (34.3, 48.9)
Survival probability at month 42[a] (95% CI)[b]	36.3 (24.5, 48.1)	41.7 (34.3, 48.9)
Survival probability at month 48[a] (95% CI)[b]	36.3 (24.5, 48.1)	41.7 (34.3, 48.9)
Kaplan-Meier estimates of time to event (months) quartiles (95% CI)[c]		
25%	19.1 (15.9, 22.5)	16.0 (13.6, 17.0)
50%	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
75%	NE (37.7, NE)	NE (NE, NE)
Versus gefitinib		
Stratified hazard ratio (95% CI)[d]	0.760 (0.582, 0.993)	
Stratified log-rank test p-value (1-sided)[e]	0.0219	
Unstratified hazard ratio (95% CI)[f]	0.802 (0.615, 1.045)	
Unstratified log-rank test p-value (1-sided)[g]	0.0510	

Source: Table 14.2.6.1.1.1.
Note: "Cause of death" as per CRF. Patient may be reported under more than 1 reason of death. The patients censored for "Other" reason discontinued study due to completion of protocol-specified survival follow-up period.
CI=confidence interval; CRF=case report form; EGFR=epidermal growth factor receptor; N=number of patients in treatment group; n=number of patients in specified group; NE=not estimable; ITT=Intent-to-Treat.

a. Estimated from the Kaplan-Meier method.
b. Calculated based on Greenwood methods.
c. Based on the Brookmeyer-Crowley method.
d. Hazard ratio and its CIs are obtained from the stratified Cox Regression.
e. p-values are based on the stratified log-rank text with race (merging mainland Chinese and other East Asian) and EGFR mutation at randomization as the stratification factors.
f. Hazard ratio and its CIs are obtained from the unstratified Cox Regression.
g. p-values are based on the unstratified log-rank test.



Source: Figure 14.2.6.3.1.
Note: Hazard ratio and its CIs were obtained from the stratified Cox Regression with Race (Japanese vs mainland Chinese and other East Asian vs non-Asian) and EGFR mutation status at randomization as the stratification factors.
CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; N=number of subjects in treatment group; ITT=Intent-to-Treat.

Figure 15: Kaplan-Meier plot of overall survival in pivotal study A7471050

Supportive Analyses of overall survival

Analysis of the Overall Survival Censoring at First Subsequent Therapy

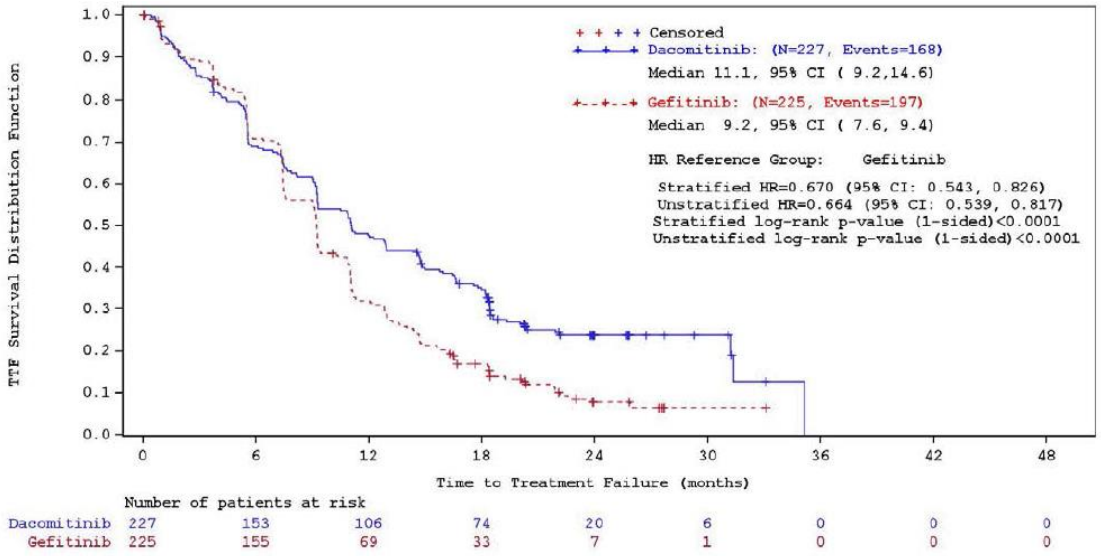
Pre-specified analyses of OS (censoring patients at the date of initiation at first subsequent therapy for those who received at least 1 subsequent therapy) were conducted to mitigate the confounding impact of subsequent therapies on OS. The estimated OS HR was 0.739 (95% CI: 0.489, 1.115) with a 1-sided p-value of 0.0737 based on stratified analysis, indicating a 26.1% reduction in the risk of death in favour of the dacomitinib arm.

First subsequent therapy during active treatment or follow-up was defined as the first systemic therapy, radiation therapy with curative intent, or surgery with curative intent.

The robustness and consistency of the OS-data were investigated in several other sensitivity analyses.

- Time to treatment failure

Overall, 168 patients (74.0%) in the dacomitinib arm and 197 patients (87.6%) in the gefitinib arm reached a treatment failure event. TTF by blinded IRC review demonstrated an improvement with dacomitinib as compared with gefitinib (HR=0.670 [95% CI: 0.543, 0.826; 1 sided p-value<0.0001] based on the stratified analysis and HR=0.664 [95% CI: 0.539, 0.817; 1 sided p-value<0.0001] based on the unstratified analysis). The estimated median TTF was 11.1 months (95% CI: 9.2, 14.6) for the dacomitinib arm and 9.2 months (95% CI: 7.6, 9.4) for the gefitinib arm.



Source: Figure 14.2.9.3.1.
Stratified HR and its CI were obtained from the stratified Cox Regression and stratified p-value was based on the stratified Log-rank test with race (Japanese vs mainland Chinese and other East Asian vs non-Asian) and EGFR mutation status at randomization as the stratification factors per IWRS.
CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; ITT=intent-to-treat; IWRS=Interactive Web Response System; N=number of patients; TTF=time to treatment failure.

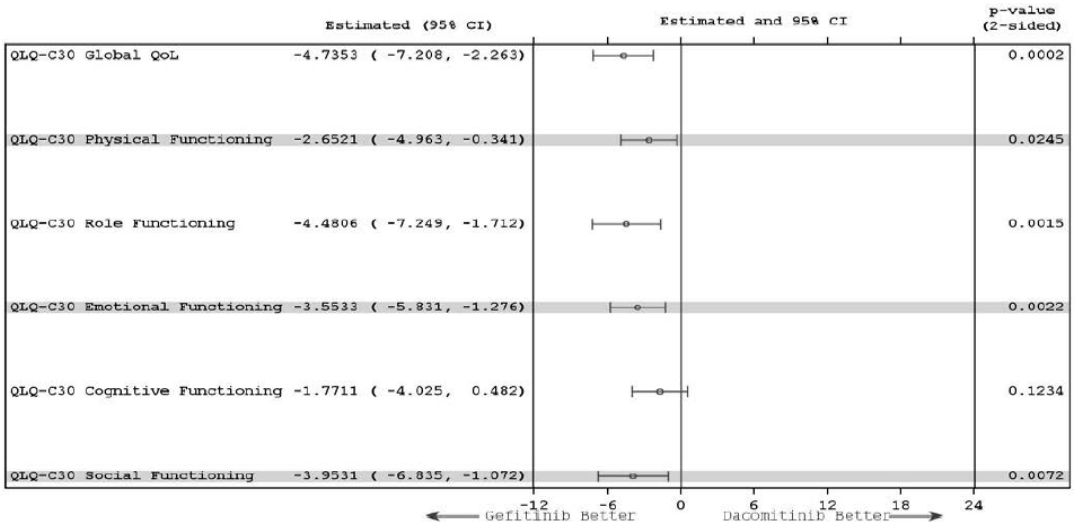
Figure 16: Kaplan-Meier plot of TTF based on independent review – ITT population

TTF HR based on investigator assessment for dacomitinib versus gefitinib was 0.695 (95% CI: 0.563, 0.858; 1-sided p-value=0.0003) based on the stratified analysis. The estimated median TTF was 13.0 months (95% CI: 11.1, 16.6) for the dacomitinib arm and 11.0 months (95% CI: 9.3, 11.1) for the gefitinib arm.

- Patient reported outcomes (PRO)

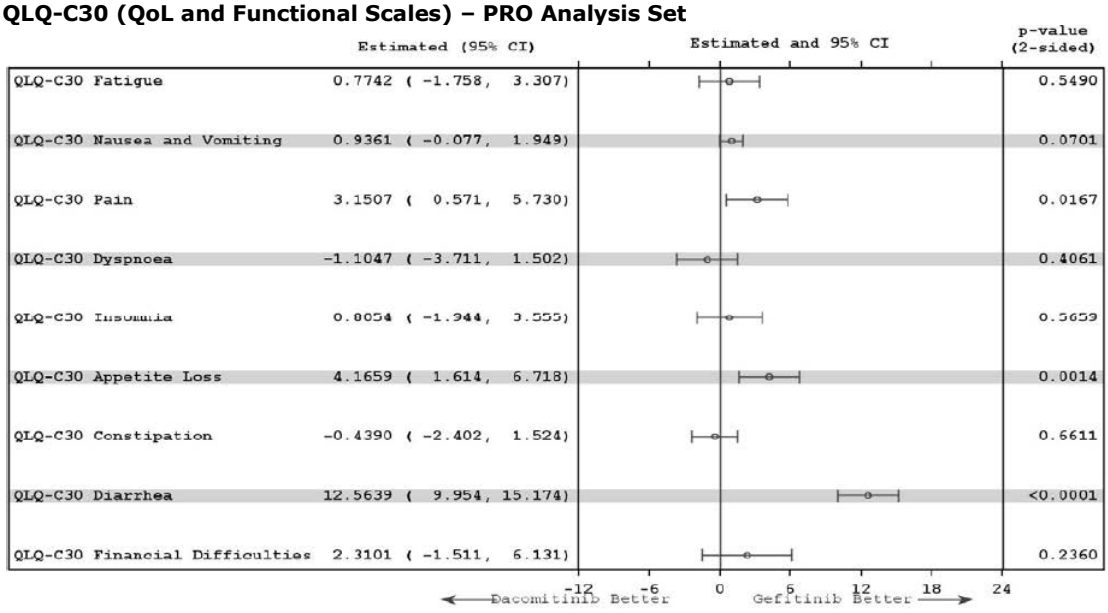
The rates of completion were high with >90% of patients answering all questions in almost all cycles for the EORTC QLQ-C30, QLQ-LC13, and EQ-5D questionnaires in the dacomitinib and gefitinib arms.

There was no statistically significant difference in TTD between the dacomitinib and gefitinib arms with respect to pain (in chest or arm/shoulder), dyspnea, fatigue, or cough as a composite endpoint (HR 1.173 [CI 95%: 0.928, 1.483]), nor its individual symptom items. The sensitive analysis confirmed the primary analysis.
In the dacomitinib arm, there was no statistically significant change from baseline observed for overall global QoL. In the gefitinib arm, a statistically significant improvement was seen in change from baselines (p<0.0001), but did not reach the 10-point threshold of being clinically meaningful. A statistically significant difference in global quality of life was observed between the two treatment groups, favouring gefitinib (P=0.0002).
The change from baseline in general health status as measured by EQ-5D/VAS was found to be statistically significantly lower in the dacomitinib arm compared with the gefitinib arm (p value=0.0008).



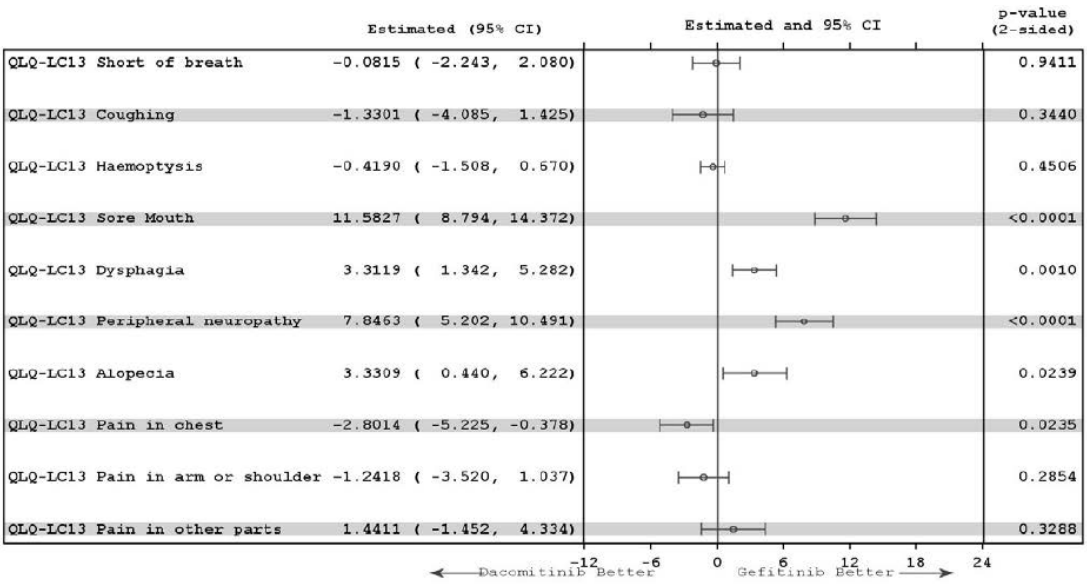
Source: Figure 14.2.11.4.1.
From a repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).
CI=confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items); EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Lung Cancer Module of the Quality of Life Questionnaire-13 (items); PRO=patient-reported outcome; QoL=quality of life.

Figure 17: Forest plot of dacomitinib versus gefitinib in overall differences in mean change from baseline EORT QLQ-C30 (QoL and Functional Scales) – PRO Analysis Set



Source: Figure 14.2.11.4.2.
From a repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).
CI=confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items); EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Lung Cancer Module of the Quality of Life Questionnaire-13 (items); PRO=patient-reported outcome.

Figure 18: Forest plot of dacomitinib versus gefitinib in overall differences in mean change from baseline EORT QLQ-C30 (Symptom Scales) – PRO Analysis Set



Source: Figure 14.2.11.4.3.
From a repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).
CI=confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items); EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Lung Cancer Module of the Quality of Life Questionnaire-13 (items); PRO=patient-reported outcome.

Figure 19: Forest plot of dacomitinib versus gefitinib in overall differences in mean change from baseline EORT QLQ-LC13 symptom scales – PRO Analysis Set

Ancillary analyses

- Subgroup analyses

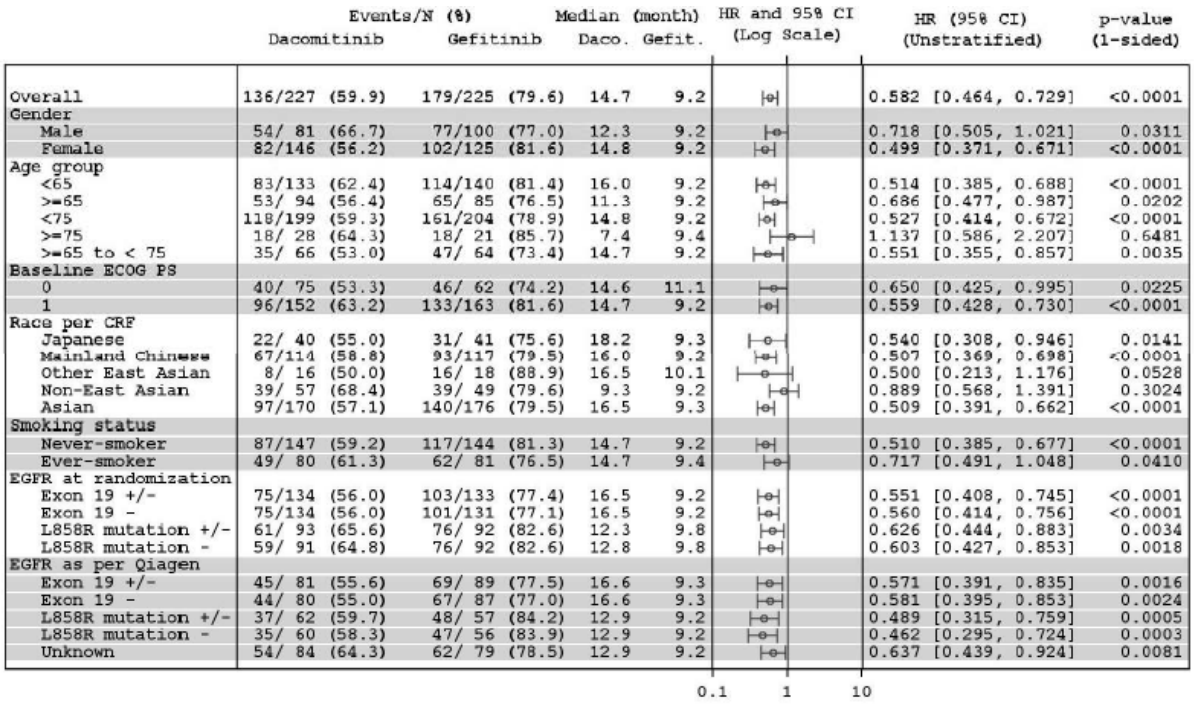


Figure 20: Forest plot of progression-free survival based on Independent Radiologic Central Review for patient subgroups in pivotal study A7471050 – ITT population

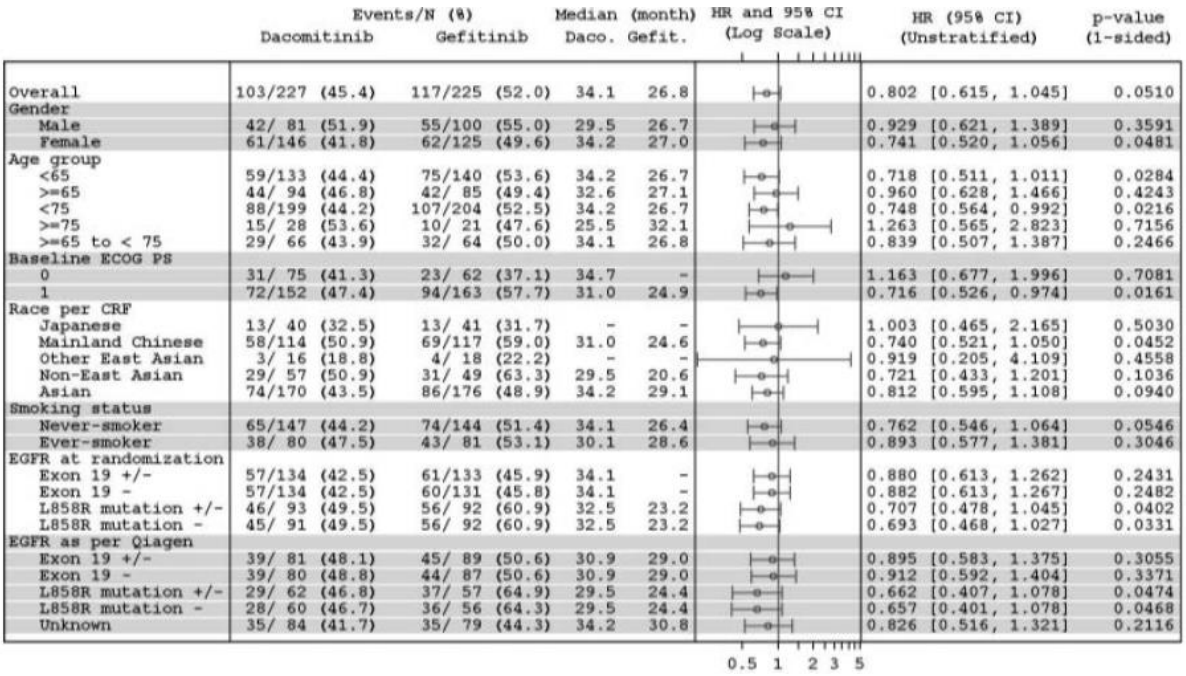


Figure 21: Forest Plot of Overall Survival – ITT Population

- Efficacy in Non-Asian versus Asian patients

Eleven (19.3%) non-Asian and 55 (32.4%) Asian patients in the dacomitinib arm, and 7 (14.3%) non-Asian and 31 (17.6%) Asian patients in the gefitinib arm were still on treatment as of the data cutoff date.

Table 32: Exposure to Dacomitinib by Race Subgroup (Non-Asian versus Asian) in Phase 3 Study A7471050 – As-Treated

Exposure Category	Dacomitinib (N=227)			Gefitinib (N=224)		
	Non-Asian	Asian	Total	Non-Asian	Asian	Total
Total number of patients (n)	57	170	227	48	176	224
Number of cycles	714	2928	3642	685	2526	3211
Number of cycles per patient	12.5	17.2	16.0	14.3	14.4	14.3
Median (range)	11.0 (1-33)	20.0 (1-41)	17.0 (1-41)	13.0 (1-34)	13.0 (1-38)	13.0 (1-38)
Duration of treatment (weeks)						
Median (range)	44.14 (2.7-131.1)	77.93 (0.3-162.7)	66.57 (0.3-162.7)	51.57 (3.9-133.1)	52.71 (0.3-148.3)	52.14 (0.3-148.3)
Relative dose intensity (%)[a]						
Mean (Std Dev)	74.41 (19.405)	72.86 (22.208)	73.25 (21.508)	96.46 (6.199)	95.88 (10.163)	96.00 (9.445)
Median (range)	69.70 (36.1-100.0)	73.20 (10.0-100.0)	72.50 (10.0-100.0)	98.90 (69.1-100.0)	99.90 (55.3-100.0)	99.80 (55.3-100.0)

Data source: Module 5.3.5.1 A7471050 CSR Tables 14.4.1.1.1.1; 14.4.1.2.1; 14.4.1.4.1; Module 5.3.5.3 NASER Tables 14.4.1.1.1.1.1.5; 14.4.1.2.1.5; 14.4.1.4.1.5; 14.4.1.7.1.

Abbreviations: CSR=Clinical Study Report; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; Std Dev=standard deviation.

Note: 1) Duration of treatment was defined as the time from the first to and including last dosing date of treatment.

2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

a. Relative dose for a cycle was defined as actual received total dose in a cycle divided by (45 mg dacomitinib × number days in cycle) or (250 mg gefitinib x number of days in cycle). Therefore, relative dose was identical to relative dose intensity for continuous dosing such as dacomitinib dosing.

Table 33: Reasons for Permanent Treatment Discontinuation by Race Subgroup (Non-Asian versus Asian) in Phase 3 Study A7471050– As-Treated Patients

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Category	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Number of patients discontinued	46 (80.7)	115 (67.6)	161 (70.9)	41 (85.4)	145 (82.4)	186 (83.0)
Primary reason for permanent discontinuation						
Progressive disease	25 (43.9)	54 (31.8)	79 (34.8)	25 (52.1)	88 (50.0)	113 (50.4)
AEs[a]	12 (21.1)	28 (16.5)	40 (17.6)	5 (10.4)	22 (12.5)	27 (12.1)
Related to treatment	4 (7.0)	18 (10.6)	22 (9.7)	2 (4.2)	13 (7.4)	15 (6.7)
Not related to treatment	8 (14.0)	10 (5.9)	18 (7.9)	3 (6.3)	9 (5.1)	12 (5.4)
Deterioration of global health	7 (12.3)	19 (11.2)	26 (11.5)	9 (18.8)	24 (13.6)	33 (14.7)
Patient withdrawal	2 (3.5)	6 (3.5)	8 (3.5)	1 (2.1)	3 (1.7)	4 (1.8)
AEs not considered to be treatment emergent	0	1 (0.6)	1 (0.4)	0	0	0
Lack of efficacy	NR	NR	NR	NR	NR	NR
Study terminated by Sponsor	0	0	0	0	0	0
Death[b]	0	0	0	0	0	0
Protocol deviation	0	0	0	0	2 (1.1)	2 (0.9)
Lost to follow-up	0	0	0	0	1 (0.6)	1 (0.4)
Other	0	7 (4.1)	7 (3.1)	1 (2.1)	5 (2.8)	6 (2.7)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.1.1.4.1; Module 5.3.5.3 NASER Table 14.1.1.4.1.5.
Abbreviations: AE=adverse event; CRF=Case Report Form; CSR=Clinical Study Report; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; NR=not reported.
Note: 1) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. AEs with missing causality assessment are classified as related to study drug.
b. Based on the Patient Summary page of the CRF.

Baseline characteristics

Table 34: Demographic and patient smoking status characteristics by race subgroup (Non-Asian vs. Asian) – ITT population

	Dacomitinib (N=227)			Gefitinib (N=225)		
Category	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Sex, n (%)						
Women	38 (66.7)	108 (63.5)	146 (64.3)	32 (65.3)	93 (52.8)	125 (55.6)
Men	19 (33.3)	62 (36.5)	81 (35.7)	17 (34.7)	83 (47.2)	100 (44.4)
Age (years)						
Median (range)	68.0 (39-87)	60 (28-83)	62.0 (28-87)	65.0 (43-83)	60.5 (33-86)	61.0 (33-86)
<65, n (%)	21 (36.8)	112 (65.9)	133 (58.6)	24 (49.0)	116 (65.9)	140 (62.2)
≥65, n (%)	36 (63.2)	58 (34.1)	94 (41.4)	25 (51.0)	60 (34.1)	85 (37.8)
<75, n (%)	41 (71.9)	158 (92.9)	199 (87.7)	42 (85.7)	162 (92.0)	204 (90.7)
≥75, n (%)	16 (28.1)	12 (7.1)	28 (12.3)	7 (14.3)	14 (8.0)	21 (9.3)
65-74, n (%)	20 (35.1)	46 (27.1)	66 (29.1)	18 (36.7)	46 (26.1)	64 (28.4)
Smoking status, n (%)						
Never smoker	38 (66.7)	109 (64.1)	147 (64.8)	29 (59.2)	115 (65.3)	144 (64.0)
Smoker	NR	NR	NR	NR	NR	NR
Current smoker	4 (7.0)	11 (6.5)	15 (6.6)	4 (8.2)	15 (8.5)	19 (8.4)
Ex-smoker	15 (26.3)	50 (29.4)	65 (28.6)	16 (32.7)	46 (26.1)	62 (27.6)
Unknown	0	0	0	0	0	0

Data source: Module 5.3.5.1 A7471050 CSR Table 14.1.2.1; Module 5.3.5.3 NASER Table 14.1.2.1.5.
Abbreviations: CSR=Clinical Study Report; ITT=intent-to-treat; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; NR=not reported.
Note: 1) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

Table 35: Previous systemic therapy and baseline disease characteristics by race subgroup (Non-Asian versus Asian) – ITT population

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=225)		
Category	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Lines of prior systemic therapy						
0	56 (98.2)	169 (99.4)	225 (99.1)	48 (98.0)	175 (99.4)	223 (99.1)
1	1 (1.8)	1 (0.6)	2 (0.9)	1 (2.0)	1 (0.6)	2 (0.9)
EGFR-activating mutations	57 (100)	170 (100)	227 (100)	49 (100)	176 (100)	225 (100)
Del exon 19	35 (61.4)	99 (58.2)	134 (59.0)	30 (61.2)	103 (58.5)	133 (59.1)
+ T790M	0	0	0	0	2 (1.1)	2 (0.9)
Exon 21 L858R mutation	22 (38.6)	71 (41.8)	93 (41.0)	19 (38.8)	73 (41.5)	92 (40.9)
+ T790M	1 (1.8)	1 (0.6)	2 (0.9)	0	0	0
Current disease stage						
Stage IIIb	5 (8.8)	13 (7.6)	18 (7.9)	1 (2.0)	15 (8.5)	16 (7.1)
Stage IV	48 (84.2)	136 (80.0)	184 (81.1)	45 (91.8)	138 (78.4)	183 (81.3)
Unknown[a]	4 (7.0)	21 (12.4)	25 (11.0)	3 (6.1)	23 (13.1)	26 (11.6)
ECOG PS, n (%)						
0	24 (42.1)	51 (30.0)	75 (33.0)	16 (32.7)	46 (26.1)	62 (27.6)
1	33 (57.9)	119 (70.0)	152 (67.0)	33 (67.3)	130 (73.9)	163 (72.4)

Data source: Module 5.3.5.1 A7471050 CSR Tables 14.1.2.7; 14.1.2.2; 14.1.2.6; 14.4.2.2.1.1.1; Module 5.3.5.3 NASER Tables 14.1.2.2.5; 14.1.2.6.5; 14.1.2.7.1; 14.4.2.2.1.1.1.5.

Abbreviations: CSR=Clinical Study Report; Del=deletion; ECOG=Eastern Cooperative Oncology Group; EGFR=Epidermal Growth Factor Receptor; ITT=intent to treat; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PS=performance status.

Note: 1) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

a. All patients with unknown current disease stage were newly diagnosed Stage IV at the time of study entry (<2 months interval from initial disease stage).

Efficacy results

PFS

Table 36: Summary of Progression-Free Survival Based on Independent Review by Race (Non-Asian versus Asian) and by Responding Status per Independent Review in Study A7471050 (ITT Population)

	N (%)[a]		Event Rate n (%)				Median PFS (months)	
	Dacomitinib	Gefitinib	Dacomitinib	Gefitinib	HR	95% CI	Dacomitinib	Gefitinib
Overall	227	225	136 (59.9)	179 (79.6)	0.589	0.469, 0.739	14.7	9.2
Non-Asian	57	49	39 (68.4)	39 (79.6)	0.889	0.568, 1.391	9.3	9.2
Responder	39 (68.4)	33 (67.3)	28 (71.8)	30 (90.9)	0.547	0.321, 0.933	10.9	9.1
Non-responder	18 (31.6)	16 (32.7)	11 (61.1)	9 (56.3)	2.498	1.004, 6.213	5.6	11.3
Asian	170	176	97 (57.1)	140 (79.5)	0.509	0.391, 0.662	16.5	9.3
Responder	131 (77.1)	128 (72.7)	69 (52.7)	107 (83.6)	0.431	0.317, 0.586	18.2	10.9
Non-responder	39 (22.9)	48 (27.3)	28 (71.8)	33 (68.8)	0.917	0.549, 1.531	5.5	7.4

Data source: Module 5.3.5.1 A7471050 CSR Table 14.2.2.5; 14.2.5.3.1.1; 14.2.5.3.1.19; Module 5.3.5.3 NASER Tables 14.2.5.3.1.19.6; 14.2.5.3.1.19.7.

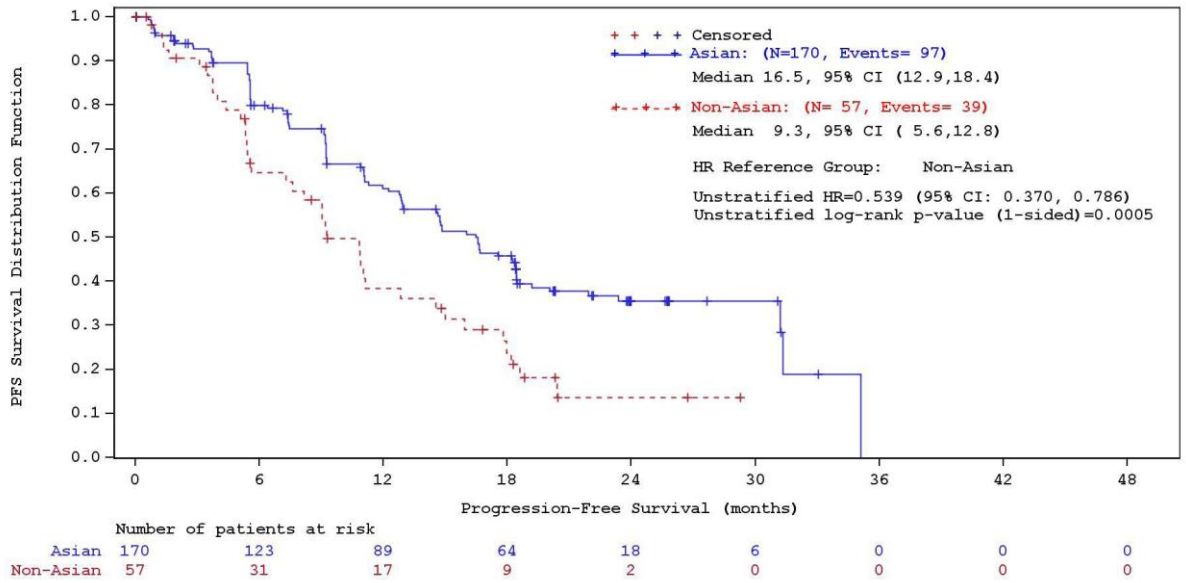
Abbreviations: BOR=best overall response; CI=confidence interval; CR=complete response; CRF=case report form; CSR=Clinical Study Report; HR=hazard ratio; ITT=intent-to-treat; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PFS=progression-free survival; PR=partial response.

Notes: 1) HR and p-values are obtained from the stratified analyses for the Overall population and unstratified analyses for all group analyses.

2) The Asian subgroup consisted of patients whose race was reported on the CRF were as Mainland Chinese, Japanese and Other East Asian. The non-Asian subgroup consisted of patients whose race was reported on the CRF as Black or White patients.

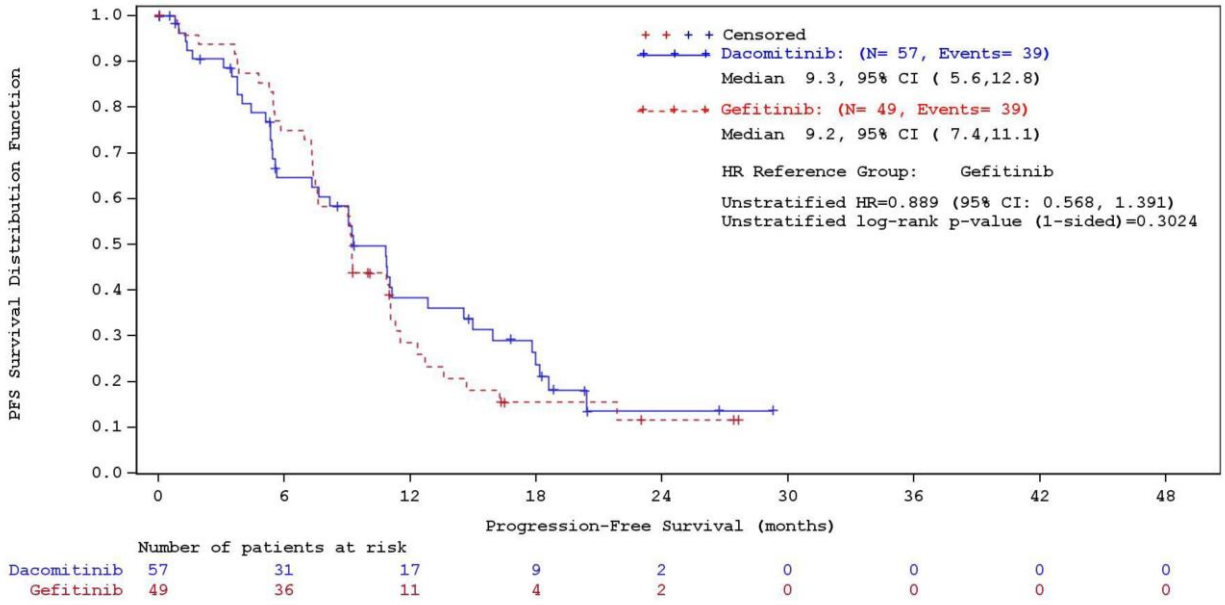
3) Responders consisted of those patients who achieved a BOR of CR or PR per independent review, while non-responders consisted of those patients who did not achieve a BOR of CR or PR.

a. Percentages for non-Asian and Asian non-responders were calculated using the denominators N=57 (dacomitinib) and N=49 (gefitinib) for non-Asian patients and N=170 (Dacomitinib) and N=176 (gefitinib) for Asian patients (Table 14.2.2.5).



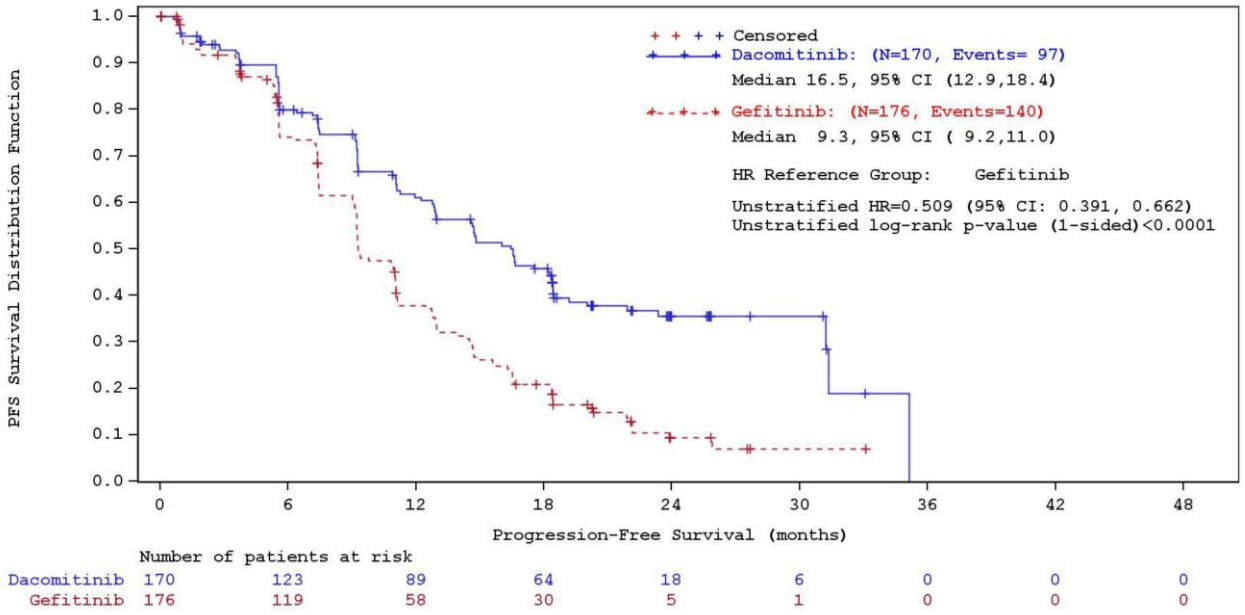
CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N=number of patients.
Note: Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

Figure 22: Kaplan-Meier Plot of PFS per Independent Review for Asian versus Non-Asian in the Dacomitinib arm in Study A7471050 – ITT Population



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N=number of patients.
Note: Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

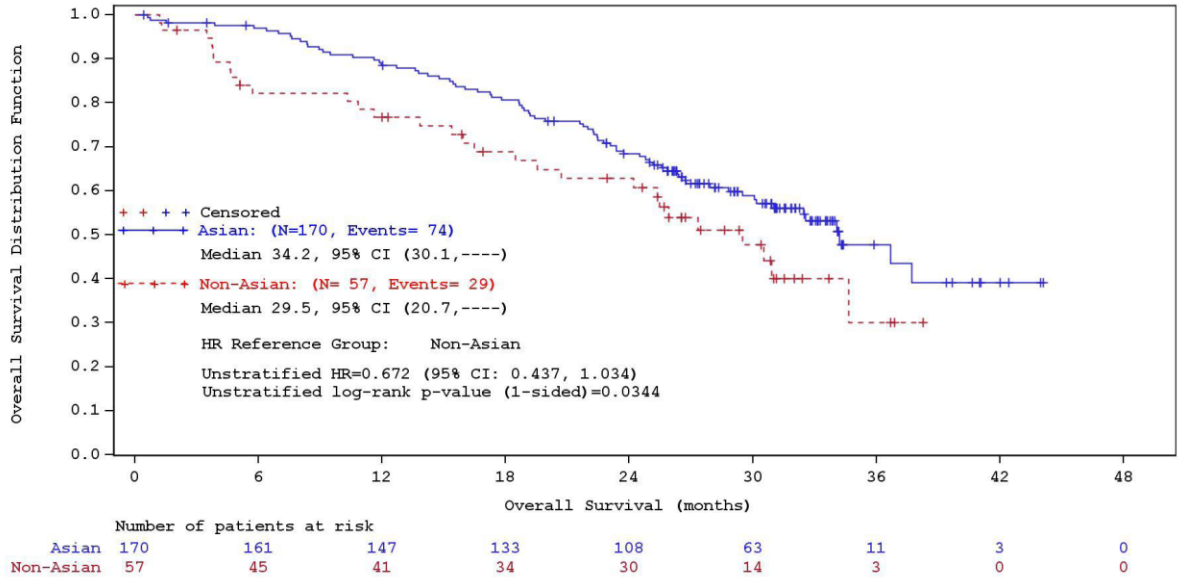
Figure 23: Kaplan-Meier Plot of PFS per Independent Review by Race per CRF in Study A7471050 – ITT Population, Non Asian



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N=number of patients.
Note: Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

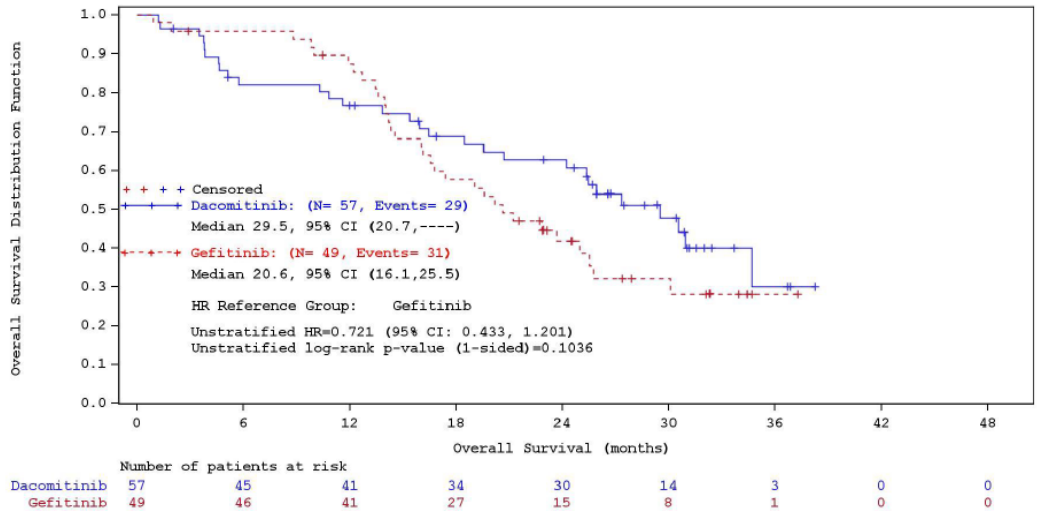
Figure 24: Kaplan-Meier Plot of PFS per Independent Review by Race per CRF in Study A7471050 – ITT Population, Asian

OS



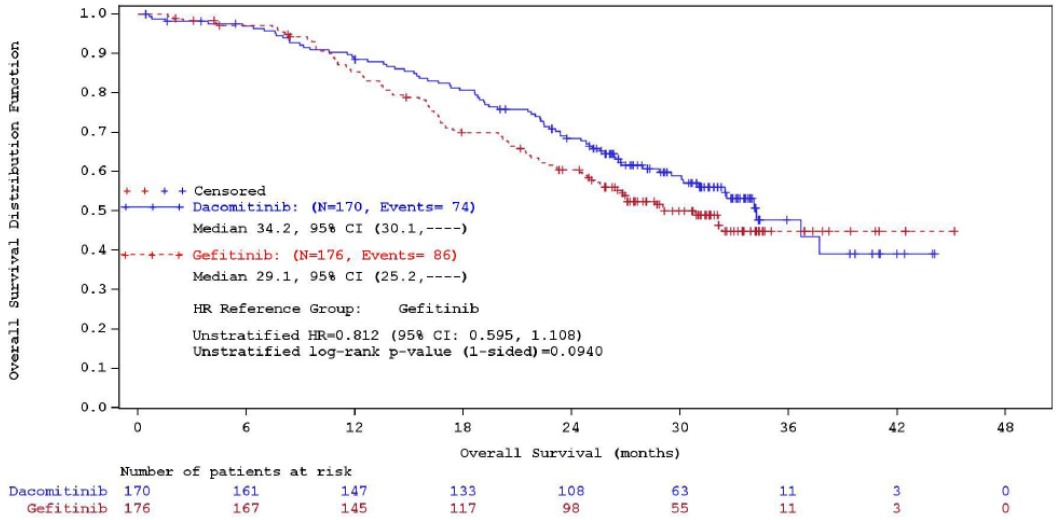
CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N=number of patients.
Note: Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

Figure 25: Kaplan-Meier Plot of OS by Race per CRF for Asian versus Non-Asian in the Dacomitinib arm in Study A7471050 – ITT Population



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N=number of patients.
Note: Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

Figure 26: Kaplan-Meier Plot of OS by Race per CRF in Study A7471050 – ITT Population, Non Asian



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N=number of patients.
Note: Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

Figure 27: Kaplan-Meier Plot of OS by Race per CRF in Study A7471050 – ITT Population, Asian

ORR

ORR based on IRC review was 68.4% (95% CI: 54.8, 80.1) for the 57 patients in the non-Asian subgroup and 77.1% (95% CI: 70.0, 83.1) for 170 patients in the Asian subgroup in the dacomitinib arm, and 67.3% (95% CI: 52.5, 80.1) for 49 patients in the non-Asian subgroup and 72.7% (95% CI: 65.5, 79.2) for 176 patients in the Asian subgroup and in the gefitinib arm.

DoR

In Study 1050, the DoR HR in responders per IRC review (dacomitinib versus gefitinib) was 0.526 (95% CI: 0.310, 0.892) for the non-Asian subgroup and 0.397 (95% CI: 0.291, 0.541) for the Asian subgroup; the

median DoR (mDoR) per IRC review for the non-Asian subgroup was 10.1 months (95% CI: 6.8, 13.8) in the dacomitinib arm and 6.6 months (95% CI: 5.2, 8.4) in the gefitinib arm; mDoR for the Asian subgroup was 16.6 months (95% CI: 13.8, 30.4) in the dacomitinib arm and 8.3 months (95% CI: 8.1, 10.2) in the gefitinib arm.

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37: Summary of efficacy for trial A7471050 (ARCHER 1050)

Title: A phase III, randomized, open-label study to A Randomized, Open-Label, Phase 3, efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic Non-Small Cell Lung Cancer in subjects with Epidermal Growth Factor Receptor (EGFR) activating mutations			
Study identifier	A7471050 (DP-312804)		
Design	Phase III, multicentre, open-label, randomized study		
	Duration of main phase:		09-May-2013 (First Patient First Visit) to 29-Jul-2016 (Primary Completion Date)
Hypothesis	Superiority over gefitinib		
Treatments groups	Dacomitinib		Dacomitinib 45 mg orally once a day; n=227
	Gefitinib		Gefitinib 250 mg orally once a day; n=225
Endpoints and definitions	Primary endpoint	PFS	PFS was defined as the time from randomization to the date of disease progression by RECIST v1.1 as determined by blinded IRC
	Secondary endpoint	ORR	Proportion of randomized patients with a BOR of either a complete response (CR) or partial response (PR), relative to the total number of patients. ORR was determined per RECIST v1.1 both IRC and INV
	Secondary endpoint	DoR	DoR in responders was defined as the time from first documentation of objective response (CR or PR) to date of progression or death due to any cause, whichever occurred first. DoR was calculated for the subgroup of patients with an objective tumour response. DoR was determined by both IRC review and INV
	Secondary endpoint	OS	Time from randomization to the date of death for any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive.
	Secondary endpoint	TTF	TTF was defined as the time from randomization to the date of treatment failure (first documentation of progression, death due to any cause, or discontinuation of treatment due to any cause, whichever occurred first). TTF was determined by both IRC review and INV.
Database lock	29-Jul-2016 (for PFS)		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat population (Dacomitinib n=227; Gefitinib n=225) Data cut-off date of main analysis of PFS is 29 July 2016 (OS is based on the data cut-off date of 17 February2017)			
Descriptive statistics and estimate variability	Treatment group	Dacomitinib	Gefitinib	
	Number of subject	227	225	
	Primary endpoint PFS (IRC) Median (months)	14.7	9.2	
	(95% CI)	(11.1, 16.6)	(9.1, 11.0)	
	Secondary endpoint ORR (IRC) n (%)	170 (74.9%)	161 (71.6%)	
	(95% CI)	(68.7, 80.4)	(65.2, 77.4)	
	Secondary endpoint DoR(IRC) Median (months)	14.8	8.3	
	(95% CI)	(12.0, 17.4)	(7.4, 9.2)	
	Secondary endpoint OS Median (months)	34.1	26.8	
	(95% CI)	(29.5, 37.7)	(23.7, 32.1)	
	Secondary endpoint TTF (IRC) Median (months)	11.1	9.2	
	(95% CI)	(9.2, 14.6)	(7.6, 9.4)	

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Dacomitinib vs. gefitinib
		HR (stratified)	0.589
		(95 CI)	(0.469, 0.739)
		P-value (1-sided)	< 0.0001
	Secondary endpoint ORR	Comparison groups	Dacomitinib vs. gefitinib
		P-value (1-sided, stratified)	0.1942
	Secondary endpoint OS	Comparison groups	Dacomitinib vs. gefitinib
		HR(stratified)	0.760
		(95% CI)	(0.582, 0.993)
		P-value (1-sided)	0.0219
	Secondary endpoint DoR	Comparison groups	Dacomitinib vs. gefitinib
		HR(stratified)	0.403
		(95% CI)	(0.307, 0.529)
		P-value (1-sided)	< 0.0001

	Secondary endpoint TTF	Comparison groups	Dacomitinib vs. gefitinib
		HR(stratified)	0.670
		(95% CI)	(0.543, 0.826)
		P-value (1-sided)	< 0.0001

Clinical studies in special populations

No dedicated clinical studies have been submitted in special populations.

Table 38: Table Number of Patients With Age ≥65 Years Enrolled in Studies of NSCLC with EGFR-Activating Mutation

	Dacomitinib			
	Age 65-74 N	**Age 75-84 N**	**Age ≥85 N**	**Total**
Controlled Trials[a]	417	130	8	555
Non Controlled Trials[b]	25	12	1	38
Total	442	142	9	593

EGFR=epidermal growth factor receptor; N= number within a specified population; NSCLC= non-small cell lung cancer.

a. Studies A7471009, A7471028, A7471011, A7471050

b. Study A7471017 (Cohort A)

Supportive studies

Study A7471017 Cohort A

Study 1017 was a multinational, multicenter, single-arm, Phase 2 clinical study of dacomitinib in patients with NSCLC genotypically selected for the presence of an EGFR-activating mutation or phenotypically selected as having the highest likelihood of having the EGFR-activating mutation (Cohort A) or for the presence of HER2 gene amplification or HER2 mutation (Cohort B). Only Cohort A is included in this SCE, as this cohort only enrolled patients who had untreated locally advanced or metastatic NSCLC with EGFR-activating mutations.

Patients received dacomitinib PO at a starting dose of 45 mg or 30 mg QD. The latter group increased their dose to 45 mg QD after 2 cycles if the 30 mg dose was tolerated according to the investigator.

- Study population

Cohort A included male or female patients ≥18 years of age with adenocarcinoma of the lung who had not received prior systemic therapy and were either 1) non-smokers or former light smokers, or 2) patients, regardless of smoking status, who were known to have an EGFR-activating mutation. All eligible patients had an ECOG PS of 0, 1, or 2. Key exclusion criteria were mixed histology lung cancer, advanced NSCLC that was known to be EGFR wild-type, and untreated brain or meningeal metastases.

- Baseline characteristics

A total of 89 patients (30 patients in the 30-mg starting dose group and 59 patients in the 45-mg starting dose group) were enrolled in Cohort A, and all were treated with dacomitinib. The majority of patients were female (67.4%), <65 years of age (57.3%), Asian (55.1%), and were non-smokers (78.7%). Of the 89 enrolled patients, 45 (50.6%) patients had tumours with EGFR-activating mutations confirmed by genetic testing (16 patients in the 30-mg starting dose group and 29 patients in the 45-mg starting dose group). 25 subjects (28.1%) had a del 19 mutation and 20 subjects (22.5%) had an L858R point mutation in exon 21. Most of the

45 patients with NSCLC with EGFR-activating mutations had Stage IV NSCLC (37 patients; 82.2%), and the remaining patients (8 patients; 17.8%) had Stage IIIB NSCLC at the time of study entry.

Previous adjuvant chemotherapy for earlier stages of NSCLC was allowed if completed >12 months prior to enrolment. Eight (8) of the 89 patients (9.0%) in the ITT population had prior systemic therapy; all 8 had chemotherapy as part of the initial treatment of their primary stage of NSCLC. Compared with Study 1050, more patients in Study 1017 Cohort A had undergone surgery (57.3%) or radiation treatment (25.8%) for NSCLC.

- Efficacy data

Overall, the median duration of treatment was 40.1 weeks (range: 1.9 to 164.0 weeks). The median number of cycles started by patients with NSCLC with EGFR-activating mutations was 18 (range 2 to 74).

PFS

The primary objective of this study was met by demonstrating that the PFS4m was 76.8% (95% CI: 66.4, 84.4) in the ITT population, with a 1-sided p-value<0.0001 for the testing of the null hypothesis (H0): PFS4m ≤50%. In the ITT population, the median PFS was 11.5 months (95% CI: 9.0, 12.9).

PFS events per investigator assessment were observed in 36 (80.0%) of the 45 patients with EGFR-activating mutations; 34 patients (75.6%) had objective progression, and 2 patients (4.4%) died without objective progression. The estimated median PFS was 18.2 months (95% CI: 12.8, 23.8) and PFS at 12 months was 73.4% (95% CI: 57.1, 84.4).

OS

Of the 45 patients with NSCLC with EGFR-activating mutations in key supportive Study 1017 Cohort A, 30 patients (66.7%) had died by the study completion date for the sCSR (30 April 2015). The median OS was 42.3 months (95% CI: 29.0, 46.6) and the probability of survival at 12 months was 95.6% (95% CI: 83.4%, 98.9%).

ORR

ORR and BOR for the subgroup of patients with NSCLC with EGFR-activating mutations in key supportive Study 1017 Cohort A are provided in Table 16.

Table 39: ORR and BOR on investigator assessment for patients with NSCLC with EGFR-activating mutation in study A7471017 Cohort A

	Dacomitinib N=45
Objective response rate (CR plus PR), n (%)	34 (75.6)
95% exact CI[a]	(60.5, 87.1)
Best overall response	
Complete response	0
Partial response	34 (75.6)
Stable/No response	10 (22.2)
Objective progression	1 (2.2)
Indeterminate	0

Source: Module 5.3.5.2 A7471017 sCSR Table 14.2.1.2
Abbreviations: EGFR=epidermal growth factor receptor; N=number; n=number of patients meeting pre-specified criteria; NSCLC=non-small cell lung cancer; sCSR=supplemental CSR.
a. Using exact method based on binomial distribution.

DoR

For the 34 patients with a response, the median DoR was 17.2 months (95% CI: [11.8, 22.1]).

Study A7471009

Multinational, multicenter, randomised, double-blind, Phase 3 clinical study of dacomitinib versus erlotinib in patients with locally advanced or metastatic NSCLC who had previously received 1 or 2 chemotherapy regimens. The study evaluated 2 patient populations: (1) all patients with advanced NSCLC regardless of the presence of an EGFR-activating mutation and (2) patients with confirmed Kirsten rat sarcoma viral oncogene homolog (KRAS) wild-type NSCLC.

The primary objective of this study was to demonstrate that dacomitinib treatment was superior to erlotinib treatment with respect to PFS in either of the co-primary populations.

This study included patients with advanced NSCLC for which there was no curative standard therapy in the judgment of the investigator after treatment with at least 1, and no more than 2, regimens of systemic therapy, including at least 1 standard chemotherapy for advanced NSCLC. All eligible patients had an ECOG PS of 0, 1, or 2. Key exclusion criteria were prior therapy with an agent known or proposed to be active by action on EGFR tyrosine kinase or other HER family proteins, and untreated brain or meningeal metastases.

A total of 878 patients (439 in each treatment arm) were randomised to study treatment; 436 patients (99.3%) in each arm were treated. The majority of patients were male (64.4%), <65 years of age (55.8%), and White (75.9%). Of these, 76 (8.7%) patients had tumours with EGFR-activating mutations (37 in the dacomitinib arm and 39 in the erlotinib arm).

The primary analysis of PFS per IRC review did not show that dacomitinib was superior to erlotinib treatment in either of the co-primary populations. In the ITT population the HR was 0.933 (95% CI: 0.797, 1.093). The estimated median PFS was 2.6 months (95% CI: 1.9, 2.8) in the dacomitinib arm and 2.5 months (95% CI: 1.9, 2.8) in the erlotinib arm.

Results for the subgroup of 76 randomized patients with NSCLC with EGFR-activating mutations (37 patients in the dacomitinib arm and 39 patients in the erlotinib arm) are presented in tables 26, 27 and 28.

Study A7471028

Multinational, multicenter, randomised, open-label, Phase 2 clinical study of dacomitinib versus erlotinib in patients with advanced NSCLC regardless of the presence of EGFR-activating mutations and had disease progression following at least 1 prior chemotherapy regimen.

This study enrolled male or female patients ≥18 years of age with a histologically confirmed diagnosis of NSCLC and evidence of progressive disease after at least 1, but no more than 2, prior chemotherapy regimens for advanced disease and with an ECOG PS of 0, 1, or 2. Key exclusion criteria were evidence of small cell or carcinoid lung cancer, and untreated brain or meningeal metastases.

A total of 188 patients were randomised, 94 in each treatment arm (ITT population). The majority of patients were male (59.0%), <65 years of age (67.0%), and White (71.8%). Of these, 25 (13.3%) were patients with NSCLC with EGFR-activating mutations (16 dacomitinib; 9 erlotinib).

The primary analysis of PFS, as assessed by the investigator, showed a statistically significant improvement in PFS for dacomitinib compared with erlotinib in the ITT population. The PFS HR for dacomitinib versus erlotinib was 0.657 (95% CI: 0.472, 0.914) with 2-sided p-value=0.012. The estimated median PFS was 2.9 months (95% CI: 1.7, 3.7) in the dacomitinib arm and 1.9 months (95% CI: 1.8, 2.7) in the erlotinib arm.

Results for the subgroup of 25 patients with NSCLC with EGFR-activating mutations (16 patients in the dacomitinib arm and 9 patients in the erlotinib arm) are presented in tables 26, 27 and 28.

Study A7471011

Multinational, multicenter, randomized, double-blind, Phase 3 clinical study of dacomitinib versus placebo in patients with incurable Stage IIIB/IV NSCLC regardless of the presence of EGFR-activating mutations after standard therapy failure for advanced or metastatic disease.

This study enrolled male and female patients ≥18 years of age with a histologically confirmed diagnosis of NSCLC after failure of up to 3 prior chemotherapy regimens and at least 1 therapy with erlotinib or gefitinib. All eligible patients had an ECOG PS of 0, 1, 2, or 3. Patients with untreated brain or meningeal metastases were excluded from enrollment.

A total of 720 patients (480 in the dacomitinib arm; 240 in the placebo arm) were randomised to study treatment; 477 patients (99.4%) in the dacomitinib arm and 239 patients (99.6%) in the placebo arm were treated. Approximately half of the patients were male (50.6%) and approximately half were <65 years of age (51.8%); the majority of the patients were White (60.0%) and were past or present smokers (61.9%). 3.5% of the patients in the dacomitinib arm and 6.7% of patients in the placebo arm had ECOG PS of 3. Of the 720 randomized patients, 135 (18.8%) were patients with NSCLC with EGFR-activating mutations (83 in the dacomitinib arm; 52 in the placebo arm).

The analysis of the primary OS endpoint in the ITT population did not show that dacomitinib was superior to placebo. The HR for dacomitinib versus placebo was 1.003 (95% CI: 0.829, 1.214) with a 1-sided p-value=0.510 based on the stratified analysis. The estimated median OS was 6.8 months (95% CI: 6.1, 7.5) for dacomitinib and 6.3 months (95% CI: 5.3, 7.5) for placebo.

Results for the subgroup of 135 randomized patients with EGFR-activating mutations (83 patients in the dacomitinib arm and 52 patients in the placebo arm) are presented in tables 26, 27 and 28.

Table 40: PFS for patients with NSCLC with EGFR-activating mutations in studies A7471050, A7471017 Cohort A, A7471009, A7471028 and A7471011 – ITT population

Study Assessment Treatment	n / N[a]	Dacomitinib vs Comparator Hazard Ratio (95% CI) p-value[b]	Median PFS (months) (95% CI)[c]
A7471050 (Pivotal Study)			
IRC Review			
Dacomitinib	136 / 227	0.589 (0.469, 0.739)	14.7 (11.1, 16.6)
Gefitinib	179 / 225	<0.0001	9.2 (9.1, 11.0)
Investigator Assessment			
Dacomitinib	140 / 227	0.622 (0.497, 0.779)	16.6 (12.9, 18.4)
Gefitinib	177 / 225	<0.0001	11.0 (9.4, 12.1)
A7471017 Cohort A (Key Supportive Study)			
Investigator Assessment			
Dacomitinib	36 / 45	Not applicable	18.2 (12.8, 23.8)
Supportive Studies in Later Lines of Therapy			
A7471009 (Supportive Study – Second- or Third-Line)			
IRC Review			
Dacomitinib	20 / 37	0.670 (0.367, 1.222)	14.6 (7.4, 34.8)
Erlotinib	24 / 39	0.095	9.6 (7.3, 16.6)
Investigator Assessment			
Dacomitinib	27 / 37	0.780 (0.465, 1.308)	13.4 (9.0, 19.6)
Erlotinib	31 / 39	0.172	10.0 (7.4, 12.8)
A7471028 (Supportive Study – Second- or Third-Line)			
Investigator Assessment			
Dacomitinib	15 / 16	0.414 (0.156, 1.099)	16.1 (3.9, 20.9)
Erlotinib	8 / 9	0.034	7.4 (2.6, 16.8)

A7471011 (Supportive Study –Third-Line or Greater)			
Investigator Assessment			
Dacomitinib	78 / 83	0.536 (0.372, 0.770)	3.3 (1.8, 3.7)
Placebo	51 / 52	<0.001	1.0 (0.9, 1.7)

Source: Module 2.7.3.3.2.1, Table 7.
Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; IRC=independent radiologic central; n=number of events; N=number of patients; NSCLC=non-small cell lung cancer; PFS=progression-free survival; vs=versus.
a. n=number of events; N=number of patients.
b. HRs and their CIs in Study A7471050 were estimated from the analysis stratified by race (Japanese vs mainland Chinese and other East Asian vs non-East Asian) and EGFR mutation status (del exon 19 vs L858R) at randomization as the stratification factors, and p-values were based on the stratified log-rank test. HRs and their CIs for analyses of PFS in the subgroups of patients with NSCLC with EGFR-activating mutations in Studies A7471009, A7471028, and A7471011 were estimated from the unstratified Cox Regression, and p-values were based on the unstratified log-rank test. All p-values were based on 1-sided tests.
c. Based on the Brookmeyer-Crowley method.

Table 41: OS for patients with NSCLC with EGFR-activating mutations in studies A7471050, A7471017 Cohort A, A7471009, A7471028 and A7471011 – ITT population

Study Assessment Treatment	n / N[a]	Dacomitinib vs Comparator Hazard Ratio (95% CI) p-value	Median OS (months) (95% CI)[b]
A7471050 (Pivotal Study)			
Dacomitinib	103 / 227	0.760 (0.582, 0.993)[c]	34.1 (29.5, 37.7)
Gefitinib	117 / 225	0.0219	26.8 (23.7, 32.1)
A7471017 Cohort A (Key Supportive Study)			
Dacomitinib	30 / 45	Not applicable	42.3 (29.0, 46.6)
Supportive Studies in Later Lines of Therapy			
A7471009 (Supportive Study – Second- or Third-Line)			
Dacomitinib	21 / 37	0.765 (0.430, 1.360)[d]	26.9 (21.6, NE)
Erlotinib	27 / 39	0.180	23.2 (16.0, 31.8)
A7471028 (Supportive Study – Second- or Third-Line)[e]			
Dacomitinib	15 / 16	0.600 (0.243, 1.482)[d]	27.3 (10.3, 45.0)
Erlotinib	8 / 9	0.132	23.6 (5.5, 39.4)
A7471011 (Supportive Study –Third-Line or Greater)			
Dacomitinib	76 / 83	0.978 (0.675, 1.417)[d]	7.5 (5.5, 9.1)
Placebo	45 / 52	0.435	8.1 (5.1, 9.5)

Source: Module 5.3.5.1, A7471050, sCSR, Table 14.2.6.1.1.1 and Module 2.7.3.3.2.2, Table 9.
Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; n=number of events; N=number of patients; OS=overall survival; vs=versus.
a. n=number of events; N=number of patients.
b. Based on the Brookmeyer-Crowley method.
c. HRs and their CIs were obtained from the stratified log-rank test with race [merging mainland Chinese and other East Asian] and EGFR mutation status at randomization as the stratification factors.
d. HRs and their CIs were estimated from the unstratified Cox Regression, and p-values were based on the unstratified log-rank test. All p-values were from 1-sided tests.
e. Results for median OS [95% CI] for patients with NSCLC with EGFR-activating mutations have been converted to months from Module 5.3.5.1, Study A7471028 CSR, Efficacy Results, which presents these results in units of weeks (118.6 weeks [44.9, 195.7] for dacomitinib and 102.4 weeks [24.0, 171.3] for erlotinib).

Table 42: ORR for patients with NSCLC with EGFR-activating mutations in studies A7471050, A7471017 Cohort A, A7471009, A7471028 and A7471011 – ITT population

Study Assessment Treatment	n / N[a]	ORR (CR + PR) (95% CI)[b]	Dacomitinib vs Comparator ORR p-value[c,d]	Median DoR (months) (95% CI)[e]
A7471050 (Pivotal Study)				
IRC Review				
Dacomitinib	170 / 227	74.9% (68.7, 80.4)	0.1942	14.8 (12.0, 17.4)
Gefitinib	161 / 225	71.6% (65.2, 77.4)	(1-sided)	8.3 (7.4, 9.2)
Investigator Assessment				
Dacomitinib	171 / 227	75.3% (69.2, 80.8)	0.0924	15.9 (13.8, 17.6)
Gefitinib	158 / 225	70.2% (63.8, 76.1)	(1-sided)	9.2 (8.2, 11.0)
A7471017 Cohort A (Key Supportive Study)				
Investigator Assessment				
Dacomitinib	34 / 45	75.6% (60.5, 87.1)	Not applicable	17.2 (11.8, 22.1)
Supportive Studies in Later Lines of Therapy				
A7471009 (Supportive Study – Second- or Third-Line)				
IRC Review				
Dacomitinib	25 / 37	67.6% (50.2, 82.0)	0.750	9.3 (5.6, 32.2)
Erlotinib	25 / 39	64.1% (47.2, 78.8)	(2-sided)	10.1 (5.6, 16.6)
Investigator Assessment				
Dacomitinib	26 / 37	70.3% (53.0, 84.1)	0.710	14.0 (7.2, 19.0)
Erlotinib	27 / 39	69.2% (52.4, 83.0)	(2-sided)	9.5 (5.7, 14.9)
A7471028 (Supportive Study – Second- or Third-Line)				
Investigator Assessment				
Dacomitinib	10 / 16	62.5% (35.4, 84.8)	0.434	Not calculated[e]
Erlotinib	4 / 9	44.4% (13.7, 78.8)	(2-sided)	Not calculated[e]
A7471011 (Supportive Study –Third-Line or Greater)				
Investigator Assessment				
Dacomitinib	10 / 83	12.0% (5.9, 21.0)	0.127	Not calculated[f]
Placebo	1 / 52	1.9% (0.0, 10.3)	(2-sided)	Not calculate[f]

Source: Module 2.7.3.3.2.3, Table 10.
Abbreviations: CI=confidence interval; CR=complete response; DoR=duration of response; ITT=intent-to-treat; IRC=independent radiologic central; n=number of events; N=number of patients; ORR=objective response rate; PR=partial response; vs=versus.

a. n=number of events; N=number of patients.
b. Using exact method based on binomial distribution.
c. p value for Study A7471050 is from the CMH test stratified by EGFR mutation status (del exon 19 vs the L858R mutation in exon 21) based on their values at randomization and by race (Japanese vs mainland Chinese and other East Asian vs Non-East Asian).
d. Unstratified p values from a Pearson chi-squared test for Study A7471009 and A7471011 and from an exact test for Study A7471028. When the number in at least 1 cell is too small (<5), an exact test is used.
e. Based on the Brookmeyer-Crowley method.
f. Not calculated due to small number of patients with a CR or PR.

2.5.3. Discussion on clinical efficacy

This application is mainly based on data from 452 patients included in the pivotal study A1050, a phase III, multinational, multicentre, open-label, randomised study comparing the efficacy and safety of dacomitinib versus gefitinib as first-line treatment in patients with locally advanced or metastatic NSCLC with EGFR-activating mutations in either exon 19 or exon 21.

Additionally, supportive data on 45 patients from Cohort A of study A1017 a multinational, multicentre, single-arm, phase 2 study were included. Cohort A included patients with untreated locally advanced or metastatic NSCLC with EGFR-activating mutations.

The applicant has also provided data on other 3 studies of dacomitinib in patients with locally advanced or metastatic NSCLC in later lines of therapy: two phase III, double-blind, randomised studies (Study A1009, erlotinib-controlled and Study A1011, placebo-controlled) and an open label, randomized phase II study (Study A1028, erlotinib-controlled).

Design and conduct of clinical studies

A double-blind study design for the pivotal trial (A1050) would have been preferable to an open-label design. The main reason for an unblinded design was the different dose reduction strategies used for dacomitinib and gefitinib in instances of AE's requiring dose adjustments. In view of the open-label design, measures were implemented in the protocol to minimise bias in the assessment of the primary endpoint (PFS).The overall study design of the pivotal study is considered adequate and in line with current European guidelines. Scientific advice on the proposed study design was sought from the CHMP in 2012 (EMEA/H/SA/1714/2/2014/II).

In study A1050, the presence of the EGFR mutations was determined by a local laboratory (except in China, where it was determined by the central laboratory) and confirmed by the central laboratory.

Tumours with EGFR-activating mutations have been associated with a higher sensitivity to EGFR TKIs, being exon 19 deletion and L858R mutation the most common EGFR mutations, accounting for approximately 85-90% of EGFR mutations. In the pivotal clinical trial only patients with Exon19del or L858R mutation were included. However, a broad indication is proposed by the applicant to include mutations other than Exon19del or L858R. Nevertheless, efficacy data of dacomitinib against other less common mutations are very limited (only 3 patients from Cohort A of study A1017). It is not expected that dacomitinib would have a lower efficacy in other mutations. Alternatives authorised in the treatment of EGFR activating mutations do not have a restricted use based on specific EGFR mutations despite very little or no clinical data in rare mutations.

Patients had to be treatment-naïve to systemic therapy for locally advanced or metastatic NSCLC. Although they could have received adjuvant or neo-adjuvant therapy in earlier stages, at least a 12-months disease free-interval was required between completion of prior therapy and recurrence of NSCLC.

Patients with brain or leptomeningeal metastases were excluded, even if the metastases were stable. Nevertheless, considering the potential activity of dacomitinib on CNS metastases, data on the use of dacomitinib in this population would have been of special interest and should be considered in future clinical trials.

Exclusion of patients with poor performance status (ECOG ≥ 2) could be a limitation of the study; however it is not unusual in oncology trials.

Dacomitinib was administered at a dose of 45 mg once-daily, determined as the maximum tolerated dose in study A1001. Gefitinib was administered according to its authorised SmPC, 250 mg once a day. Crossover of patients from one treatment arm to the other after disease progression was not allowed.

The comparator is considered acceptable since gefitinib constitutes one of the standards of care treatments for NSCLC with EGFR-activating mutations in the first-line setting. Erlotinib, afatinib and the recently approved osimertinib, represent suitable treatment options in this setting in the EU.

Erlotinib is a reversible EGFR TKI authorised in the first-line setting based on the results of the EURTAC study in which superiority over platinum based chemotherapy was demonstrated in terms of PFS and ORR while no statistically significant differences in terms of OS were reported. No major differences in efficacy are expected between gefitinib and erlotinib in the first-line setting. Neither between both of them and the second generation irreversible EGFR TKI, afatinib, which was not widely available at the time the A1050 study initiation. A recent meta-analysis (Batson et al. 2017) concluded that there is no difference in efficacy among afatinib, erlotinib, and gefitinib. Osimertinib, the newest EGFR TKI (third generation) has recently been approved in Europe for the first line treatment of patients with NSCLC with EGFR activating mutations based on the results of the phase III study FLAURA (Sora et al. 2018) in which osimertinib was proven superior to the SoC (erlotinib and gefitinib) in terms

of PFS. Importantly, patients with CNS metastases whose condition was neurologically stable were included in the trial.

The primary efficacy endpoint in study A1050 was PFS as determined by blinded IRC review according to RECIST v1.1. The secondary endpoints were OS, ORR and DoR by IRC and by investigator assessment according to RECIST v1.1, TTF, PFS based on investigator assessment and PRO. Demonstration of superiority over gefitinib in terms of PFS is considered adequate and sufficient from a regulatory point of view, however this does not exempt from the need of assessing how the introduction of dacomitinib could impact next-line therapies and the impact on long-term outcome of the disease. No PFS2 data is available although it would have been of special interest in this first line setting. Hence, OS as secondary endpoint could provide information on the effect of dacomitinib use over subsequent lines of therapy. The rest of secondary endpoints are considered acceptable and are supportive.

Efficacy data and additional analyses

Overall, baseline and demographic characteristics were well-balanced between arms. The median age at study entry was 62 years (range: 28 – 87 years) with only 49 (10.8%) patients aged ≥75 years. Most of the patients were female, with a higher proportion of female patients in the dacomitinib arm (64.3% dacomitinib vs. 55.6% gefitinib) and had never smoked (64.4%). The majority of patients were Asian (76.5%), which could be expected considering that EGFR mutations are most frequent in Asian population. As this could be a limitation for an application in the EU, the applicant has provided a supplemental evaluation of the benefit-risk profile of dacomitinib in non-Asian patients. All the included patients had an ECOG PS of 0 or 1, with a higher proportion of patients with ECOG 1 in the gefitinib arm (67.0% dacomitinib vs. 72.4% gefitinib).

Regarding disease characteristics, all patients had NSCLC adenocarcinoma histology and the vast majority of them were metastatic (81%). Patients with brain or leptomeningeal metastasis were not allowed, however 5 patients (1 in the dacomitinib arm and 4 in the gefitinib arm) with brain lesions entered the study.

At randomisation 134 (59%) patients in the dacomitinib arm and 133 (59.1%) patients in the gefitinib arm had a deletion in exon 19 whereas 93 (41%) patients and 92 (40.9%) patients in the dacomitinib and gefitinib arm, respectively, had L858R mutation in exon 21. Mutations determined at the randomisation required confirmation by the central laboratory. Determination of EGFR mutations by central laboratory using the FDA-approved Qiagen *therascreen* EGFR test classified 81 (35.7%) patients in the dacomitinib arm and 89 (39.6%) patients in the gefitinib arm as having deletion in exon 19 vs. 62 (27.3%) and 57 (25.3%) patients, dacomitinib and gefitinib, respectively, as having a mutation in exon 21. The EGFR status was "unknown" in 84 patients in the dacomitinib arm and 79 patients in the gefitinib arm due to insufficient tissue for analysis. The overall percent of agreement between local and central test was 96.5%. Despite patients with T790 mutations were allowed to enter the trial, only 4 patients were determined to have such resistance mutation which is consistent with the low prevalence expected for first-line patients.

Per protocol, all randomised patients were to be treatment-naïve for their advanced NSCLC. Nevertheless, two patients (one patient in each treatment arm) had received prior systemic therapy for advanced NSCLC (1 platinum-based chemotherapy regimen), which is an important protocol deviation, although it is unlikely that it could have any effect on the results of the study.

Six amendments to protocol were carried out. They were mainly related to modifications of the inclusion/exclusion criteria, possibility of continuing therapy after PD and statistical issues (IA). The introduced changes are not considered critical for the outcome of the trial.

Study A1050 met its primary objective, showing a statistically significant and clinically meaningful improvement in terms of PFS as determined by the IRC according to RECIST v1.1, with dacomitinib compared to gefitinib (HR 0.589 [95% CI: 0.469, 0.739]; 1-sided p-value: < 0.0001). At the time of the data cut-off (29 July 2016), the number of events was 59.9% in the dacomitinib arm vs. 79.6% in the gefitinib arm, thus data could be considered mature enough.

The estimated median PFS was 14.7 months (95% CI: 11.1, 16.6) in the dacomitinib arm and 9.2 months (95% CI: 9.1, 11.0) in the gefitinib arm. The K-M curves overlapped in the first six months and separated afterwards.

The probability of being PFS event free at 1 year of treatment was also higher in the dacomitinib arm than in the gefitinib arm (55.7% vs. 35.9%) and so it was at 2 years (30.6% vs. 9.6%).

Results of the primary analysis are supported by a number of sensitivity analyses. Results in PFS as assessed by the investigator were consistent with the primary analysis with a HR of 0.622 (95% CI: 0.497, 0.779). The median PFS was 16.6 months in the dacomitinib arm and 11.0 months in the gefitinib arm. Overall differential disagreement rate was -10.2% (44.9% for dacomitinib vs. 55.1% for gefitinib).

While a longer PFS was seen with dacomitinib compared to gefitinib, no statistically significant differences were reported in terms of ORR between treatment arms. Only a numerical trend was observed with an ORR of 74.9% in the dacomitinib arm and 71.6% in the gefitinib arm. However, DoR was longer in patients treated with dacomitinib, with a median DoR of 14.8 months (95% CI: 12.0, 17.4) compared to 8.3 months (95% CI: 7.4, 9.2) in the gefitinib arm.

The higher inhibitory potency of dacomitinib compared to gefitinib as well as the longer inhibition due to its irreversible action, are potential causes justifying the longer PFS reached with dacomitinib compared to gefitinib. In addition, dacomitinib inhibitory activity against HER2 could have also contributed, since HER2 gene amplification has been reported as a potential mechanism of resistance following treatment with EGFR signal blocking agents, such as gefitinib or erlotinib (Planchard et al 2018). The mechanisms of resistance to dacomitinib have not been discussed.

OS results from the final analysis (17- Feb-2017) when 48.7% of events had occurred showed a HR of 0.760 (95% CI: 0.582, 0.993; p=0.0219) and a gain of 7.3 months in OS in the dacomitinib arm. However, according to the hierarchical approach, the analysis was stopped with the testing of ORR as the statistical significance was not reached. Therefore, a statistical benefit in OS could not be formally assessed.

Focusing on the analysis of subgroups for PFS based on IRC assessment, results were in general consistent with the whole population in most of the analysed subgroups (including subsets according to EGFR mutations) except for patients ≥ 75 years. The apparently lower efficacy in the subgroup of very elderly patients (≥75 years) could be driven by the lower sample size of this subgroup that leads to wide 95% CIs.

In the study A1050 the majority of patients were Asian (76.5%), while Non-Asian patients represented only 23.5% of the population. For this reason, the applicant has provided a supplemental analysis of the benefit/risk profile of dacomitinib in non-Asian patients (105 White patients + 1 Black patient).

Although race was a stratification factor, analysis of Asian vs. non-Asian population may be limited by the sample size of the latter. Analysis of PFS points towards lower benefit for the subgroup of non-Asian patients (HR: 0.889, 95%CI: 0.568, 1.391) compared to Asian patients (HR: 0.509, 95%CI: 0.391, 0.662), suggesting that the observed effect in the overall population may be driven by the subset of Asian patients. The percentage of PFS events is pretty similar or even higher in the Non-Asian patients (68%-80%) as compared to ITT population (60%-80%), which would reject the immaturity as a potential explanation for the differences in the non-Asian group.

Moreover, the submitted literature review indicates that there is no consistent pattern that would suggest that non-Asian patients respond differently from Asian patients to this class of drug (Lee and Wu 2015).

Further, the provided PK/PD data do not suggest a biological distinction between Asians and non-Asians that could explain the observed difference in the estimated treatment effect between these subgroups.

Few patients died during the first 12 months and it is not possible to conclude that the differences in deaths per month were due to either lack of efficacy, toxicity related to treatment or patient characteristics. The early crossing in survival curves observed in Study 1050 could be due to random chance. The applicant has as part of the pre-specified analysis examined and found the proportional hazards assumption to hold.

PRO questionnaires were completed by more than 90% of patients for almost all cycles. Regarding PROs in the overall population, no differences were observed in time to deterioration between treatment arms. Improvements in most of the symptoms were reported in both treatment arms. In the dacomitinib arm, there was no statistically significant change from baseline observed for overall global QoL. In the gefitinib arm, a statistically significant improvement was seen in change from baselines scores ($p<0.0001$), but did not reach the 10-point threshold of being clinically meaningful. A statistically significant difference in global quality of life was observed between the two treatment groups, favouring gefitinib ($P=0.0002$). In any case, PRO are considered of limited value considering the open label design of the clinical trial.

Supportive studies

The phase 2 Study 1017 Cohort A included first-line NSCLC patients with EGFR-activating mutations, thus a can be consider a population comparable to that of the pivotal trial. A median PFS of 18.2 months (95% CI: 12.8, 23.8) was observed for patients with NSCLC with EGFR-activating mutations which is supportive of findings from the pivotal trial.

Positive trends in PFS were observed in the other supportive studies in the subgroup of patients with EGFR-activating mutations. However, the sample size and the exploratory nature of these subgroup analyses do not allow to draw firm conclusions, even though all of them are pointing out in the same direction, favouring the dacomitinib arm.

2.5.4. Conclusions on the clinical efficacy

In this MAA Dacomitinib was proven to significantly prolong PFS when compared to gefitinib (gain 5.5 months in median estimate) in the population of NSCLC patients with activating mutations as compared to SOC gefitinib.

The efficacy of dacomitinib in the applied indication is considered sufficiently demonstrated.

2.6. Clinical safety

The dacomitinib clinical development program consists of a total of 26 clinical studies. As of the data cut-off date of 29 July 2016, a total of 3141 patients with solid malignant tumours, including non-small cell lung cancer (NSCLC), have received dacomitinib or a comparator.

Safety analyses are presented for populations comprising patients who received at least 1 dose of study drug and whose data were analyzed in accordance with the study drug received.

To obtain a broader perspective of the safety profile of dacomitinib, safety data were pooled across studies for dacomitinib-treated patients in the following populations:

- Serious Adverse Event (SAE) Pool (All Tumours Pool): all patients with solid tumours who received at least 1 dose of single-agent dacomitinib independent of dose, line of therapy, or the presence or absence of EGFR-activating mutations (1975 treated patients in 14 completed studies).
- Pool B (All NSCLC Pool): previously treated or first-line patients with NSCLC who received single-agent dacomitinib at a starting dose of 45 mg QD in the presence or absence of EGFR-activating mutations (1473 treated patients in 10 completed studies).
- Pool A (Any-Line Activating Mutation Pool): previously treated or first-line patients with NSCLC with EGFR-activating mutations who received single-agent dacomitinib at a starting dose of 45 mg QD (394 treated patients in 3 completed Phase 3 studies [Studies 1050, 1009, and 1011], completed Phase 2 Study 1017 Activating Mutation Cohort only [Cohort A], and completed Phase 2 Study 1028).
- First-Line Pool (First-Line Activating Mutation Pool): patients with NSCLC with EGFR-activating mutations who received single-agent dacomitinib at a starting dose of 45 mg QD as first-line treatment (255 treated patients in completed Study 1050 and completed Study 1017 Cohort A).

Patient exposure

With the exception of 66 (29.1%) patients still on treatment in the dacomitinib arm of Study 1050 as of the data cut-off date of 29 July 2016, all patients in Pool B, Pool A, and the First-Line Pool have been permanently discontinued from treatment.

Table 43: Exposure to dacomitinib – pooled populations – as-treated patients

Exposure Category	Pool B	Pool A	First-Line Pool
Total number of patients	1473	394	255
Number of cycles[a] per patient			
Median (range)	3 (1-75)	12.0 (1-75)	17.0 (1-75)
Duration of treatment (weeks)			
Median (range)	12.0 (0.1-296.3)	46.9 (0.3-296.3)	66.7 (0.3-296.3)
>0-4, n (%)	251 (17.0)	34 (8.6)	10 (3.9)
>4-8, n (%)	334 (22.7)	34 (8.6)	14 (5.5)
>8-12, n (%)	162 (11.0)	18 (4.6)	7 (2.7)
>12-16, n (%)	137 (9.3)	19 (4.8)	10 (3.9)
>16-20, n (%)	88 (6.0)	13 (3.3)	7 (2.7)
>20-24, n (%)	56 (3.8)	17 (4.3)	6 (2.4)
>24-52, n (%)	213 (14.5)	78 (19.8)	51 (20.0)
>52-78, n (%)	73 (5.0)	49 (12.4)	38 (14.9)
>78-104, n (%)	86 (5.8)	74 (18.8)	66 (25.9)
>104-156, n (%)	51 (3.5)	46 (11.7)	41 (16.1)
>156-260, n (%)	18 (1.2)	10 (2.5)	4 (1.6)
>260, n (%)	4 (0.3)	2 (0.5)	1 (0.4)
Relative dose intensity (%)[b]			
Mean (Std Dev)	85.6 (18.8)	78.0 (21.4)	75.4 (21.3)
Median (range)	97.5 (21.7-133.3)	79.3 (21.7-100.0)	75.1 (21.7-100.0)

Data source: SCS Tables 14.4.1.1.B, 14.4.1.2.B, 14.4.1.3.B, 14.4.1.1.A, 14.4.1.2.A; 14.4.1.3.A, 14.4.1.1.N, 14.4.1.2.N, and 14.4.1.3.N.
Abbreviations: ISS=Integrated Summary of Safety Information; n=number of patients meeting prespecified criteria; SCS=Summary of Clinical Safety; Std Dev=standard deviation.
Note: Definitions of pools are provided in Section 2.7.4.1.2.1.
a. Cycle length is summarized for clinical studies of dacomitinib conducted by Pfizer or a collaborating partner in ISS Appendix 5.
b. Relative dose was summarized in SCS Tables 14.4.1.2.B, 14.4.1.2.A, and 14.4.1.2.N. Relative dose (%) for a cycle is defined as actual received total dose in a cycle divided by (45 mg dacomitinib × number days in cycle) × 100. Relative dose is therefore identical to relative dose intensity for continuous dosing with the actual cycle length equal to planned cycle length such as dacomitinib dosing.

Table 44: Exposure to dacomitinib – phase 3 Study A7471050 – As-treated patients

	A7471050 (N=451)	
Exposure Category	Dacomitinib	Gefitinib
Total number of patients	227	224
Number of cycles[a] per patient		
Median (range)	17.0 (1-41)	13.0 (1-38)
Duration of treatment (weeks)		
Median (range)	66.6 (0.3-162.7)	52.1 (0.3-148.3)
>0-4, n (%)	9 (4.0)	6 (2.7)
>4-8, n (%)	15 (6.6)	13 (5.8)
>8-12, n (%)	7 (3.1)	4 (1.8)
>12-16, n (%)	9 (4.0)	5 (2.2)
>16-20, n (%)	5 (2.2)	4 (1.8)
>20-24, n (%)	3 (1.3)	7 (3.1)
>24-52, n (%)	47 (20.7)	73 (32.6)
>52-78, n (%)	32 (14.1)	53 (23.7)
>78-104, n (%)	60 (26.4)	31 (13.8)
>104-156, n (%)	38 (16.7)	28 (12.5)
>156-260, n (%)	2 (0.9)	0
>260, n (%)	0	0
Relative dose intensity (%)[b]		
Mean (Std Dev)	73.3 (21.5)	96.0 (9.5)
Median (range)	72.5 (10.0-100.0)	99.8 (55.3-100.0)
>125%, n (%)	0	0
>100%-125%, n (%)	0	0
>90%-100%, n (%)	67 (29.5)	201 (89.7)
>75%-90%, n (%)	38 (16.7)	8 (3.6)
≤75%, n (%)	122 (53.7)	15 (6.7)

Data source: A7471050 CSR Tables 14.4.1.2.1, 14.4.1.3.1, and 14.4.1.4.1; SCS Table 14.4.1.1.C.
Abbreviations: CSR=Clinical Study Report; ISS=Integrated Summary of Safety Information; n=number of patients meeting prespecified criteria; N=total number of patients; SCS=Summary of Clinical Safety; Std Dev=standard deviation.
a. Cycle = 28 days (ISS Appendix 5).
b. Relative dose was summarized in the A7471050 CSR Table 14.4.1.4.1. Relative dose for a cycle is defined as actual received total dose in a cycle divided by (planned dose of study drug × number days in cycle) × 100. Relative dose is therefore identical to relative dose intensity for continuous dosing with the actual cycle length equal to planned cycle length such as dacomitinib or gefitinib.

Table 45: Dacomitinib treatment modifications – Pooled Populations – As-Treated patients.

	Number (%) of Patients		
Category	Pool B (N=1473)	Pool A (N=394)	First-Line Pool (N=255)
Dose reductions per patient[a]			
≥1	584 (39.6)	235 (59.6)	170 (66.7)
1	395 (26.8)	133 (33.8)	94 (36.9)
2	177 (12.0)	94 (23.9)	69 (27.1)
>2[b]	12 (0.8)	8 (2.0)	7 (2.7)
Temporary treatment discontinuations per patient[c]			
≥1	756 (51.3)	270 (68.5)	186 (72.9)
≥2	396 (26.9)	171 (43.4)	119 (46.7)

Data source: SCS Tables 14.4.1.3.B, 14.4.1.3.A, and 14.4.1.3.N.
Abbreviations: N=total number of patients; SCS=Summary of Clinical Safety.
Note: Definitions of pools are provided in Section 2.7.4.1.2.1.
a. Dose reduction is defined as reduction by ≥33% but <100% of the prescribed dose on any day for any reason.
b. Patients with more than 2 dose reductions had their dose reduced, then increased, and subsequently reduced again during the course of treatment on several occasions.
c. Temporary treatment discontinuation is defined as a dosing interval of any duration with daily dose of 0 mg.

Table 46: Treatment modifications – Phase 3 Studies and Phase 2 Study A7471028 – As-Treated Patients

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study A7471028 (N=187)	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)			
Category	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Dose reduction per patient[a]								
≥1	150 (66.1)	18 (8.0)	132 (30.3)	56 (12.8)	167 (35.0)	6 (2.5)	38 (40.9)	16 (17.0)
1	84 (37.0)	11 (4.9)	96 (22.0)	44 (10.1)	116 (24.3)	5 (2.1)	29 (31.2)	16 (17.0)
2	61 (26.9)	6 (2.7)	36 (8.3)	12 (2.8)	47 (9.9)	1 (0.4)	8 (8.6)	0
>2[b]	5 (2.2)	1 (0.4)	0	0	4 (0.8)	0	1 (1.1)	0
Temporary treatment discontinuation per patient[c]								
≥1	177 (78.0)	120 (53.6)	269 (61.7)	238 (54.6)	390 (81.8)	144 (60.3)	40 (43.0)	20 (21.3)
≥2	122 (53.7)	56 (25.0)	137 (31.4)	105 (24.1)	210 (44.0)	54 (22.6)	15 (16.1)	4 (4.3)

Data source: A7471050 CSR Tables 14.4.1.5.1 and 14.4.1.6.1; A7471009 CSR Tables 14.4.1.5.1 and 14.4.1.6.1; A7471011 CSR Tables 14.4.1.5, and 14.4.1.6; A7471028 CSR Tables 14.4.1.5 and 14.4.1.6.

Abbreviations: CSR=Clinical Study Report; N=total number of patients.

a. Dose reduction is defined as reduction by ≥33% but <100% of the prescribed dose on any day for any reason.

b. Patients with more than 2 dose reductions had their dose reduced, then increased, and subsequently reduced again during the course of treatment on several occasions.

c. Temporary treatment discontinuation is defined as a dosing interval of any duration with daily dose of 0 mg.

Table 47: Reasons for Permanent Treatment Discontinuations – Pooled Populations – As-Treated Patients.

	Number (%) of Patients		
Category	Pool B (N=1473)	Pool A (N=394)	First-Line Pool (N=255)
Number of patients discontinued	1407 (95.5)	328 (83.2)	189 (74.1)
Primary reason for permanent discontinuation			
Progressive disease[a]	948 (64.4)	198 (50.3)	97 (38.0)
AEs	235 (16.0)	61 (15.5)	44 (17.3)
Related to treatment[b]	92 (6.2)	30 (7.6)	25 (9.8)
Not related to treatment	143 (9.7)	31 (7.9)	19 (7.5)
Patient withdrawal	54 (3.7)	13 (3.3)	9 (3.5)
Deterioration of global health	48 (3.3)	27 (6.9)	27 (10.6)
AEs not considered to be treatment emergent[c]	44 (3.0)	11 (2.8)	2 (0.8)
Lack of efficacy	27 (1.8)	0	0
Study terminated by Applicant	17 (1.2)	9 (2.3)	1 (0.4)
Death	11 (0.7)	0	0
Protocol deviation	1 (<0.1)	0	0
Lost to follow-up	1 (<0.1)	0	0
Other[d]	21 (1.4)	9 (2.3)	9 (3.5)

Data source: SCS Tables 14.1.1.4.B, Table 14.1.1.4.A, and Table 14.1.1.4.N.

Abbreviations: AEs=adverse events; CRF=Case Report Form; N=total number of patients; SCS=Summary of Clinical Safety.

a. Some cases of progressive disease were denoted as "Other".

b. AEs with missing causality assessment are classified as related to treatment.

c. A patient was considered to have discontinued from treatment due to a nontreatment-emergent AE if the Subject Summary CRF page for end of treatment did not have a record of discontinuation reason as an AE, or an AE leading to permanent discontinuation of treatment was not documented on the AE CRF page.

d. "Other" reason predominantly included patients starting subsequent therapy due to disease progression or lack of additional benefit.

Table 48: Reasons for Permanent Treatment Discontinuation – Phase 3 Studies and Phase 2 Study A7471028 – As-Treated Patients.

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
Category	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Number of patients discontinued	161 (70.9)	186 (83.0)	436 (100.0)	436 (100.0)	477 (100.0)	239 (100.0)	90 (96.8)[a]	94 (100.0)
Primary reason for permanent discontinuation								
Progressive disease	79 (34.8)	113 (50.4)	297 (68.1)	314 (72.0)	339 (71.1)	190 (79.5)	69 (74.2)	85 (90.4)
AEs	40 (17.6)	27 (12.1)	56 (12.8)	49 (11.2)	64 (13.4)	8 (3.3)	14 (15.1)	6 (6.4)
Related to treatment[b]	22 (9.7)	15 (6.7)	33 (7.6)	20 (4.6)	43 (9.0)	2 (0.8)	9 (9.7)	4 (4.3)
Not related to treatment	18 (7.9)	12 (5.4)	23 (5.3)	29 (6.7)	21 (4.4)	6 (2.5)	5 (5.4)	2 (2.1)
Deterioration of global health	26 (11.5)	33 (14.7)	14 (3.2)	12 (2.8)	0	0	4 (4.3)	1 (1.1)
Patient withdrawal	8 (3.5)	4 (1.8)	25 (5.7)	18 (4.1)	12 (2.5)	7 (2.9)	1 (1.1)	1 (1.1)
AEs not considered to be treatment emergent	1 (0.4)	0	NR	NR	NR	NR	0	0
Lack of efficacy	0	0	0	0	0	0	0	0
Study terminated by Applicant	0	0	12 (2.8)	8 (1.8)	0	0	0	0
Death	0	0	28 (6.4)	30 (6.9)	23 (4.8)	13 (5.4)	3 (3.2)[c]	4 (4.3)[c]
Protocol deviation	0	2 (0.9)	1 (0.2)	1 (0.2)	0	0	0	0
Lost to follow-up	0	1 (0.4)	1 (0.2)	0	0	0	1 (1.1)	3 (2.3)
Other	7 (3.1)	6 (2.7)	2 (0.5)	4 (0.9)	6 (1.3)	1 (0.4)	2 (2.2)	1 (1.1)

Data source: A7471050 CSR Table 14.1.1.4.1; A7471009 sCSR Table 14.1.1.4.1; A7471011 CSR Table 14.1.1.4.1; A7471011 sCSR Table 16.2.1.4.2; A7471028 CSR Tables 14.1.1.1.1, 14.1.1.3, 14.1.1.4.1, and 14.3.1.1.1.2; A7471028 sCSR Table 16.2.1.1.1.

Abbreviations: AEs=adverse events; CRF=Case Report Form; CSR=Clinical Study Report; N=total number of patients; NR=not reported; sCSR=supplemental Clinical Study Report.

a. Three patients were receiving dacomitinib as of the clinical database snapshot date (22 June 2012) of the CSR. Of these 3 patients, 1 patient was discontinued from treatment thereafter due to objective progression or relapse and subsequently died (84 days after the last dose of study drug) and 2 patients were transitioned off study onto compassionate use (Study A7471028 sCSR).

b. AEs with missing causality assessment are classified as related to treatment.

c. Permanent discontinuation from treatment due to Grade 5 AEs (A7471028 Table 14.3.1.1.1.2).

Adverse events

Of note, none of the analyses of AEs reported in Study 1050 were adjusted for the longer median treatment duration in the dacomitinib arm (66.6 weeks) compared with that in the gefitinib arm (52.1 weeks) except for the analysis of the exposure-adjusted incidence rates, per 1000 person-years of exposure, performed for AEoSIs.

Table 49: Overview of treatment-related adverse events – Pooled Populations – As-Treated Patients

Category	Pool B (N=1473)	Pool A (N=394)	First-Line Pool (N=255)
Number of TRAEs[a]	9004	3251	2415
Patients with TRAEs, n (%)	1400 (95.0)	383 (97.2)	248 (97.3)
Patients with treatment-related SAEs, n (%)	138 (9.4)	32 (8.1)	25 (9.8)
Patients with Grade 5 TRAEs, n (%)	9 (0.6)	2 (0.5)	2 (0.8)
Patients permanently discontinued treatment due to TRAEs, n (%)	92 (6.2)	30 (7.6)	25 (9.8)
Patients with dose reduced due to TRAEs, n (%)	267 (26.8)[b]	174 (55.9)[b]	159 (62.4)
Patients with temporary discontinuation due to TRAEs, n (%)	440 (29.9)	168 (42.6)	136 (53.3)

Data source: SCS Tables 14.3.1.3.1.B, 14.3.1.3.1.A, and 14.3.1.3.1.N.

Abbreviations: AE=adverse event; CRF=Case Report Form; CTCAE=Common Terminology Criteria for Adverse Events; n=number of patients meeting prespecified criteria; SAEs=serious adverse events; SCS=Summary of Clinical Safety; TRAEs=treatment-related adverse events.

Notes: 1) Definitions of pools are provided in Section 2.7.4.1.2.1.

2) Patients are counted once per pool in each row.

3) TRAE severity was assessed using CTCAE Version 4.03.

4) Grade 3 and Grade 4 TRAEs are summarized by maximum severity in Table 23.

a. Number of TRAEs is a sum of unique TRAEs calculated for each patient.

b. Information on dose reductions associated with AEs in Study A7471011 is not provided for Pool B and Pool A, as dose reduction field was not available on the Study A7471011 AE CRF page. Therefore, percentages of patients with dose reduced due to AEs in Pool B and Pool A are based on the denominators (N=996 in Pool B and N=311 in Pool A) calculated using the total numbers of treated patients in these pools (N=1473 in Pool B and N=394 in Pool A) minus the numbers of dacomitinib-treated patients in Study A7471011 included in these pools (N=477 in Pool B and N=83 in Pool A [SCS Table 14.1.1]).

Table 50: Overview of adverse events – Phase 3 studies and phase 2 study A7471028 – As treated patients

	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
Category	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Number of AEs[a]	2953	2212	3719	3500	4101	1083	899	726
Patients with AEs, n (%)	226 (99.6)	220 (98.2)	431 (98.9)	427 (97.9)	474 (99.4)	212 (88.7)	93 (100.0)	93 (98.9)
Patients with SAEs, n (%)	62 (27.3)	50 (22.3)	178 (40.8)	169 (38.8)	191 (40.0)	87 (36.4)	33 (35.5)	30 (31.9)
Patients with Grade 5 AEs, n (%)	22 (9.7)	20 (8.9)	83 (19.0)	71 (16.3)	95 (19.9)	48 (20.1)	22 (23.7)	19 (20.2)
Patients permanently discontinued treatment due to AEs, n (%)	40 (17.6)	27 (12.1)	121 (27.8)	100 (22.9)	53 (11.1)	24 (10.0)	27 (29.0)	17 (18.1)
Patients with dose reduced due to AEs, n (%)	150 (66. 1)	18 (8.0)	41 (9.4)	21 (4.8)	NR[b]	NR[b]	32 (34.4)	8 (8.5)
Patients temporarily discontinued treatment due to AEs, n (%)	130 (57.3)	60 (26.8)	213 (48.9)	145 (33.3)	65 (13.6)	22 (9.2)	39 (41.9)	21 (22.3)

Data source: A7471050 CSR Table 14.3.1.2.1; A7471009 sCSR Table 14.3.1.2.1.1; SCS Table 14.3.1.2.1.E; A7471028 CSR Table 14.3.1.2.1.
Abbreviations: AEs=adverse events; CRF=Case Report Form; CSR=Clinical Study Report; N=total number of patients; n=number of patients meeting prespecified criteria; NR=not reported; SAEs=serious adverse events; SCS=Summary of Clinical Safety; sCSR=supplemental Clinical Study Report.
Notes: 1) Patients are counted once per treatment arm in each row.
2) Grade 3 and Grade 4 AEs are summarized by maximum severity in Table 26.
a. Number of AEs is a sum of unique AEs calculated for each patient.
b. Information on dose reductions associated with AEs in Study A7471011 is not provided, as dose reduction field was not available on the AE CRF page.

Table 51: Overview of Treatment-Related Adverse Events – Phase 3 Studies and Study A7471028 – As-Treated Patients

	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
Category	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Number of TRAEs[a]	2048	1212	2189	1891	2431	236	568	390
Patients with TRAEs, n (%)	220 (96.9)	213 (95.1)	410 (94.0)	392 (89.9)	445 (93.3)	100 (41.8)	89 (95.7)	88 (93.6)
Patients with treatment-related SAEs, n (%)	21 (9.3)	10 (4.5)	50 (11.5)	39 (8.9)	44 (9.2)	0	7 (7.5)	7 (7.4)
Patients with Grade 5 TRAEs, n (%)	2 (0.9)	2 (0.9)	2 (0.5)	0	3 (0.6)	0	2 (2.2)	2 (2.1)
Patients permanently discontinued due to TRAEs, n (%)	22 (9.7)	15 (6.7)	34 (7.8)	20 (4.6)	13 (2.7)	0	10 (10.8)	4 (4.3)
Patients with dose reduced due to TRAEs, n (%)	147 (64.8)	18 (8.0)	37 (8.5)	20 (4.6)	NR[b]	NR[b]	31 (33.3)	8 (8.5)
Patients with temporary discontinuation due to TRAEs, n (%)	118 (52.0)	47 (21.0)	175 (40.1)	108 (24.8)	25 (5.2)	0	30 (32.3)	16 (17.0)

Data source: A7471050 CSR Table 14.3.1.3.1; A7471009 sCSR 14.3.1.3.1.1; SCS Table 14.3.1.3.1.E; A7471028 CSR 14.3.1.3.1.
Abbreviations: AE=adverse event; CRF=Case Report Form; CSR=Clinical Study Report; n=number of patients meeting prespecified criteria; NR=not reported; SAEs=serious adverse events; SCS=Summary of Clinical Safety; sCSR=supplemental Clinical Study Report; TRAEs=treatment-related adverse events.
Notes: 1) Patients are counted once per treatment arm in each row.
2) Grade 3 and Grade 4 TRAEs are summarized in Table 29.
a. Number of TRAEs is a sum of unique TRAE calculated for each patient.
b. Information on dose reductions associated with TRAEs in Study A7471011 is not provided, as dose reduction field was not available on the AE CRF page.

Table 52: Adverse events reported for at least 10% of patients in any treatment arm, by SOC and PT sorted by descending frequency with each SOC in the dacomitinib arm of study A7471050 – Phase 3 studies and phase 2 study A7471028

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
MedDRA SOC and PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Any AE[b]	226 (99.6)	220 (98.2)	431 (98.9)	428 (98.2)	474 (99.4)	212 (88.7)	93 (100)	94 (100)
Blood and lymphatic system disorders	35 (15.4)	24 (10.7)	57 (13.1)	57 (13.1)	5 (1.0)	1 (0.4)	9 (9.7)	9 (9.6)
Anaemia	22 (9.7)	16 (7.1)	37 (8.5)	48 (11.0)	3 (0.6)	0	6 (6.5)	6 (6.4)
Gastrointestinal disorders	212 (93.4)	175 (78.1)	367 (84.2)	310 (71.1)	430 (90.1)	120 (50.2)	80 (86.0)	68 (72.3)
Diarrhoea	198 (87.2)	125 (55.8)	324 (74.3)	218 (50.0)	375 (78.6)	42 (17.6)	68 (73.1)	47 (50.0)
Stomatitis	99 (43.6)	40 (17.9)	81 (18.6)	52 (11.9)	205 (43.0)	7 (2.9)	27 (29.0)	10 (10.6)
Nausea	43 (18.9)	49 (21.9)	91 (20.9)	83 (19.0)	141 (29.6)	41 (17.2)	20 (21.5)	21 (22.3)
Constipation	29 (12.8)	31 (13.8)	44 (10.1)	60 (13.8)	55 (11.5)	37 (15.5)	9 (9.7)	12 (12.8)
Mouth ulceration	28 (12.3)	13 (5.8)	2 (0.5)	5 (1.1)	0	0	3 (3.2)	5 (5.3)
Vomiting	20 (8.8)	29 (12.9)	74 (17.0)	70 (16.1)	126 (26.4)	32 (13.4)	11 (11.8)	15 (16.0)
General disorders and administration site conditions	118 (52.0)	104 (46.4)	265 (60.8)	272 (62.4)	241 (50.5)	105 (43.9)	64 (68.8)	66 (70.2)
Asthenia	29 (12.8)	28 (12.5)	68 (15.6)	59 (13.5)	0	0	13 (14.0)	11 (11.7)
Chest pain	22 (9.7)	32 (14.3)	21 (4.8)	38 (8.7)	0	0	5 (5.4)	13 (13.8)
Fatigue	21 (9.3)	19 (8.5)	78 (17.9)	94 (21.6)	163 (34.2)	63 (26.4)	25 (26.9)	33 (35.1)
Mucosal inflammation	21 (9.3)	8 (3.6)	67 (15.4)	28 (6.4)	0	0	23 (24.7)	7 (7.4)
Pyrexia	19 (8.4)	17 (7.6)	46 (10.6)	37 (8.5)	43 (9.0)	14 (5.9)	4 (4.3)	4 (4.3)
Disease progression	8 (3.5)	11 (4.9)	53 (12.2)	50 (11.5)	0	0	14 (15.1)	16 (17.0)
Infections and infestations	180 (79.3)	115 (51.3)	210 (48.2)	162 (37.2)	244 (51.2)	41 (17.2)	54 (58.1)	39 (41.5)
Paronychia	140 (61.7)	45 (20.1)	94 (21.6)	44 (10.1)	139 (29.1)	0	24 (25.8)	8 (8.5)
Conjunctivitis	43 (18.9)	9 (4.0)	29 (6.7)	14 (3.2)	50 (10.5)	0	9 (9.7)	3 (3.2)
Upper respiratory tract infection	28 (12.3)	28 (12.5)	13 (3.0)	12 (2.8)	17 (3.6)	6 (2.5)	3 (3.2)	6 (6.4)
Investigations	134 (59.0)	140 (62.5)	113 (25.9)	100 (22.9)	65 (13.6)	19 (7.9)	29 (31.2)	17 (8.1)
Weight decreased	58 (25.6)	37 (16.5)	64 (14.7)	38 (8.7)	62 (13.0)	15 (6.3)	18 (19.4)	13 (13.8)
Alanine aminotransferase increased	44 (19.4)	88 (39.3)	8 (1.8)	23 (5.3)	0	0	4 (4.3)	2 (2.1)
Aspartate aminotransferase increased	42 (18.5)	81 (36.2)	10 (2.3)	22 (5.0)	0	0	4 (4.3)	1 (1.1)
Metabolism and nutrition disorders	106 (46.7)	79 (35.3)	197 (45.2)	159 (36.5)	172 (36.1)	59 (24.7)	34 (36.6)	36 (38.3)
Decreased appetite	70 (30.8)	55 (24.6)	139 (31.9)	120 (27.5)	150 (31.4)	51 (21.3)	27 (29.0)	29 (30.9)
Musculoskeletal and connective tissue disorders	84 (37.0)	86 (38.4)	108 (24.8)	113 (25.9)	123 (25.8)	65 (27.2)	27 (29.0)	19 (20.2)
Pain in extremity	31 (13.7)	26 (11.6)	26 (6.0)	27 (6.2)	42 (8.8)	19 (7.9)	5 (5.4)	2 (2.1)
Musculoskeletal pain	26 (11.5)	28 (12.5)	21 (4.8)	19 (4.4)	2 (0.4)	1 (0.4)	4 (4.3)	2 (2.1)
Back pain	18 (7.9)	35 (15.6)	35 (8.0)	30 (6.9)	32 (6.7)	19 (7.9)	11 (11.8)	10 (10.6)
Psychiatric disorders	33 (14.5)	45 (20.1)	46 (10.6)	61 (14.0)	58 (12.2)	24 (10.0)	12 (12.9)	14 (14.9)
Insomnia	24 (10.6)	33 (14.7)	14 (3.2)	25 (5.7)	32 (6.7)	12 (5.0)	2 (2.2)	5 (5.3)
Respiratory, thoracic and mediastinal disorders	124 (54.6)	98 (43.8)	200 (45.9)	210 (48.2)	270 (56.6)	114 (47.7)	51 (54.8)	53 (56.4)
Cough	48 (21.1)	42 (18.8)	54 (12.4)	73 (16.7)	67 (14.0)	35 (14.6)	17 (18.3)	21 (22.3)
Dyspnoea	30 (13.2)	30 (13.4)	81 (18.6)	87 (20.0)	120 (25.2)	61 (25.5)	25 (26.9)	20 (21.3)
Epistaxis	21 (9.3)	5 (2.2)	37 (8.5)	23 (5.3)	73 (15.3)	3 (1.3)	7 (7.5)	2 (2.1)
Skin and subcutaneous tissue disorders	208 (91.6)	167 (74.6)	367 (84.2)	341 (78.2)	393 (82.4)	67 (28.0)	82 (88.2)	80 (85.1)
Dermatitis acneiform	111 (48.9)	64 (28.6)	81 (18.6)	88 (20.2)	271 (56.8)	20 (8.4)	60 (64.5)	54 (57.4)
Dry skin	63 (27.8)	38 (17.0)	86 (19.7)	84 (19.3)	143 (30.0)	18 (7.5)	22 (23.7)	15 (16.0)
Alopecia	53 (23.3)	28 (12.5)	14 (3.2)	18 (4.1)	9 (1.9)	3 (1.3)	9 (9.7)	3 (3.2)
Pruritus	45 (19.8)	31 (13.8)	49 (11.2)	54 (12.4)	79 (16.6)	22 (9.2)	14 (15.1)	15 (16.0)
Rash	40 (17.6)	24 (10.7)	218 (50.0)	203 (46.6)	0	0	2 (2.2)	2 (2.1)
Palmar-plantar erythrodysaesthesia syndrome	33 (14.5)	7 (3.1)	16 (3.7)	7 (1.6)	55 (11.5)	2 (0.8)	11 (11.8)	5 (5.3)
Rash maculo-papular	28 (12.3)	27 (12.1)	18 (4.1)	12 (2.8)	73 (15.3)	14 (5.9)	0	1 (1.1)
Dermatitis	25 (11.0)	9 (4.0)	6 (1.4)	3 (0.7)	1 (0.2)	0	1 (1.1)	0
Acne	20 (8.8)	13 (5.8)	23 (5.3)	19 (4.4)	0	0	12 (12.9)	11 (11.7)
Exfoliative rash	1 (0.4)	0	2 (0.5)	1 (0.2)	0	0	16 (17.2)	14 (14.9)
Erythema multiforme	0	0	2 (0.5)	0	13 (2.7)	1 (0.4)	10 (10.8)	4 (4.3)

Data source: A7471050 CSR Table 14.3.1.2.9.1; SCS Tables 14.3.1.2.9.1.D, 14.3.1.2.9.1.E, and 14.3.1.2.9.1.F.

Abbreviations: AE=adverse event; CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety; SOC=System Organ Class.

Note: Shading is applied to the meaningfully higher AE frequencies in either treatment arm of A7471050 (ie, ≥10% absolute difference in AE frequency between the arms).

a. MedDRA Version 19.1.

b. Any AE without consideration for the minimum 10% frequency cutoff used in this table.

Table 53: Treatment-Related Adverse Events Reported for at Least 10% of Patients in Any Treatment Arm, by PT in Study a7471050 – Phase 3 Studies and Phase 2 Study A7471028 – As-Treated Patients.

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Any TRAE[b]	220 (96.9)	213 (95.1)	410 (94.0)	391 (89.7)	445 (93.3)	100 (41.8)	89 (95.7)	88 (93.6)
Diarrhoea	193 (85.0)	115 (51.3)	313 (71.8)	208 (47.7)	369 (77.4)	35 (14.6)	68 (73.1)	45 (47.9)
Paronychia	140 (61.7)	45 (20.1)	92 (21.1)	44 (10.1)	131 (27.5)	0	24 (25.8)	8 (8.5)
Dermatitis acneiform	111 (48.9)	64 (28.6)	80 (18.3)	88 (20.2)	268 (56.2)	17 (7.1)	60 (64.5)	54 (57.4)
Stomatitis	93 (41.0)	34 (15.2)	81 (18.6)	51 (11.7)	197 (41.3)	4 (1.7)	27 (29.0)	10 (10.6)
Dry skin	62 (27.3)	36 (16.1)	85 (19.5)	82 (18.8)	136 (28.5)	16 (6.7)	22 (23.7)	14 (14.9)
Decreased appetite	57 (25.1)	34 (15.2)	100 (22.9)	91 (20.9)	97 (20.3)	17 (7.1)	24 (25.8)	21 (22.3)
Alopecia	46 (20.3)	19 (8.5)	12 (2.8)	16 (3.7)	8 (1.7)	3 (1.3)	9 (9.7)	3 (3.2)
Pruritus	44 (19.4)	29 (12.9)	46 (10.6)	50 (11.5)	74 (15.5)	18 (7.5)	14 (15.1)	15 (16.0)
Alanine aminotransferase increased	42 (18.5)	81 (36.2)	7 (1.6)	17 (3.9)	0	0	4 (4.3)	2 (2.1)
Aspartate aminotransferase increased	39 (17.2)	77 (34.4)	7 (1.6)	16 (3.7)	0	0	4 (4.3)	1 (1.1)
Rash	39 (17.2)	23 (10.3)	213 (48.9)	201 (46.1)	0	0	2 (2.2)	2 (2.1)
Conjunctivitis	38 (16.7)	6 (2.7)	27 (6.2)	12 (2.8)	45 (9.4)	0	9 (9.7)	3 (3.2)
Palmar-plantar erythrodysaesthesia syndrome	33 (14.5)	7 (3.1)	16 (3.7)	7 (1.6)	54 (11.3)	2 (0.8)	11 (11.8)	5 (5.3)
Nausea	29 (12.8)	27 (12.1)	76 (17.4)	59 (13.5)	91 (19.1)	17 (7.1)	16 (17.2)	15 (16.0)
Mouth ulceration	28 (12.3)	13 (5.8)	2 (0.5)	4 (0.9)	0	0	2 (2.2)	5 (5.3)
Rash maculo-papular	28 (12.3)	27 (12.1)	18 (4.1)	12 (2.8)	73 (15.3)	11 (4.6)	0	1 (1.1)
Dermatitis	24 (10.6)	8 (3.6)	4 (0.9)	2 (0.5)	1 (0.2)	0	1 (1.1)	0
Weight decreased	24 (10.6)	5 (2.2)	43 (9.9)	21 (4.8)	28 (5.9)	4 (1.7)	11 (11.8)	9 (9.6)
Acne	20 (8.8)	13 (5.8)	23 (5.3)	19 (4.4)	0	0	12 (12.9)	11 (11.7)
Mucosal inflammation	20 (8.8)	8 (3.6)	67 (15.4)	28 (6.4)	0	0	23 (24.7)	6 (6.4)
Epistaxis	18 (7.9)	4 (1.8)	23 (5.3)	14 (3.2)	48 (10.1)	0	4 (4.3)	1 (1.1)
Fatigue	14 (6.2)	9 (4.0)	45 (10.3)	56 (12.8)	100 (21.0)	22 (9.2)	15 (16.1)	20 (21.3)
Vomiting	11 (4.8)	11 (4.9)	53 (12.2)	48 (11.0)	92 (19.3)	4 (1.7)	8 (8.6)	10 (10.6)
Exfoliative rash	1 (0.4)	0	2 (0.5)	1 (0.2)	0	0	16 (17.2)	14 (14.9)
Erythema multiforme	0	0	2 (0.5)	0	12 (2.5)	0	10 (10.8)	4 (4.3)

Data source: A7471050 CSR Table 14.3.1.3.9.1; SCS Tables 14.3.1.3.11.1.D, 14.3.1.3.11.1.E, and 14.3.1.3.11.1.F.

Abbreviations: CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety; TRAE=treatment-related adverse event.

a. MedDRA Version 19.1.

b. Any TRAE without consideration for the minimum 10% frequency cutoff used in this table.

Table 54: Grade 3 or grade 4 adverse events reported for at least 3% of patients in any treatment arm, by maximum severity grade and MedDRA PT sorted by descending frequency of grade 3 events in the dacomitinib arm of study A7471050 –Phase 3 studies –As treated patients

	Number (%) of Patients															
	Phase 3 Studies												Phase 2 Study			
	A7471050 (N=451)				A7471009 (N=872)				A7471011 (N=716)				A7471028 (N=187)			
	Dacomitinib (N=227)		Gefitinib (N=224)		Dacomitinib (N=436)		Erlotinib (N=436)		Dacomitinib (N=477)		Placebo (N=239)		Dacomitinib (N=93)		Erlotinib (N=94)	
MedDRA PT[a]	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any AE[b]	116 (51.1)	5 (2.2)	67 (29.9)	5 (2.2)	149 (34.2)	20 (4.6)	142 (32.6)	19 (4.4)	184 (38.6)	16 (3.4)	45 (18.8)	10 (4.2)	31 (33.3)	7 (7.5)	29 (30.9)	4 (4.3)
Dermatitis acneiform	31 (13.7)	0	0	0	5 (1.1)	0	7 (16)	0	47 (9.9)	1 (0.2)	1 (0.4)	0	10 (10.8)	0	6 (6.4)	0
Diarrhoea	19 (8.4)	0	2 (0.9)	0	48 (11.0)	1 (0.2)	11 (2.5)	0	59 (12.4)	1 (0.2)	0	0	11 (11.8)	0	4 (4.3)	0
Paronychia	17 (7.5)	0	3 (1.3)	0	5 (1.1)	0	3 (0.7)	0	10 (2.1)	0	0	0	3 (3.2)	0	1 (1.1)	0
Rash	10 (4.4)	0	0	0	28 (6.4)	0	11 (2.5)	0	0	0	0	0	0	0	0	0
Rash maculo-papular	10 (4.4)	0	1 (0.4)	0	2 (0.5)	0	2 (0.5)	0	11 (2.3)	0	0	0	0	0	0	0
Hypokalaemia	9 (4.0)	2 (0.9)	4 (1.8)	0	9 (2.1)	1 (0.2)	4 (0.9)	2 (0.5)	2 (0.4)	2 (0.4)	2 (0.8)	0	1 (1.1)	1 (1.1)	0	0
Rash pustular	8 (3.5)	0	0	0	1 (0.2)	0	1 (0.2)	0	3 (0.6)	0	0	0	0	0	0	0
Stomatitis	8 (3.5)	0	1 (0.4)	0	6 (1.4)	1 (0.2)	1 (0.2)	0	15 (3.1)	1 (0.2)	0	0	1 (1.1)	0	1 (1.1)	0
Decreased appetite	7 (3.1)	0	1 (0.4)	0	14 (3.2)	0	18 (4.1)	0	14 (2.9)	0	4 (1.7)	0	1 (1.1)	0	1 (1.1)	0
Asthenia	5 (2.2)	0	3 (1.3)	0	15 (3.4)	0	18 (4.1)	1 (0.2)	0	0	0	0	3 (3.2)	0	0	0
Dyspnoea	4 (1.8)	1 (0.4)	4 (1.8)	0	16 (3.7)	6 (1.4)	17 (3.9)	3 (0.7)	28 (5.9)	16 (3.4)	16 (6.7)	7 (2.9)	7 (7.5)	5 (5.4)	6 (6.4)	1 (1.1)
Alanine aminotransferase increased	2 (0.9)	0	19 (8.5)	0	2 (0.5)	0	4 (0.9)	0	0	0	0	0	3 (3.2)	0	0	0
Anaemia	2 (0.9)	0	5 (2.2)	0	11 (2.5)	1 (0.2)	21 (4.8)	1 (0.2)	2 (0.4)	0	0	0	1 (1.1)	2 (2.2)	1 (1.1)	1 (1.1)
Pneumonia	2 (0.9)	0	3 (1.3)	0	11 (2.5)	2 (0.5)	10 (2.3)	1 (0.2)	0	0	0	0	3 (3.2)	0	0	2 (2.1)
Vomiting	2 (0.9)	0	0	0	5 (1.1)	0	3 (0.7)	0	9 (1.9)	0	2 (0.8)	0	3 (3.2)	0	2 (2.1)	0
Dehydration	1 (0.4)	0	0	0	15 (3.4)	2 (0.5)	4 (0.9)	1 (0.2)	17 (3.6)	1 (0.2)	0	0	2 (2.2)	0	1 (1.1)	0
Aspartate aminotransferase increased	0	0	9 (4.0)	0	1 (0.2)	0	3 (0.7)	0	0	0	0	0	2 (2.2)	0	0	0
Back pain	0	0	1 (0.4)	0	6 (1.4)	0	4 (0.9)	0	5 (1.0)	0	4 (1.7)	0	4 (4.3)	0	1 (1.1)	0
Cough	0	0	1 (0.4)	0	1 (0.2)	0	3 (0.7)	0	1 (0.2)	0	1 (0.4)	0	0	0	4 (4.3)	0
Fatigue	0	0	0	0	14 (3.2)	0	15 (3.4)	0	32 (6.7)	0	15 (6.3)	0	3 (3.2)	1 (1.1)	4 (4.3)	0

Data source: A7471050 CSR Table 14.3.1.2.9.1; SCS Tables 14.3.1.2.9.1.D, 14.3.1.2.9.1.E, and 14.3.1.2.9.1.F.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety.
Notes: 1) Shading is applied to the meaningfully higher AE frequencies in either treatment arm of A7471050 (ie, ≥4% absolute difference in AE frequency between the arms).
2) AE severity was assessed using CTCAE Version 4.03.
3) Grade 5 AEs are summarized in Section 2.7.4.2.1.3.2.
a. MedDRA Version 19.1.
b. Any Grade 3 AE without consideration for the minimum 3% frequency used in this table.

Table 55: Treatment-Related Grade 3 or Grade 4 Adverse Events Reported for at Least 2% of Patients, by Maximum Severity and MedDRA PT in Phase 3 Studies and Phase 2 Study A7471028 – As-Treated Patients.

	Number (%) of Patients														
	Phase 3 Studies											Phase 2 Study A7471028 (N=187)			
	A7471050 (N=451)				A7471009 (N=872)				A7471011 (N=716)						
	Dacomitinib (N=227)		Gefitinib (N=224)		Dacomitinib (N=436)		Erlotinib (N=436)		Dacomitinib (N=477)		Placebo (N=239)[b]	Dacomitinib (N=93)		Erlotinib (N=94)	
MedDRA PT[a]	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 3	Grade 4	Grade 3	Grade 4
Any TRAE[c]	107 (47.1)	2 (0.9)	41 (18.3)	2 (0.9)	136 (31.2)	6 (1.4)	92 (21.1)	2 (0.5)	161 (33.8)	9 (1.9)	8 (3.3)	30 (32.3)	1 (1.1)	20 (21.3)	1 (1.1)
Dermatitis acneiform	31 (13.7)	0	0	0	5 (1.1)	0	7 (1.6)	0	47 (9.9)	1 (0.2)	1 (0.4)	10 (10.8)	0	6 (6.4)	0
Diarrhoea	18 (7.9)	0	1 (0.4)	0	46 (10.6)	1 (0.2)	10 (2.3)	0	58 (12.2)	1 (0.2)	0	11 (11.8)	0	4 (4.3)	0
Paronychia	17 (7.5)	0	3 (1.3)	0	5 (1.1)	0	3 (0.7)	0	10 (2.1)	0	0	3 (3.2)	0	1 (1.1)	0
Rash maculo-papular	10 (4.4)	0	1 (0.4)	0	2 (0.5)	0	2 (0.5)	0	11 (2.3)	0	0	0	0	0	0
Rash	9 (4.0)	0	0	0	28 (6.4)	0	11 (2.5)	0	0	0	0	0	0	0	0
Rash pustular	8 (3.5)	0	0	0	1 (0.2)	0	1 (0.2)	0	3 (0.6)	0	0	0	0	0	0
Stomatitis	8 (3.5)	0	0	0	6 (1.4)	1 (0.2)	1 (0.2)	0	15 (3.1)	1 (0.2)	0	1 (1.1)	0	1 (1.1)	0
Decreased appetite	5 (2.2)	0	0	0	10 (2.3)	0	13 (3.0)	0	12 (2.5)	0	1 (0.4)	1 (1.1)	0	0	0
Asthenia	3 (1.3)	0	0	0	10 (2.3)	0	11 (2.5)	0	0	0	0	1 (1.1)	0	0	0
Acne	2 (0.9)	0	0	0	3 (0.7)	0	2 (0.5)	0	0	0	0	2 (2.2)	0	0	0
Alanine aminotransferase increased	2 (0.9)	0	18 (8.0)	0	1 (0.2)	0	3 (0.7)	0	0	0	0	2 (2.2)	0	0	0
Mucosal inflammation	2 (0.9)	1 (0.4)	0	0	6 (1.4)	1 (0.2)	1 (0.2)	0	0	0	0	2 (2.2)	0	0	0
Dehydration	1 (0.4)	0	0	0	9 (2.1)	1 (0.2)	3 (0.7)	0	10 (2.1)	1 (0.2)	0	2 (2.2)	0	0	0
Vomiting	1 (0.4)	0	0	0	4 (0.9)	0	1 (0.2)	0	5 (1.0)	0	0	2 (2.2)	0	1 (1.1)	0
Nausea	2 (0.9)	0	1 (0.4)	0	6 (1.4)	0	0	0	2 (0.4)	0	1 (0.4)	2 (2.2)	0	1 (1.1)	0
Aspartate aminotransferase increased	0	0	8 (3.6)	0	0	0	2 (0.5)	0	0	0	0	1 (1.1)	0	0	0
Exfoliative rash	0	0	0	0	0	0	1 (0.2)	0	0	0	0	2 (2.2)	0	1 (1.1)	0
Fatigue	0	0	0	0	7 (1.6)	0	9 (2.1)	0	13 (2.7)	0	4 (1.7)	1 (1.1)	0	1 (1.1)	0

Data source: A7471050 CSR Table 14.3.1.3.9.1; SCS Tables 14.3.1.3.11.1.D, 14.3.1.3.11.1.E, and 14.3.1.3.11.1.F.
Abbreviations: CSR=Clinical Study Report; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety; TRAE=treatment-related adverse event.
Notes: 1) TRAE severity was assessed using CTCAE Version 4.03.
2) Grade 5 TRAEs are summarized in Section 2.7.4.2.1.3.2.
a. MedDRA Version 19.1.
b. No Grade 4 AEs were reported in the placebo arm of Study A7471011.
c. Any Grade 3 or Grade 4 TRAE without consideration for the minimum 2% frequency cutoff used in this table.

Adverse Drug Reactions

ADRs were identified based on whether an AE was reasonably associated with dacomitinib treatment in the First-Line Pool (Study 1050 and Cohort A of study 2017); taking into consideration the mechanism of action of dacomitinib, temporal relationship, underlying disease and concomitant medication confounders, the available nonclinical toxicity data, and the overall assessment of AEs by the investigators. Some ADRs are denoted as clusters of MedDRA PTs in order to minimize ADR frequency underestimation.

Table 56: All-Causality Adverse Drug Reactions, by MedDRA SOC, Adverse Drug Reaction Term, and Maximum Severity Grade – Study A7471050 – As-Treated Patients

	Dacomitinib (N=227)			**Gefitinib (N=224)**		
MedDRA SoC/ADRs (MedDRA PT[a] or cluster term)	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Metabolism and nutrition disorders						
Decreased appetite	30.8	3.1	0.0	25.0	0.4	0.0
Hypokalemia[b]	10.1	4.0	0.9	5.8	1.8	0.0
Dehydration	1.3	0.4	0.0	0.4	0.0	0.0
Nervous system disorders						
Dysgeusia	7.0	0.0	0.0	4.9	0.0	0.0
Respiratory, thoracic and mediastinal disorders						
Interstitial lung disease[c]	2.6	0.4	0.0	1.3	0.4	0.0
Eye disorders						
Conjunctivitis[d]	24.2	0.0	0.0	8.9	0.0	0.0
Gastrointestinal disorders						
Diarrhoea[e]	87.2	8.4	0.0	55.8	0.9	0.0
Stomatitis[f]	69.6	4.4	0.4	33.5	0.4	0.0
Nausea	18.9	1.3	0.0	21.9	0.4	0.0
Vomiting	8.8	0.9	0.0	12.9	0.0	0.0
Skin and subcutaneous tissue disorders						
Rash[g]	77.1	24.2	0.0	57.6	0.9	0.0
Palmar-plantar erythrodysaesthesia syndrome	14.5	0.9	0.0	3.1	0.0	0.0
Skin fissures	9.3	0.0	0.0	2.7	0.0	0.0
Skin exfoliation[h]	3.5	0.0	0.0	3.6	0.0	0.0
Hypertrichosis	1.3	0.0	0.0	0.0	0.0	0.0
Dry skin[i]	29.5	1.8	0.0	18.8	0.4	0.0
Pruritus[j]	20.3	0.9	0.0	14.3	1.3	0.0
Nail disorder[k]	65.6	7.9	0.0	21.4	1.3	0.0
Alopecia	23.3	0.4	0.0	12.5	0.0	0.0
General disorders and administration site conditions						
Asthenia	12.8	2.2	0.0	12.5	1.3	0.0
Fatigue	9.3	0.0	0.0	8.5	0.0	0.0
Investigations						
Transaminases increased[l]	23.8	0.9	0.0	40.2	9.8	0.0
Weight decreased	25.6	2.2	0.0	16.5	0.4	0.0

[a] MedDRA version 19.1.
[b] Hypokalaemia includes the following preferred terms (PTs): Blood potassium decreased, Hypokalaemia.
[c] Interstitial lung disease includes the following PTs: Interstitial lung disease and Pneumonitis
[d] Conjunctivitis includes the following PTs: Blepharitis, Conjunctivitis, Dry eye, Keratitis, Noninfective conjunctivitis.
[e] 1 fatal event was reported in the dacomitinib arm.
[f] Stomatitis includes the following PTs: Aphthous ulcer, Cheilitis, Dry mouth, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, Stomatitis.
[g] Rash includes the following PTs: Acne, Dermatitis acneiform, Erythema, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular.
[h] Skin exfoliation (also referred to as Exfoliative skin conditions) includes the following PTs: Exfoliative rash, Skin exfoliation.
[i] Dry skin includes the following PTs: Dry skin, Xerosis.
[j] Pruritus includes the following PTs: Pruritus, Rash pruritic.
[k] Nail disorder includes the following PTs: Ingrowing nail, Nail discolouration, Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia.
[l] Transaminases increased includes the following PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased.

Adverse Events of Special Interest

Given that the frequency of the AEoSIs may have been underestimated by reliance on a single MedDRA PT, selected PTs were analyzed in aggregate using cluster terms denoted in ALL CAPITALS.

Table 57: Overview of All-Causality and treatment-related AEoSIs , by Cluster Term, in Study A7471050

	Number (%) of Patients			
	Study A7471050 (N=451)			
	Dacomitinib (N=227)		Gefitinib (N=224)	
Cluster Term	AEs	TRAEs	AEs	TRAEs
DIARRHOEA AND ASSOCIATED AEs	198 (87.2)	193 (85.0)	126 (56.3)	115 (51.3)
RASH/DERMATITIS ACNEIFORM	176 (77.5)	174 (76.7)	122 (54.5)	121 (54.0)
OTHER SKIN TOXICITY	173 (76.2)	172 (75.8)	71 (31.7)	71 (31.7)
STOMATITIS	157 (69.2)	151 (66.5)	74 (33.0)	61 (27.2)
LIVER-RELATED LABORATORY TEST AEs	67 (29.5)	64 (28.2)	95 (42.4)	90 (40.2)
ACUTE RENAL FAILURE	11 (4.8)	9 (4.0)	13 (5.8)	8 (3.6)
SEVERE SKIN TOXICITY	8 (3.5)	8 (3.5)	8 (3.6)	8 (3.6)
INTERSTITIAL LUNG DISEASE	6 (2.6)	5 (2.2)	3 (1.3)	3 (1.3)
HEPATOTOXICITY	4 (1.8)	3 (1.3)	8 (3.6)	7 (3.1)
KERATITIS	4 (1.8)	4 (1.8)	0	0
QT INTERVAL PROLONGATION	3 (1.3)	1 (0.4)	0	0
LEFT VENTRICULAR DYSFUNCTION	2 (0.9)	0	1 (0.4)	1 (0.4)
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY	2 (0.9)	0	1 (0.4)	0
GASTROINTESTINAL PERFORATION	1 (0.4)	0	1 (0.4)	0

Data source: A7471050 CSR Tables 14.3.1.2.1.C.S1, 14.3.1.3.1.C.S1, 14.3.1.2.1.C.S2, 14.3.1.3.1.C.S2, 14.3.1.2.1.C.S3, 14.3.1.3.1.C.S3, 14.3.1.2.1.C.S4, 14.3.1.3.1.C.S4, 14.3.1.2.1.C.S5, 14.3.1.3.1.C.S5, 14.3.1.2.1.C.S8, 14.3.1.3.1.C.S8, 14.3.1.2.1.C.S10, 14.3.1.3.1.C.S10, 14.3.1.2.1.C.S11, 14.3.1.3.1.C.S11, 14.3.1.2.1.C.S12, 14.3.1.3.1.C.S12, 14.3.1.2.1.C.S13, 14.3.1.3.1.C.S13, 14.3.1.2. 1.C.S6, 14.3.1.3. 1.C.S6, 14.3.1.2. 1.C.S7, 14.3.1.31.C.S7, 14.3.1.2. 1.C.S9, and 14.3.1.3. 1.C.S9; SCS Table 14.3.1.2.9.1.C.S14.
Abbreviations: AEs=adverse events; CSR=Clinical Study Report; ISS=Integrated Summary of Safety Information; N=total number of patients; SCS=Summary of Clinical Safety; TRAEs=treatment-related adverse events.
Note: Definitions of cluster terms are provided in ISS Appendix 4.

Gastrointestinal events

- DIARRHOEA AND ASSOCIATED AEs: The incidence of all-causality DIARRHOEA AND ASSOCIATED AEs per 1000 person-years in the dacomitinib arm was statistically significantly higher than that in the gefitinib arm ($p<0.0001$). At least 1 SAE was reported for 2.6% of patients in the dacomitinib arm, while no SAEs were reported in the gefitinib arm. One Grade 5 AE was reported in the dacomitinib arm. Permanent discontinuations from treatment associated with DIARRHOEA AND ASSOCIATED AEs were reported in the dacomitinib arm only (2 [0.9%] patients). Most events reported in either treatment arm were considered to be related to treatment. Excluding Disease progression, Diarrhoea was the next most frequently reported SAE (5 [2.2%] patients) in the dacomitinib arm of Study 1050. In the dacomitinib arm, the median time to first onset of any severity grade DIARRHOEA AND ASSOCIATED AEs was 7.0 days, while the median time to onset of maximum grade event was 14.0 days; both shorter times than those in the gefitinib arm (17.0 days and 18.5 days, respectively). The median total duration of any grade Diarrhoea throughout the treatment period by patient was approximately twice as long in the dacomitinib arm (109.5 days) than in the gefitinib arm (50.0 days). The median total duration by patient of Grade 3 Diarrhoea was also twice as long in the dacomitinib arm (5.0 days) than in the gefitinib arm (2.5 days); no Grade 4 Diarrhoea was reported in either treatment arm.
- GASTROINTESTINAL PERFORATION: AEs within this cluster were reported for 1 patient in each treatment arm. Neither AE was serious, considered to be related to study treatment, or required treatment modification.
- STOMATITIS: The incidence per 1000 person-years in the dacomitinib arm was statistically significantly higher than that in the gefitinib arm ($p<0.0001$). An SAE was reported for 1 (0.4%) patient in the dacomitinib

arm, while no SAEs were reported in the gefitinib arm. No Grade 5 STOMATITS was reported in either treatment arm. Permanent treatment discontinuations associated with STOMATITIS were reported in the dacomitinib arm only (2 [0.9%] patients). Dose reductions or temporary treatment discontinuations associated with STOMATITIS were reported in the dacomitinib arm only (4.4% of patients and 8.4%, respectively). Most events reported in both treatment arms were considered to be related to treatment. In the dacomitinib arm, the median time to first onset of any severity grade STOMATITIS was 8.0 days, while the median time to onset of maximum grade event was 11.0 days; the shorter times to first onset than those reported in the gefitinib arm (18.5 days and 20.0 days, respectively).

Table 58: AEs within the DIARRHOEA AND ASSOCIATED ADVERSE EVENTS cluster, by maximum severity grade and MedDRA PT sorted by descending frequency in the dacomitinib arm (any grade) of Study A7471050 – As-Treated Patients

	Number (%) of Patients						
	Study A7471050 (N=451)						
	Dacomitinib (N=227)				Gefitinib (N=224)		
Cluster Term/MedDRA PT[a]	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade[b]	Grade 3	Grade 4
DIARRHOEA AND ASSOCIATED AEs	198 (87.2)	20 (8.8)	1 (0.4)	1 (0.4)	126 (56.3)	2 (0.9)	0
Diarrhoea	198 (87.2)	19 (8.4)	0	1 (0.4)	125 (55.8)	2 (0.9)	0
Dehydration	3 (1.3)	1 (0.4)	0	0	1 (0.4)	0	0
Azotaemia	1 (0.4)	0	0	0	0	0	0
Electrolyte imbalance	1 (0.4)	0	1 (0.4)	0	0	0	0

Data source: SCS Table 14.3.1.2.9.1.C.S1.

Abbreviations: AEs=adverse events; CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety Information; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term.

Notes: 1) Definition of DIARRHOEA AND ASSOCIATED AEs is provided in ISS Appendix 4.
2) Shading is applied to the meaningfully higher AE frequencies in the dacomitinib arm than in the gefitinib arm of Study A7471050 (ie, ≥10% absolute difference in AE frequency or ≥4% absolute difference in Grade 3 AE frequency between the arms).
3) The cluster term may not be the sum of individual PTs as more than 1 PT within the cluster may have been reported for the same patient.
4) AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. No Grade 5 AEs were reported in the gefitinib arm.

Table 59: AEs within the all-causality STOMATITIS cluster, by maximum severity grade and MedDRA PT sorted by descending frequency in the dacomitinib arm (any grade) of Study A7471050 – As-Treated Patients

	Number (%) of Patients					
	A7471050 (N=451)					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Cluster Term/MedDRA PT[a]	Any Grade[b]	Grade 3	Grade 4	Any Grade[b]	Grade 3	Grade 4
STOMATITIS	157 (69.2)	10 (4.4)	1 (0.4)	74 (33.0)	1 (0.4)	0
Stomatitis	99 (43.6)	8 (3.5)	0	40 (17.9)	1 (0.4)	0
Mouth ulceration	28 (12.3)	0	0	13 (5.8)	0	0
Mucosal inflammation	21 (9.3)	2 (0.9)	1 (0.4)	8 (3.6)	0	0
Aphthous ulcer	13 (5.7)	0	0	6 (2.7)	0	0
Oral pain	12 (5.3)	0	0	1 (0.4)	0	0
Cheilitis	10 (4.4)	0	0	5 (2.2)	0	0
Oropharyngeal pain	9 (4.0)	0	0	8 (3.6)	0	0
Oropharyngeal discomfort	0	0	0	3 (1.3)	0	0

Data source: SCS Table 14.3.1.2.9.1.C.S12.

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety Information; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term.

Notes: 1) Definition of STOMATITIS is provided in ISS Appendix 4.
2) Shading is applied to the meaningfully higher any grade AE frequency in the dacomitinib arm than in the gefitinib arm of Study A7471050 (ie, ≥10% absolute difference in any grade AE frequency between the arms).
3) The cluster term may not be the sum of individual PTs as more than 1 PT within the cluster may have been reported for the same patient.
4) AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. No Grade 5 AEs were reported in either treatment arm.

Skin and other dermal conditions

- SEVERE SKIN TOXICITY: the frequencies were balanced across treatment arms (3.5% dacomitinib, 3.6% gefitinib). All AEs were considered to be related to treatment. No Grade 5 AEs, SAEs, or treatment modifications were reported in either treatment arm.
- RASH/DERMATITIS ACNEIFORM: The incidence per 1000 person-years in the dacomitinib arm was statistically significantly higher than that in the gefitinib arm (p<0.0001). No Grade 5 AE was reported in either treatment arm. In the dacomitinib arm, at least 1 SAE was reported for 3 (1.3%) patients, while no SAEs were reported in the gefitinib arm. Permanent discontinuations from treatment were reported for 6 (2.6%) patients in the dacomitinib arm and no patients in the gefitinib arm. Dose reductions or temporary treatment discontinuations were reported for the higher proportions of patients in the dacomitinib arm (32.2% or 25.6% of patients, respectively) than in the gefitinib arm (1.3% or 2.7%). Most events reported in either treatment arm were considered to be related to treatment. In the dacomitinib arm, the median time to first onset of any severity grade RASH/DERMATITIS ACNEIFORM was 13.0 days, comparable to that in the gefitinib arm (16.0 days). However, the median time to first onset of maximum severity grade RASH/DERMATITIS ACNEIFORM was more than 2-fold longer in the dacomitinib arm (56.5 days) than in the gefitinib arm (26.5 days).
- OTHER SKIN TOXICITY: The incidence per 1000 person-years in the dacomitinib arm was statistically significantly higher than that in the gefitinib arm (p<0.0001). No Grade 5 AEs, SAEs, or permanent treatment discontinuations associated with OTHER SKIN TOXICITY were reported in either treatment arm. Dose reductions or temporary treatment discontinuations were reported in the higher proportions of patients in the dacomitinib arm (20.7% and 14.1% of patients, respectively) than in the gefitinib arm (0.9% each). Most events were considered to be related to treatment in either treatment arm. Most AEs within were Grade 1 or Grade 2 in severity. The frequency of Grade 3 Paronychia was meaningfully higher in the dacomitinib arm.

Table 60: AEs within the RASH/DERMATITIS ACNEIFORM cluster, by MedDRA PT, in Study A7471050

	Number (%) of Patients					
	A7471050 (N=451)					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Cluster Term/MedDRA PT[a]	Any Grade[b]	Grade 3	Grade 4	Any Grade[b]	Grade 3	Grade 4
RASH/DERMATITIS ACNEIFORM	176 (77.5)	57 (25.1)	0	122 (54.5)	1 (0.4)	0
Dermatitis acneiform	111 (48.9)	31 (13.7)	0	64 (28.6)	0	0
Rash	40 (17.6)	10 (4.4)	0	24 (10.7)	0	0
Rash maculo-papular	28 (12.3)	10 (4.4)	0	27 (12.1)	1 (0.4)	0
Acne	20 (8.8)	2 (0.9)	0	13 (5.8)	0	0
Drug eruption	9 (4.0)	2 (0.9)	0	4 (1.8)	0	0
Rash erythematous	5 (2.2)	1 (0.4)	0	0	0	0
Rash generalised	2 (0.9)	0	0	0	0	0
Rash pruritic	2 (0.9)	1 (0.4)	0	0	0	0
Acne pustular	1 (0.4)	1 (0.4)	0	0	0	0

Data source: SCS Table 14.3.1.2.9.1.C.S11.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety Information; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term.
Notes: 1) Definition of RASH/DERMATITIS ACNEIFORM is provided in ISS Appendix 4.
2) Shading is applied to the meaningfully higher any grade or Grade 3 AE frequencies in the dacomitinib arm than in the gefitinib arm of Study 1050 (ie, ≥10% absolute difference in any grade AE frequency or ≥4% absolute difference in Grade 3 AE frequency between the arms).
3) The cluster term may not be the sum of individual PTs as more than 1 PT within the cluster may have been reported for the same patient.
4) AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. No Grade 5 AEs within the RASH/DERMATITIS ACNEIFORM cluster were reported in either treatment arm.

Table 61: AEs within the OTHER SKIN TOXICITY cluster, by MedDRA PT, in Study

	Number (%) of Patients					
	A7471050 (N=451)					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Cluster Term/MedDRA PT[a]	Any Grade[b]	Grade 3	Grade 4	Any Grade[b]	Grade 3	Grade 4
OTHER SKIN TOXICITY	173 (76.2)	23 (10.1)	0	71 (31.7)	4 (1.8)	0
Paronychia	140 (61.7)	17 (7.5)	0	45 (20.1)	3 (1.3)	0
Dry skin	63 (27.8)	3 (1.3)	0	38 (17.0)	0	0
Palmar-plantar erythrodysaesthesia syndrome	33 (14.5)	2 (0.9)	0	7 (3.1)	0	0
Skin fissures	21 (9.3)	0	0	6 (2.7)	0	0
Nail disorder	5 (2.2)	1 (0.4)	0	1 (0.4)	0	0
Skin ulcer	5 (2.2)	0	0	1 (0.4)	0	0
Xerosis	5 (2.2)	1 (0.4)	0	4 (1.8)	1 (0.4)	0

Data source: SCS Table 14.3.1.2.9.1.C.S10.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety Information; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term.
Notes: 1) Definition of OTHER SKIN TOXICITY is provided in ISS Appendix 4.
2) Shading is applied to the meaningfully higher any grade or Grade 3 AE frequencies in the dacomitinib arm than in the gefitinib arm of Study A7471050 (ie, ≥10% absolute difference in any grade AE or ≥4% absolute difference in Grade 3 AE frequency between the arms).
3) The cluster term may not be the sum of individual PTs as more than 1 PT within the cluster may have been reported for the same patient.
4) AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. No Grade 5 AEs within the OTHER SKIN TOXICITY cluster were reported.

Renal events

- ACUTE RENAL FAILURE: At least 1 AE of ACUTE RENAL FAILURE was reported for comparable proportions of patients in the dacomitinib arm (4.8%) and the gefitinib arm (5.8%) of Study 1050. No Grade 5 AEs or permanent treatment discontinuations were reported. Most AEs in the dacomitinib arm and more than half of AEs in the gefitinib arm were considered to be related to treatment. Most AEs reported in the dacomitinib arm al all AEs in the gefitinib arm were Grade 1 or Grade 2 in severity. In the dacomitinib arm, Grade 3 Anuria and Grade 4 Acute kidney injury were reported for 1 (0.4%) patient each. Overall, the AE frequencies reported in the dacomitinib arm were comparable with those reported in the gefitinib arm.
- CREATININE ABNORMAL LABORATORY FINDINGS: Most patients in both treatment arms of Study 1050 had Grade 1-2 increased Creatinine postbaseline. The only shift in creatinine values from Grade ≤2 at baseline was reported in the gefitinib arm to Grade 3 postbaseline.

Interstitial lung disease

At least 1 AE of INTERSTITIAL LUNG DISEASE was reported for 6 (2.6%) patients in the dacomitinib arm and 3 (1.3%) patients in the gefitinib arm, while at least 1 SAE was reported for 3 (1.3%) patients in the dacomitinib arm and 2 (0.9%) patients in the gefitinib arm of Study 1050. A Grade 5 event was reported for 1 (0.4%) patient in the dacomitinib arm, and none in the gefitinib arm. Permanent treatment discontinuations were reported for 4 (1.8%) patients in the dacomitinib arm and 3 (1.3%) patients in the gefitinib arm, while temporary treatment discontinuations were reported for 2 (0.9%) patients in the dacomitinib arm and none in the gefitinib arm. All but 1 event in the dacomitinib arm and all AEs in the gefitinib arm were considered to be related to treatment.

Only 2 unique AEs, Interstitial lung disease and Pneumonitis, were reported in both the dacomitinib arm (3 [1.3%] patients each) and gefitinib arm (1 [0.4%] and 2 [0.9%] patients, respectively) of Study 1050. Grade 3 and Grade 5 AEs of Pneumonitis (1 [0.4%] patient each) were reported in the dacomitinib arm, while Grade 3 Pneumonitis was reported for 1 (0.4%) patient in the gefitinib arm of this study.

The median time to the first episode of any grade ILD/pneumonitis was 16 weeks and the median time to the worst episode of ILD/pneumonitis was 16 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 ILD/pneumonitis was 13 weeks and 1.5 weeks, respectively (see section 4.8 of the SmPC).

Hepatic events

- Hepatotoxicity: At least 1 AE was reported for 4 (1.8%) patients in the dacomitinib arm and 8 (3.6%) patients in the gefitinib arm of Study 1050, while at least 1 SAE was reported for 3 (1.3%) patients in the dacomitinib arm and 2 (0.9%) patients in the gefitinib arm. No Grade 5 AE was reported in either treatment arm. Permanent or temporary treatment discontinuations or dose reductions were reported infrequently. All but 1 AEs in each treatment arm were considered to be related to treatment. Grade 3 AEs of Drug-induced liver injury, Liver injury, and Ascites were reported in the dacomitinib arm of Study 1050 for 1 (0.4%) patient each. In the gefitinib arm, the reported Grade 3 AEs were Liver injury (3 [1.3%] patients), Drug-induced liver injury (1 [0.4%]), and Hepatic failure (1 [0.4%]). No Grade 4 or Grade 5 AEs were reported in either treatment arm.
- Liver-related laboratory adverse events: Most AEs reported were Grade 1-2 in severity. The incidence of all-causality liver-related laboratory test AEs per 1000 person-years in the gefitinib arm was statistically significantly higher than that in the dacomitinib arm (p=0.0001). In the dacomitinib arm no Grade 5 AEs, SAEs, or permanent treatment discontinuations were reported. Dose reductions or temporary treatment discontinuations were reported for 1 (0.4%) and 2 (0.9%) patients, respectively, in the dacomitinib arm. Most liver-related laboratory test AEs were considered to be related to treatment in either treatment arm.

  The median time to the first episode of any grade of transaminases increased was approximately 12 weeks and the median time to the worst episode of transaminases increased was 12 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 transaminases increased was 11 weeks and 1 week, respectively.

Table 62: AEs within the LIVER-RELATED LABORATORY TEST ADVERSE EVENTS cluster, by maximum severity grade and MedDRA PT - Study A7471050 – As-Treated

	Number (%) of Patients					
	A7471050 (N=451)					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Cluster Term/MedDRA PT[a]	Any Grade[b]	Grade 3	Grade 4	Any Grade[b]	Grade 3	Grade 4
LIVER-RELATED LABORATORY TEST AEs	67 (29.5)	2 (0.9)	0	95 (42.4)	21 (9.4)	2 (0.9)
Alanine aminotransferase increased	44 (19.4)	2 (0.9)	0	88 (39.3)	19 (8.5)	0
Aspartate aminotransferase increased	42 (18.5)	0	0	81 (36.2)	9 (4.0)	0
Blood bilirubin increased	20 (8.8)	0	0	19 (8.5)	0	0
Bilirubin conjugated increased	3 (1.3)	0	0	8 (3.6)	0	0
Hyperbilirubinaemia	1 (0.4)	0	0	0	0	0
Transaminases increased	1 (0.4)	0	0	1 (0.4)	0	0
Hepatic enzyme increased	0	0	0	2 (0.9)	0	2 (0.9)

Data source: SCS Table 14.3.1.2.9.1.C.S13.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety Information; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term.
Notes: 1) Definition of the LIVER-RELATED LABORATORY TEST AEs cluster is provided in ISS Appendix 4.
2) Shading is applied to the meaningfully higher any grade AE or Grade 3 AE frequencies in the gefitinib arm than in the dacomitinib arm (ie, ≥10% absolute difference in any grade AE frequency or ≥4% absolute difference in Grade 3 AE frequency between the treatment arms).
3) The cluster term may not be the sum of individual PTs as more than 1 PT within the cluster may have been reported for the same patient.
4) AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. No Grade 5 AEs within the LIVER-RELATED LABORATORY TEST AEs cluster were reported in either treatment arm.

Keratitis

Keratitis was reported for 4 (1.8%) patients in the dacomitinib arm and no patients in the gefitinib arm. An SAE, permanent or temporary treatment discontinuation associated with keratitis, and dose reduction associated with keratitis were reported for 1 (0.4%) patient each in the dacomitinib arm. All reported events were considered to be related to treatment. One AE of Keratitis was Grade 3 in severity, while none were Grade 4 in severity.

Cardiovascular events

- QT interval prolongation: AEs were reported for 3 (1.3%) patients in the dacomitinib arm. The AEs reported were Electrocardiogram QT prolonged, Long QT syndrome, and Syncope, for 1 (0.4%) patient each. Only the case of long QT syndrome was considered to be related to dacomitinib treatment. No Grade 5 AE, SAEs, permanent or temporary treatment discontinuations or dose reductions were reported. Four (1.9%) patients had a ≥60 msec increase in QTcF from baseline, while none had postbaseline QTcF of ≥500 msec.

  Regarding data on Pool B, the proportion of patients who had events within the QT interval prolongation cluster was in line with study A1050 (19 [1.3%]). Most of the events were among the PTs of syncope (6 [0.6%]), cardiac arrest (2 [0.1%]) and electrocardiogram QT prolonged (2 [0.1%]). There were 3 (0.2%) fatal events (2 cardiac arrests and 1 sudden death). Additionally, 1 patient in study 1042 reported an AE of cardiac arrest. None of the events were considered by the investigator to be related to study drug. Sudden death was of unknown cause and as a precautionary measure was considered to be related to dacomitinib by the applicant.

  No events of Torsades de pointes, ventricular fibrillation or ventricular flutter have been reported with dacomitinib. One (0.2%) patient had a maximum postbaseline QTcF≥ 500 msec (study A1011) and 10 (2.8%) patients had maximum QTcF increased from baseline of ≥60 msec (4 in the dacomitinib arm of study A1050). No cardiac AEs were reported for these patients.

- Left ventricular function (LVEF): AEs were reported for 2 (0.9%) patients in the dacomitinib arm and 1 (0.4%) patient in the gefitinib arm. No Grade 5 AEs, SAEs, or permanent treatment discontinuations were reported. A dose reduction was reported for 1 patient in the dacomitinib arm, while a temporary treatment discontinuation was reported for 1 patient in the gefitinib arm. None of the events reported in the dacomitinib arm were considered to be related to treatment. In the dacomitinib arm of Study 1050, 2 AEs within the cluster were reported: Grade 4 Cardiopulmonary failure and Grade 1 Ejection fraction decreased (1 [0.4%] patient each). Grade 2 Ejection fraction decreased (1 [0.4%] patient) was the only AE reported in the gefitinib arm of the study.

  In the Pool B the incidence of left ventricular dysfunction was also low (12 [0.8%]) and the majority of events were grade 1 or 2. There was one fatal event (pulmonary oedema) but it was not considered to be related to dacomitinib. The proportion of patients with a maximum relative decrease from baseline in LVEF > 20% in the First Line Pool (n=255) was 3.2% and only 2 (0.9%) patients with normal baseline LVEF (≥ 55%) had a postbaseline LVEF < 55%.

Reproductive and developmental toxicity

No cases within the REPRODUCTIVE AND DEVELOPMENTAL TOXICITY were retrieved considered to be relevant in Study 1050 or supporting studies 1009, 1011 and 1028.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Table 63: SAEs reported for at least 1% of patients in Phase 3 Studies, and for at least 2% of patients in the Phase 2 Study A7471050, by MedDRA PT- Study A7471050 – Phase 3 Studies and Phase 2 Study A7471050

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study A7471028 (N=187)	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)			
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Any SAE[b]	62 (27.3)	50 (22.3)	178 (40.8)	170 (39.0)	191 (40.0)	87 (36.4)	35 (37.6)	31 (33.0)
Disease progression	8 (3.5)	11 (4.9)	53 (12.2)	50 (11.5)	0	0	10 (10.8)	13 (13.8)
Diarrhoea	5 (2.2)	0	20 (4.6)	7 (1.6)	17 (3.6)	1 (0.4)	2 (2.2)	2 (2.1)
Pleural effusion	5 (2.2)	2 (0.9)	2 (0.5)	2 (0.5)	8 (1.7)	3 (1.3)	0	0
Pneumonia	5 (2.2)	2 (0.9)	15 (3.4)	15 (3.4)	0	0	6 (6.5)	4 (4.3)
Abdominal pain	2 (0.9)	0	2 (0.5)	1 (0.2)	4 (0.8)	3 (1.3)	0	2 (2.2)
Haemoptysis	2 (0.9)	0	5 (1.1)	1 (0.2)	0	0	1 (1.1)	1 (1.1)
Respiratory failure	2 (0.9)	0	4 (0.9)	5 (1.1)	6 (1.3)	2 (0.8)	1 (1.1)	1 (1.1)
Acute kidney injury	1 (0.4)	0	4 (0.9)	2 (0.5)	6 (1.3)	0	1 (1.1)	0
Death	1 (0.4)	1 (0.4)	5 (1.1)	1 (0.2)	2 (0.4)	0	0	0
Dehydration	1 (0.4)	0	13 (3.0)	6 (1.4)	16 (3.4)	0	1 (1.1)	1 (1.1)
Dyspnoea	1 (0.4)	4 (1.8)	8 (1.8)	8 (1.8)	26 (5.5)	14 (5.9)	8 (8.6)	4 (4.3)
Lung infection	1 (0.4)	1 (0.4)	1 (0.2)	3 (0.7)	31 (6.5)	12 (5.0)	1 (1.1)	0
Pulmonary embolism	1 (0.4)	0	4 (0.9)	3 (0.7)	0	0	1 (1.1)	3 (3.2)
Pyrexia	1 (0.4)	0	5 (1.1)	2 (0.5)	7 (1.5)	1 (0.4)	0	0
Stomatitis	1 (0.4)	0	2 (0.5)	1 (0.2)	5 (1.0)	0	0	0
Vomiting	1 (0.4)	0	5 (1.1)	3 (0.7)	8 (1.7)	3 (1.3)	2 (2.2)	1 (1.1)
Cerebrovascular accident	0	1 (0.4)	0	1 (0.2)	2 (0.4)	3 (1.3)	0	0
Confusional state	0	0	0	0	3 (0.6)	1 (0.4)	2 (2.2)	1 (1.1)
Embolism	0	0	1 (0.2)	1 (0.2)	12 (2.5)	3 (1.3)	0	0
Anaemia	0	0	3 (0.7)	8 (1.8)	1 (0.2)	0	0	1 (1.1)
General physical health deterioration	0	1 (0.4)	4 (0.9)	10 (2.3)	0	0	0	0
Non-small cell lung cancer	0	0	2 (0.5)	1 (0.2)	76 (15.9)	42 (17.6)	0	0
Pulmonary haemorrhage	0	0	0	1 (0.2)	6 (1.3)	4 (1.7)	1 (1.1)	0
Sepsis	0	0	2 (0.5)	3 (0.7)	2 (0.4)	3 (1.3)	1 (1.1)	0

Data source: A7471050 CSR Table 14.3.2.3; SCS Tables 14.3.2.4.2.11.1.D, 14.3.2.4.2.11.1.E, and 14.3.2.4.2.11.1.F.
Abbreviations: CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SAE=serious adverse event; SCS=Summary of Clinical Safety.
a. MedDRA Version 19.1.
b. Any SAE without consideration for the minimum 1% (Phase 3 studies) and 2% (Phase 2 Study A7471028) frequency cutoffs used in this table.

Table 64: Treatment-related SAEs reported for at least 2 patients in any treatment arm, by MedDRA PT sorted by descending frequency in the dacomitinib arm of Study A7471050 – Phase 3 Studies and Phase 2 Study A7471028 – As-Treated Patients

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Any treatment-related SAE	21 (9.3)	10 (4.5)	50 (11.5)	39 (8.9)	44 (9.2)	0	7 (7.5)	7 (7.4)
Diarrhoea	5 (2.2)	0	18 (4.1)	6 (1.4)	16 (3.4)	0	2 (2.2)	2 (2.1)
Abdominal pain	2 (0.9)	0	1 (0.2)	0	0	0	0	0
Liver injury	2 (0.9)	1 (0.4)	0	0	0	0	0	0
Acute kidney injury	1 (0.4)	0	2 (0.5)	1 (0.2)	4 (0.8)	0	1 (1.1)	0
Decreased appetite	1 (0.4)	0	1 (0.2)	4 (0.9)	2 (0.4)	0	0	0
Dehydration	1 (0.4)	0	9 (2.1)	3 (0.7)	9 (1.9)	0	1 (1.1)	0
Dermatitis acneiform	1 (0.4)	0	0	0	2 (0.4)	0	1 (1.1)	0
Interstitial lung disease	1 (0.4)	1 (0.4)	2 (0.5)	3 (0.7)	0	0	0	0
Pneumonia	1 (0.4)	1 (0.4)	1 (0.2)	0	0	0	1 (1.1)	2 (2.1)
Stomatitis	1 (0.4)	0	2 (0.5)	1 (0.2)	5 (1.0)	0	0	0
Vomiting	1 (0.4)	0	4 (0.9)	2 (0.5)	7 (1.5)	0	1 (1.1)	0
Embolism	0	0	0	0	3 (0.6)	0	0	0
Hepatic enzyme increased	0	2 (0.9)	0	1 (0.2)	0	0	0	0
Nausea	0	0	3 (0.7)	4 (0.9)	2 (0.4)	0	1 (1.1)	0
Fatigue	0	0	1 (0.2)	2 (0.5)	0	0	0	0
Lung infection	0	0	0	0	2 (0.4)	0	0	0
Pyrexia	0	0	0	2 (0.5)	1 (0.2)	0	0	0
Rash	0	0	1 (0.2)	2 (0.5)	0	0	0	0
Respiratory failure	0	0	0	0	2 (0.4)	0	0	0

Data source: A7471050 CSR Table 14.3.2.4; SCS Tables 14.3.2.4.3.11.1.D, 14.3.2.4.3.11.1.E, and 14.3.2.4.3.11.1.F.
Abbreviations: CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SAE=serious adverse event; SCS=Summary of Clinical Safety; sCSR=supplemental Clinical Study Report.
a. MedDRA Version 19.1.
b. Any SAE without consideration for the minimum 2-patient frequency cutoff used in this table.

Deaths

Table 65: Summary of deaths (patient status) – ATT population

	Dacomitinib N=227 n (%)	Gefitinib N=224 n (%)
Deaths from all causes	76 (33.5)	91 (40.6)
Cause of death		
Disease under study	68 (30.0)	85 (37.9)
Study treatment toxicity	2 (0.9)	1 (0.4)
Unknown	2 (0.9)	4 (1.8)
Other[a]	4 (1.8)	1 (0.4)
Deaths from all causes prior to or on 28 days after last dose	21 (9.3)	19 (8.5)
Cause of death		
Disease under study	15 (6.6)	16 (7.1)
Study treatment toxicity	2 (0.9)	1 (0.4)
Unknown	0	1 (0.4)
Other[a]	4 (1.8)	1 (0.4)
Deaths from all causes post 28 days after last dose	55 (24.2)	72 (32.1)
Cause of death		
Disease under study	53 (23.3)	69 (30.8)
Study treatment toxicity	0	0
Unknown	2 (0.9)	3 (1.3)
Other	0	0

Source: Table 14.3.2.1.2.
Notes: (1) Data source is from the Notice of Death CRF page.
(2) Patients who died may have more than 1 'Cause of Death' recorded on CRF.
(3) Percentages are based on the total number of patients in the AT Population.
AT=as-treated; CRF=case report form; N=number of patients; n=number of patients meeting prespecified criteria.
a. Other=bronchopulmonary aspergillosis (Patient 03409004), pneumonia (Patient 08204009), diazepam overdose (Patient 08601009), and lung infection (Patient 08615025) in the dacomitinib arm; malnutrition (Patient 08608001) in the gefitinib arm.

Table 66: Grade 5 AEs reported for at least 2 patients in the SAE Pool, by MedDRA PT sorted by descending frequency in the SAE Pool – Pooled Populations – As-Treated patients

	Number (%) of Patients			
MedDRA PT[a]	SAE Pool (N=1975)	Pool B (N=1473)	Pool A (N=394)	First-Line Pool (N=255)
Any Grade 5 AE[b]	311 (15.7)	245 (16.7)	44 (11.2)	24 (9.4)
Disease progression	126 (6.4)	90 (6.1)	10 (2.5)	9 (3.5)
Non-small cell lung cancer	80 (4.1)	78 (5.3)	14 (3.6)	0
Respiratory failure	11 (0.6)	8 (0.5)	2 (0.5)	2 (0.8)
Lung infection	10 (0.5)	10 (0.7)	5 (1.3)	1 (0.4)
Death	8 (0.4)	8 (0.5)	2 (0.5)	1 (0.4)
Pneumonia	7 (0.4)	6 (0.4)	2 (0.5)	2 (0.8)
Lung cancer metastatic	4 (0.2)	2 (0.1)	0	0
Cardiac arrest	3 (0.2)	2 (0.1)	0	0
Dyspnoea	3 (0.2)	2 (0.1)	0	0
Sepsis	3 (0.2)	1 (<0.1)	0	0
Septic shock	3 (0.2)	0	0	0
Acute respiratory failure	2 (0.1)	2 (0.1)	0	0
Cardio-respiratory arrest	2 (0.1)	0	0	0
Haemoptysis	2 (0.1)	2 (0.1)	0	0
Hypovolaemic shock	2 (0.1)	1 (<0.1)	0	0
Lung neoplasm malignant	2 (0.1)	2 (0.1)	0	0
Non-small cell lung cancer metastatic	2 (0.1)	1 (<0.1)	0	0
Pneumonitis	2 (0.1)	2 (0.1)	1 (0.3)	1 (0.4)
Pulmonary embolism	2 (0.1)	1 (<0.1)	0	0
Pulmonary haemorrhage	2 (0.1)	2 (0.1)	0	0

Data source: SCS Tables 14.3.1.2.11.3.S, 14.3.1.2.11.3.B, 14.3.1.2.11.3.A, and 14.3.1.2.9.1.N.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SAE=serious adverse event; SCS=Summary of Clinical Safety.
Notes: 1) Definitions of pools are provided in Section 2.7.4.1.2.1.
2) AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. Any Grade 5 AE without consideration for the minimum 2-patient frequency cutoff used in this table.

Table 67: Grade 5 AEs, by MedDRA PT reported for at least 2 patients in any treatment arm sorted by descending frequency in the dacomitinib arm of Study A7471050 – Phase 3 Studies and Phase 2 Study A7471028 – As-Treated patients

	Number (%) of Patients							
	Phase 3 Studies						Phase 2 Study	
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)		A7471028 (N=187)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)	Dacomitinib (N=93)	Erlotinib (N=94)
Any Grade 5 AE[b]	22 (9.7)	20 (8.9)	85 (19.5)	73 (16.7)	95 (19.9)	48 (20.1)	23 (24.7)	21 (22.3)
Disease progression	8 (3.5)	11 (4.9)	53 (12.2)	50 (11.5)	0	0	14 (15.1)	16 (17.0)
Pneumonia	2 (0.9)	1 (0.4)	2 (0.5)	0	0	0	2 (2.2)	2 (2.1)
Respiratory failure	2 (0.9)	0	0	2 (0.5)	2 (0.4)	1 (0.4)	1 (1.1)	0
Death	1 (0.4)	1 (0.4)	5 (1.1)	1 (0.2)	2 (0.4)	0	0	0
Lung infection	1 (0.4)	0	0	1 (0.2)	9 (1.9)	4 (1.7)	0	0
Acute respiratory failure	0	0	2 (0.5)	0	0	0	0	0
Dyspnoea	0	2 (0.9)	1 (0.2)	0	1 (0.2)	0	0	1 (1.1)
General physical health deterioration	0	1 (0.4)	0	3 (0.7)	0	0	0	0
Lung neoplasm malignant	0	0	1 (0.2)	2 (0.5)	0	0	1 (1.1)	0
Non-small cell lung cancer	0	0	2 (0.5)	1 (0.2)	75 (15.7)	37 (15.5)	0	0
Pulmonary embolism	0	0	0	2 (0.5)	0	0	1 (1.1)	1 (1.1)
Sudden death	0	0	0	0	1 (0.2)	2 (0.8)	0	0

Data source: A7471050 CSR Table 14.3.1.2.9.1; SCS Tables 14.3.1.2.9.1.D, 14.3.1.2.9.1.E, and 14.3.1.2.9.1.F.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety.
Note: AE severity was assessed using CTCAE Version 4.03.
a. MedDRA Version 19.1.
b. Any Grade 5 AE without consideration for the minimum 2-patient frequency cutoff used in this table.

Laboratory findings

Haematology

In Study 1050, anaemia (56.1% in the dacomitinib and 39.2% in the gefitinib arm) and lymphopenia (44.0% and 40.1%) were the more frequently observed abnormal postbaseline haematology laboratory test findings. Most abnormal postbaseline haematology findings were Grade 1-2 in severity in either treatment arm. The most common Grade 3 postbaseline haematology test findings were lymphopenia (6.5% in the dacomitinib arm, and 3.0% in the gefitinib arm) and anaemia (0.9% and 2.7%). Lymphopenia was the only Grade 4 finding reported in the dacomitinib arm (1 [0.5%] patient). No Grade 4 haematology test findings were reported in the gefitinib arm.

In the dacomitinib arm, the most frequently reported shift (frequency ≥1% of patients) from Grade ≤2 at baseline to Grade 3 postbaseline was in lymphopenia (5.3% of patients). In the gefitinib arm, the most frequently reported shifts (frequency ≥1% of patients) from Grade ≤2 at baseline to Grade 3 postbaseline were in lymphopenia and anaemia (2.7% of patients each).

Chemical chemistry

Table 68: Number (%) of patients with clinical chemistry laboratory test increased from baseline and increased from baseline to grade 3 or grade 4 severity postbaseline by maximum postbaseline grade – Study A7471050 – AT population

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Laboratory Parameter[a]	N	Increase from Baseline All Grades	Increase from Baseline to Grades 3 or 4	N	Increase from Baseline All Grades	Increase from Baseline to Grades 3 or 4
Alkaline phosphatase	205	46 (22.4)	1 (0.5)	205	44 (21.5)	4 (2.0)
Aspartate aminotransferase	220	76 (34.5)	1 (0.5)	221	125 (56.6)	17 (7.7)
Alanine aminotransferase	220	87 (39.5)	3 (1.4)	221	139 (62.9)	28 (12.7)
Bilirubin (Total)	220	36 (16.4)	1 (0.5)	221	49 (22.2)	1 (0.5)
Hypercalcemia	208	6 (2.9)	1 (0.5)	205	7 (3.4)	0
Hypocalcemia	208	68 (32.7)	3 (1.4)	205	57 (27.8)	4 (2.0)
Hypermagnesemia	197	10 (5.1)	6 (3.0)	196	19 (9.7)	6 (3.1)
Hypomagnesemia	197	44 (22.3)	1 (0.5)	196	18 (9.2)	0
Hyperkalemia	208	20 (9.6)	0	205	17 (8.3)	1 (0.5)
Hypokalemia	208	61 (29.3)	15 (7.2)	205	36 (17.6)	4 (2.0)
Hyperglycemia	202	72 (35.6)	2 (1.0)	204	78 (38.2)	5 (2.5)
Hypoglycemia	202	18 (8.9)	0	204	17 (8.3)	2 (1.0)
Hypernatremia	207	38 (18.4)	0	205	24 (11.7)	0
Hyponatremia	207	53 (25.6)	6 (2.9)	205	41 (20.0)	3 (1.5)
Creatinine	220	208 (94.5)	0	221	194 (87.8)	1 (0.5)
Hypoalbuminemia	208	92 (44.2)	0	204	69 (33.8)	0

Source: Module 5.3.5.3, ISS, Appendix 1.5, Table 14.3.4.1.5.4.4.C.
Abbreviations: N=number of patients.
a. Based on the number of patients with available baseline and follow-up laboratory data.

Safety in special populations

Intrinsic factors

- Age

Table 69: Overview of Adverse Events, by age group – Pool B and Study A7471050

			Study A7471050 (N=451)			
	Pool B (N=1473)		Dacomitinib (N=227)		Gefitinib (N=224)	
Category	<65 Years	≥65 Years	<65 Years	≥65 Years	<65 Years	≥65 Years
Number of patients[a]	846	627	133	94	140	84
Number of AEs[b]	8170	6313	1720	1233	1257	955
Patients with AEs, n (%)	844 (99.8)	620 (98.9)	133 (100.0)	93 (98.9)	138 (98.6)	82 (97.6)
Patients with SAEs, n (%)	284 (33.6)	239 (38.1)	31 (23.3)	31 (33.0)	25 (17.9)	25 (29.8)
Patients with Grade 3 AEs, n (%)[c]	321 (37.9)	256 (40.8)	64 (48.1)	52 (55.3)	43 (30.7)	24 (28.6)
Patients with Grade 4 AEs, n (%)[c]	29 (3.4)	29 (4.6)	2 (1.5)	3 (3.2)	1 (0.7)	4 (4.8)
Patients with Grade 5 AEs, n (%)	133 (15.7)	113 (18.0)	13 (9.8)	9 (9.6)	10 (7.1)	10 (11.9)
Patients permanently discontinued treatment due to AEs, n (%)	107 (12.6)	128 (20.4)	15 (11.3)	25 (26.6)	15 (10.7)	12 (14.3)
Patients with dose reduced due to AEs, n (%)[d]	158 (26.8)[d]	118 (29.1)[d]	88 (66.2)	62 (66.0)	10 (7.1)	8 (9.5)
Patients temporarily discontinued treatment due to AEs, n (%)	291 (34.4)	262 (41.8)	73 (54.9)	57 (60.6)	36 (25.7)	24 (28.6)

Data source: SCS Tables 14.3.1.2.1.B.2, 14.3.1.2.11.1.B.2, 14.3.1.2.1.C.2, and 14.3.1.2.11.1.C.2

Abbreviations: AEs=adverse events; CRF=Case Report Form; CTCAE=Common Terminology Criteria for Adverse Events ; N=total number of patients; n=number of patients meeting prespecified criteria; SCS=Summary of Clinical Safety.

Notes: 1) Definition of Pool B is provided in Section 2.7.4.1.2.1.

2) AE severity was assessed using CTCAE Version 4.03.

a. Patients are counted once per pool in each row.

b. Number of AEs is a sum of unique AEs calculated for each patient.

c. Data for Grade 3 or Grade 4 AEs are summarized by maximum severity.

d. Information on dose reductions associated with AEs in Study A7471011 is not provided for Pool B, as dose reduction field was not available on the Study A7471011 AE CRF page. Therefore, percentages of patients with dose reduced due to AEs in each age group in Pool B are based on the denominators calculated using the total numbers of treated patients in these age groups minus the numbers of dacomitinib-treated patients in those age groups in Study A7471011.

Table 70: AEs reported for at least 15% of patients in any age group, by MedDRA PT sorted by descending frequency for patients younger than 65 years of age in Pool B and Study A7471050

	Number (%) of Patients					
			Study A7471050 (N=451)			
	Pool B (N=1473)		Dacomitinib (N=227)		Gefitinib (N=224)	
MedDRA PT[a]	<65 Years	≥65 Years	<65 Years	≥65 Years	<65 Years	≥65 Years
Number of patients	846	627	133	94	140	84
Any AE[b]	844 (99.8)	620 (98.9)	133 (100.0)	93 (98.9)	138 (98.6)	82 (97.6)
Diarrhoea	661 (78.1)	518 (82.6)	117 (88.0)	81 (86.2)	71 (50.7)	54 (64.3)
Dermatitis acneiform	410 (48.5)	275 (43.9)	66 (49.6)	45 (47.9)	36 (25.7)	28 (33.3)
Stomatitis	276 (32.6)	222 (35.4)	57 (42.9)	42 (44.7)	24 (17.1)	16 (19.0)
Paronychia	275 (32.5)	196 (31.3)	83 (62.4)	57 (60.6)	21 (15.0)	24 (28.6)
Decreased appetite	248 (29.3)	218 (34.8)	32 (24.1)	38 (40.4)	25 (17.9)	31 (36.9)
Dry skin	234 (27.7)	171 (27.3)	33 (24.8)	30 (31.9)	16 (11.4)	22 (26.2)
Nausea	225 (26.6)	142 (22.6)	27 (20.3)	16 (17.0)	26 (18.6)	23 (27.4)
Fatigue	224 (26.5)	166 (26.5)	12 (9.0)	9 (9.6)	11 (7.9)	8 (9.5)
Vomiting	167 (19.7)	117 (18.7)	14 (10.5)	6 (6.4)	17 (12.1)	12 (14.3)
Dyspnoea	161 (19.0)	133 (21.2)	16 (12.0)	14 (14.9)	16 (11.4)	14 (16.7)
Pruritus	143 (16.9)	100 (15.9)	23 (17.3)	22 (23.4)	21 (15.0)	11 (13.1)
Rash	141 (16.7)	144 (23.0)	15 (11.3)	25 (26.6)	14 (10.0)	10 (11.9)
Weight decreased	135 (16.0)	94 (15.0)	38 (28.6)	20 (21.3)	19 (13.6)	18 (21.4)
Cough	126 (14.9)	111 (17.7)	26 (19.5)	22 (23.4)	27 (19.3)	15 (17.9)
Constipation	99 (11.7)	74 (11.8)	17 (12.8)	13 (13.8)	22 (15.7)	9 (10.7)
Mucosal inflammation	91 (10.8)	63 (10.0)	6 (4.5)	15 (16.0)	4 (2.9)	4 (4.8)
Palmar-plantar erythrodysaesthesia syndrome	86 (10.2)	66 (10.5)	22 (16.5)	11 (11.7)	3 (2.1)	4 (4.8)
Pain in extremity	79 (9.3)	42 (6.7)	20 (15.0)	11 (11.7)	18 (12.9)	8 (9.5)
Back pain	69 (8.2)	54 (8.6)	12 (9.0)	6 (6.4)	23 (16.4)	12 (14.3)
Rash maculo-papular	65 (7.7)	56 (8.9)	19 (14.3)	9 (9.6)	11 (7.9)	16 (19.0)
Conjunctivitis	63 (7.4)	80 (12.8)	23 (17.3)	20 (21.3)	4 (2.9)	5 (6.0)
Alopecia	57 (6.7)	44 (7.0)	30 (22.6)	23 (24.5)	16 (11.4)	12 (14.3)
Asthenia	57 (6.7)	63 (10.0)	11 (8.3)	18 (19.1)	15 (10.7)	13 (15.5)
Upper respiratory tract infection	57 (6.7)	25 (4.0)	23 (17.3)	5 (5.3)	17 (12.1)	11 (13.1)
Insomnia	52 (6.1)	37 (5.9)	13 (9.8)	11 (11.7)	13 (9.3)	20 (23.8)
Alanine aminotransferase increased	50 (5.9)	13 (2.1)	38 (28.6)	6 (6.4)	59 (42.1)	29 (34.5)
Aspartate aminotransferase increased	49 (5.8)	20 (3.2)	35 (26.3)	7 (7.4)	56 (40.0)	25 (29.8)
Chest pain	42 (5.0)	31 (4.9)	14 (10.5)	8 (8.5)	22 (15.7)	10 (11.9)
Mouth ulceration	24 (2.8)	11 (1.8)	20 (15.0)	8 (8.5)	8 (5.7)	5 (6.0)

Data source: SCS Tables 14.3.1.2.11.1.B.2 and 14.3.1.2.11.1.C.2.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety.
Note: Definition of Pool B is provided in Section 2.7.4.1.2.1.
a. MedDRA Version 19.1.
b. Any AE without consideration for the minimum 15% frequency cutoff used in this table..

- Race (non-Asian vs. Asian)
    - *Exposure to Dacomitinib*

Table 71: Exposure to dacomitinib by race subgroup (Non-Asian vs. Asian) in phase 3 study A7471050- As-treated patients

Exposure Category	Dacomitinib (N=227)			Gefitinib (N=224)		
	Non-Asian	Asian	Total	Non-Asian	Asian	Total
Total number of patients (n)	57	170	227	48	176	224
Number of cycles	714	2928	3642	685	2526	3211
Number of cycles per patient	12.5	17.2	16.0	14.3	14.4	14.3
Median (range)	11.0 (1-33)	20.0 (1-41)	17.0 (1-41)	13.0 (1-34)	13.0 (1-38)	13.0 (1-38)
Duration of treatment (weeks)						
Median (range)	44.14 (2.7-131.1)	77.93 (0.3-162.7)	66.57 (0.3-162.7)	51.57 (3.9-133.1)	52.71 (0.3-148.3)	52.14 (0.3-148.3)
Relative dose intensity (%)[a]						
Mean (Std Dev)	74.41 (19.405)	72.86 (22.208)	73.25 (21.508)	96.46 (6.199)	95.88 (10.163)	96.00 (9.445)
Median (range)	69.70 (36.1-100.0)	73.20 (10.0-100.0)	72.50 (10.0-100.0)	98.90 (69.1-100.0)	99.90 (55.3-100.0)	99.80 (55.3-100.0)

Data source: Module 5.3.5.1 A7471050 CSR Tables 14.4.1.1.1.1; 14.4.1.2.1; 14.4.1.4.1; Module 5.3.5.3 NASER Tables 14.4.1.1.1.1.1.5; 14.4.1.2.1.5; 14.4.1.4.1.5; 14.4.1.7.1.
Abbreviations: CSR=Clinical Study Report; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; Std Dev=standard deviation.
Note: 1) Duration of treatment was defined as the time from the first to and including last dosing date of treatment.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. Relative dose for a cycle was defined as actual received total dose in a cycle divided by (45 mg dacomitinib × number days in cycle) or (250 mg gefitinib x number of days in cycle). Therefore, relative dose was identical to relative dose intensity for continuous dosing such as dacomitinib dosing.

    - *Adverse events*

Table 72: Overview of AE, by race subgroup (Non-Asian Versus Asian) in Phase 3 Study A7471050

Category	Dacomitinib (N=227)			Gefitinib (N=224)		
	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Number of AEs[a]	736	2217	2953	450	1762	2212
Patients with AEs, n (%)	57 (100.0)	169 (99.4)	226 (99.6)	48 (100.0)	172 (97.7)	220 (98.2)
Patients with SAEs, n (%)	25 (43.9)	37 (21.8)	62 (27.3)	15 (31.3)	35 (19.9)	50 (22.3)
Patients with Grade 5 AEs, n (%)	9 (15.8)	13 (7.6)	22 (9.7)	6 (12.5)	14 (8.0)	20 (8.9)
Patients permanently discontinued treatment due to AEs, n (%)	12 (21.1)	28 (16.5)	40 (17.6)	5 (10.4)	22 (12.5)	27 (12.1)
Patients with dose reduced due to AEs, n (%)	36 (63.2)	114 (67.1)	150 (66.1)	1 (2.1)	17 (9.7)	18 (8.0)
Patients temporarily discontinued treatment due to AEs, n (%)	40 (70.2)	90 (52.9)	130 (57.3)	14 (29.2)	46 (26.1)	60 (26.8)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.2.1; Module 5.3.5.3 NASER Table 14.3.1.2.1.5.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; SAE=serious adverse event.
Notes: 1) Patients are counted once per treatment arm in each row.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. Number of AEs was a sum of unique AE calculated for each patient.

Table 73: AEs reported for at least 15% of patients in any race subgroup (Non-Asian versus Asian), by MedDRA PT sorted by descending frequency in the total dacomitinib arm of Phase 3 Study A7471050

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
MedDRA PT[a]	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Any AE[b]	57 (100)	169 (99.4)	226 (99.6)	48 (100)	172 (97.7)	220 (98.2)
Diarrhoea	44 (77.2)	154 (90.6)	198 (87.2)	25 (52.1)	100 (56.8)	125 (55.8)
Paronychia	30 (52.6)	110 (64.7)	140 (61.7)	9 (18.8)	36 (20.5)	45 (20.1)
Dermatitis acneiform	15 (26.3)	96 (56.5)	111 (48.9)	7 (14.6)	57 (32.4)	64 (28.6)
Stomatitis	12 (21.1)	87 (51.2)	99 (43.6)	4 (8.3)	36 (20.5)	40 (17.9)
Decreased appetite	13 (22.8)	57 (33.5)	70 (30.8)	8 (16.7)	47 (26.7)	55 (24.6)
Dry skin	21 (36.8)	42 (24.7)	63 (27.8)	5 (10.4)	33 (18.8)	38 (17.0)
Weight decreased	0	58 (34.1)	58 (25.6)	2 (4.2)	35 (19.9)	37 (16.5)
Alopecia	13 (22.8)	40 (23.5)	53 (23.3)	6 (12.5)	22 (12.5)	28 (12.5)
Cough	10 (17.5)	38 (22.4)	48 (21.1)	6 (12.5)	36 (20.5)	42 (18.8)
Pruritus	14 (24.6)	31 (18.2)	45 (19.8)	6 (12.5)	25 (14.2)	31 (13.8)
Alanine aminotransferase increased	3 (5.3)	41 (24.1)	44 (19.4)	7 (14.6)	81 (46.0)	88 (39.3)
Conjunctivitis	14 (24.6)	29 (17.1)	43 (18.9)	3 (6.3)	6 (3.4)	9 (4.0)
Nausea	12 (21.1)	31 (18.2)	43 (18.9)	9 (18.8)	40 (22.7)	49 (21.9)
Aspartate aminotransferase increased	2 (3.5)	40 (23.5)	42 (18.5)	6 (12.5)	75 (42.6)	81 (36.2)
Rash	29 (50.9)	11 (6.5)	40 (17.6)	15 (31.3)	9 (5.1)	24 (10.7)
Palmar-plantar erythrodysaesthesia syndrome	5 (8.8)	28 (16.5)	33 (14.5)	0	7 (4.0)	7 (3.1)
Pain in extremity	4 (7.0)	27 (15.9)	31 (13.7)	4 (8.3)	22 (12.5)	26 (11.6)
Dyspnoea	13 (22.8)	17 (10.0)	30 (13.2)	9 (18.8)	21 (11.9)	30 (13.4)
Asthenia	20 (35.1)	9 (5.3)	29 (12.8)	16 (33.3)	12 (6.8)	28 (12.5)
Mouth ulceration	0	28 (16.5)	28 (12.3)	0	13 (7.4)	13 (5.8)
Upper respiratory tract infection	0	28 (16.5)	28 (12.3)	0	28 (15.9)	28 (12.5)
Insomnia	4 (7.0)	20 (11.8)	24 (10.6)	5 (10.4)	28 (15.9)	33 (14.7)
Chest pain	3 (5.3)	19 (11.2)	22 (9.7)	3 (6.3)	29 (16.5)	32 (14.3)
Mucosal inflammation	20 (35.1)	1 (0.6)	21 (9.3)	6 (12.5)	2 (1.1)	8 (3.6)
Skin fissures	12 (21.1)	9 (5.3)	21 (9.3)	0	6 (3.4)	6 (2.7)
Back pain	4 (7.0)	14 (8.2)	18 (7.9)	10 (20.8)	25 (14.2)	35 (15.6)
Urinary tract infection	9 (15.8)	7 (4.1)	16 (7.0)	2 (4.2)	6 (3.4)	8 (3.6)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.2.9.2; Module 5.3.5.3 NASER Table 14.3.1.2.9.2.5.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PT=preferred term.
Note: 1) Patients are counted only once, at the maximum CTC grade reported, for each preferred term.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. MedDRA Version 19.1.
b. Any AE without consideration for the minimum 15% frequency cutoff used in this table.

Table 74: Grade 3 AEs reported for at least 4% or Grade 4 AEs reported for at least 3 patients in any race subgroup (Non-Asian versus Asian) in Phase 3 Study A7471050

	Number (%) of Patients											
	Dacomitinib (N=227)						Gefitinib (N=224)					
	Non-Asian n (%)		Asian n (%)		Total n (%)		Non-Asian n (%)		Asian n (%)		Total n (%)	
MedDRA PT[a]	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any AE[b]	32 (56.1)	4 (7.0)	84 (49.4)	1 (0.6)	116 (51.1)	5 (2.2)	14 (29.2)	1 (2.1)	53 (30.1)	4 (2.3)	67 (29.9)	5 (2.2)
Dermatitis acneiform	4 (7.0)	0	27 (15.9)	0	31 (13.7)	0	0	0	0	0	0	0
Diarrhoea	7 (12.3)	0	12 (7.1)	0	19 (8.4)	0	0	0	2 (1.1)	0	2 (0.9)	0
Paronychia	2 (3.5)	0	15 (8.8)	0	17 (7.5)	0	0	0	3 (1.7)	0	3 (1.3)	0
Rash	8 (14.0)	0	2 (1.2)	0	10 (4.4)	0	0	0	0	0	0	0
Rash maculo-papular	1 (1.8)	0	9 (5.3)	0	10 (4.4)	0	0	0	1 (0.6)	0	1 (0.4)	0
Hypokalaemia	3 (5.3)	1 (1.8)	6 (3.5)	1 (0.6)	9 (4.0)	2 (0.9)	1 (2.1)	0	3 (1.7)	0	4 (1.8)	0
Rash pustular	1 (1.8)	0	7 (4.1)	0	8 (3.5)	0	0	0	0	0	0	0
Stomatitis	0	0	8 (4.7)	0	8 (3.5)	0	0	0	1 (0.6)	0	1 (0.4)	0
Asthenia	4 (7.0)	0	1 (0.6)	0	5 (2.2)	0	3 (6.3)	0	0	0	3 (1.3)	0
Lymphocyte count decreased	3 (5.3)	0	2 (1.2)	0	5 (2.2)	0	0	0	0	0	0	0
Pleural effusion	3 (5.3)	0	2 (1.2)	0	5 (2.2)	0	1 (2.1)	0	0	0	1 (0.4)	0
Dyspnoea	2 (3.5)	1 (1.8)	2 (1.2)	0	4 (1.8)	1 (0.4)	2 (4.2)	0	2 (1.1)	0	4 (1.8)	0
Dermatitis	3 (5.3)	0	1 (0.6)	0	4 (1.8)	0	1 (2.1)	0	0	0	1 (0.4)	0
Alanine aminotransferase increased	1 (1.8)	0	1 (0.6)	0	2 (0.9)	0	1 (2.1)	0	18 (10.2)	0	19 (8.5)	0
Anaemia	1 (1.8)	0	1 (0.6)	0	2 (0.9)	0	4 (8.3)	0	1 (0.6)	0	5 (2.2)	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	9 (5.1)	0	9 (4.0)	0
Hyponatraemia	1 (1.8)	0	1 (0.6)	0	2 (0.9)	0	3 (6.3)	1 (2.1)	0	0	3 (1.3)	1 (0.4)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.2.9.2; Module 5.3.5.3 NASER Table 14.3.1.2.9.2.5.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PT=preferred term.
Note: 1) TRAE severity was assessed using CTCAE Version 4.03.
2) Patients are counted only once, at the maximum CTC grade reported, for each preferred term.
3) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. MedDRA v19.1.
b. Any Grade 3 AE without consideration for the minimum 4% frequency cutoff or Grade 4 AE without consideration for the minimum 3 patients used in this table.

- *Treatment-Related Adverse Events*

Table 75: Overview of Treatment-Related AEs, by race subgroup in Phase 3 Study A7471050

	Dacomitinib (N=227)			Gefitinib (N=224)		
Category	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Number of TRAEs[a]	525	1523	2048	221	991	1212
Patients with TRAEs, n (%)	52 (91.2)	168 (98.8)	220 (96.9)	46 (95.8)	167 (94.9)	213 (95.1)
Patients with treatment-related SAEs, n (%)	5 (8.8)	16 (9.4)	21 (9.3)	2 (4.2)	8 (4.5)	10 (4.5)
Patients with Grade 5 TRAEs, n (%)	1 (1.8)	1 (0.6)	2 (0.9)	1 (2.1)	1 (0.6)	2 (0.9)
Patients permanently discontinued due to TRAEs, n (%)	4 (7.0)	18 (10.6)	22 (9.7)	2 (4.2)	13 (7.4)	15 (6.7)
Patients with dose reduced due to TRAEs, n (%)	35 (61.4)	112 (65.9)	147 (64.8)	1 (2.1)	17 (9.7)	18 (8.0)
Patients with temporary discontinuation due to TRAEs, n (%)	34 (59.6)	84 (49.4)	118 (52.0)	9 (18.8)	38 (21.6)	47 (21.0)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.3.1; Module 5.3.5.3 NASER Table 14.3.1.3.1.5,
Abbreviations: AE=adverse event; CSR=Clinical Study Report; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; SAE=serious adverse event; TRAE=treatment related adverse event.
Notes: 1) Patients are counted once per treatment arm in each row.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. Number of TRAEs was a sum of unique TRAE calculated for each patient.

Table 76: Treatment-Related AEs reported for at least 10% of patients in any race subgroup in Study A7471050

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
MedDRA PT[a]	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Any TRAE[b]	52 (91.2)	168 (98.8)	220 (96.9)	46 (95.8)	167 (94.9)	213 (95.1)
Diarrhoea	43 (75.4)	150 (88.2)	193 (85.0)	23 (47.9)	92 (52.3)	115 (51.3)
Paronychia	30 (52.6)	110 (64.7)	140 (61.7)	9 (18.8)	36 (20.5)	45 (20.1)
Dermatitis acneiform	15 (26.3)	96 (56.5)	111 (48.9)	7 (14.6)	57 (32.4)	64 (28.6)
Stomatitis	11 (19.3)	82 (48.2)	93 (41.0)	3 (6.3)	31 (17.6)	34 (15.2)
Dry skin	20 (35.1)	42 (24.7)	62 (27.3)	4 (8.3)	32 (18.2)	36 (16.1)
Decreased appetite	11 (19.3)	46 (27.1)	57 (25.1)	4 (8.3)	30 (17.0)	34 (15.2)
Alopecia	13 (22.8)	33 (19.4)	46 (20.3)	5 (10.4)	14 (8.0)	19 (8.5)
Pruritus	14 (24.6)	30 (17.6)	44 (19.4)	5 (10.4)	24 (13.6)	29 (12.9)
Alanine aminotransferase increased	3 (5.3)	39 (22.9)	42 (18.5)	5 (10.4)	76 (43.2)	81 (36.2)
Aspartate aminotransferase increased	2 (3.5)	37 (21.8)	39 (17.2)	5 (10.4)	72 (40.9)	77 (34.4)
Rash	29 (50.9)	10 (5.9)	39 (17.2)	15 (31.3)	8 (4.5)	23 (10.3)
Conjunctivitis	12 (21.1)	26 (15.3)	38 (16.7)	1 (2.1)	5 (2.8)	6 (2.7)
Palmar-plantar erythrodysaesthesia syndrome	5 (8.8)	28 (16.5)	33 (14.5)	0	7 (4.0)	7 (3.1)
Nausea	12 (21.1)	17 (10.0)	29 (12.8)	4 (8.3)	23 (13.1)	27 (12.1)
Mouth ulceration	0	28 (16.5)	28 (12.3)	0	13 (7.4)	13 (5.8)
Rash maculo-papular	3 (5.3)	25 (14.7)	28 (12.3)	2 (4.2)	25 (14.2)	27 (12.1)
Dermatitis	6 (10.5)	18 (10.6)	24 (10.6)	4 (8.3)	4 (2.3)	8 (3.6)
Weight decreased	0	24 (14.1)	24 (10.6)	0	5 (2.8)	5 (2.2)
Acne	7 (12.3)	13 (7.6)	20 (8.8)	2 (4.2)	11 (6.3)	13 (5.8)
Blood bilirubin increased	3 (5.3)	17 (10.0)	20 (8.8)	2 (4.2)	17 (9.7)	19 (8.5)
Mucosal inflammation	19 (33.3)	1 (0.6)	20 (8.8)	6 (12.5)	2 (1.1)	8 (3.6)
Skin fissures	12 (21.1)	8 (4.7)	20 (8.8)	0	6 (3.4)	6 (2.7)
Asthenia	16 (28.1)	1 (0.6)	17 (7.5)	12 (25.0)	3 (1.7)	15 (6.7)
Constipation	3 (5.3)	11 (6.5)	14 (6.2)	5 (10.4)	12 (6.8)	17 (7.6)
Erythema	8 (14.0)	3 (1.8)	11 (4.8)	1 (2.1)	1 (0.6)	2 (0.9)
Folliculitis	6 (10.5)	3 (1.8)	9 (4.0)	1 (2.1)	3 (1.7)	4 (1.8)
Skin toxicity	7 (12.3)	0	7 (3.1)	4 (8.3)	0	4 (1.8)
Onycholysis	6 (10.5)	0	6 (2.6)	4 (8.3)	0	4 (1.8)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.3.9.1; Module 5.3.5.3 NASER Table 14.3.1.3.9.2.5.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; CTC=Common Toxicity Criteria; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PT=preferred term; TRAE=treatment related adverse event.
Note: 1) Patients are counted only once, at the maximum CTC grade reported, for each preferred term.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. MedDRA Version 19.1.
b. Any TRAE without consideration for the minimum 10% frequency cutoff used in this table.

Table 77: Treatment-related Grade 3 (at least 4% of patients) or Grade 4 (at least 2 patients) Aes reported in any race subgroup in Study A7471050

	Number (%) of Patients											
	Dacomitinib (N=227)						Gefitinib (N=224)					
	Non-Asian		Asian		Total		Non-Asian		Asian		Total	
MedDRA PT[a]	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any TRAE[b]	30 (52.6)	2 (3.5)	77 (45.3)	0	107 (47.1)	2 (0.9)	4 (8.3)	0	37 (21.0)	2 (1.1)	41 (18.3)	2 (0.9)
Dermatitis acneiform	4 (7.0)	0	27 (15.9)	0	31 (13.7)	0	0	0	0	0	0	0
Diarrhoea	7 (12.3)	0	11 (6.5)	0	18 (7.9)	0	0	0	1 (0.6)	0	1 (0.4)	0
Paronychia	2 (3.5)	0	15 (8.8)	0	17 (7.5)	0	0	0	3 (1.7)	0	3 (1.3)	0
Rash maculo-papular	1 (1.8)	0	9 (5.3)	0	10 (4.4)	0	0	0	1 (0.6)	0	1 (0.4)	0
Rash	8 (14.0)	0	1 (0.6)	0	9 (4.0)	0	0	0	0	0	0	0
Rash pustular	1 (1.8)	0	7 (4.1)	0	8 (3.5)	0	0	0	0	0	0	0
Stomatitis	0	0	8 (4.7)	0	8 (3.5)	0	0	0	0	0	0	0
Dermatitis	3 (5.3)	0	1 (0.6)	0	4 (1.8)	0	1 (2.1)	0	0	0	1 (0.4)	0
Alanine aminotransferase increased	1 (1.8)	0	1 (0.6)	0	2 (0.9)	0	1 (2.1)	0	17 (9.7)	0	18 (8.0)	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	8 (4.5)	0	8 (3.6)	0

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.3.9.2; Module 5.3.5.3 NASER Table 14.3.1.3.9.2..
Abbreviations: CSR=Clinical Study Report; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PT=preferred term; TRAE=treatment related adverse event.
Notes: 1) TRAE severity was assessed using CTCAE Version 4.03.
2) Grade 5 TRAEs are summarized in Section 3.4.1.2.
3) Patients are counted only once, at the maximum CTC grade reported, for each preferred term.
4) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. MedDRA Version 19.1.
b. Any Grade 3 TRAE without consideration for the minimum 4% frequency cutoff or any Grade 4 TRAE without consideration for the minimum 2-patient frequency cutoff used in this table.

- *Serious Adverse Events:*

Table 78: SAEs reported for at least 2 patients in any race subgroup in the Phase 3 Study A7471050

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
MedDRA PT[a]	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Any SAE[b]	25 (43.9)	37 (21.8)	62 (27.3)	15 (31.3)	35 (19.9)	50 (22.3)
Disease progression	4 (7.0)	4 (2.4)	8 (3.5)	3 (6.3)	8 (4.5)	11 (4.9)
Diarrhoea	1 (1.8)	4 (2.4)	5 (2.2)	0	0	0
Pleural effusion	3 (5.3)	2 (1.2)	5 (2.2)	2 (4.2)	0	2 (0.9)
Pneumonia	2 (3.5)	3 (1.8)	5 (2.2)	0	2 (1.1)	2 (0.9)
Liver injury	0	2 (1.2)	2 (0.9)	0	1 (0.6)	1 (0.4)
Respiratory tract infection	2 (3.5)	0	2 (0.9)	1 (2.1)	0	1 (0.4)
Pneumonitis	1 (1.8)	1 (0.6)	2 (0.9)	0	1 (0.6)	1 (0.4)
Abdominal pain	2 (3.5)	0	2 (0.9)	0	0	0
Urinary tract infection	2 (3.5)	0	2 (0.9)	0	0	0
Decreased appetite	0	2 (1.2)	2 (0.9)	0	0	0
Haemoptysis	1 (1.8)	1 (0.6)	2 (0.9)	0	0	0
Pneumothorax	1 (1.8)	1 (0.6)	2 (0.9)	0	0	0
Respiratory failure	0	2 (1.2)	2 (0.9)	0	0	0
Dyspnoea	0	1 (0.6)	1 (0.4)	0	4 (2.3)	4 (1.8)
Cerebral infarction	0	1 (0.6)	1 (0.4)	0	2 (1.1)	2 (0.9)
Subdural haematoma	0	0	0	1 (2.1)	1 (0.6)	2 (0.9)
Hepatic enzyme increased	0	0	0	0	2 (1.1)	2 (0.9)
Hyponatraemia	0	0	0	2 (4.2)	0	2 (0.9)

Data source: Module 5.3.5.1 A747150 CSR Table 14.3.2.3; Module 5.3.5.3 NASER Table 14.3.2.3.5.
Abbreviations: CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PT=preferred term; SAE=serious adverse event.
Note: 1) Patients are counted only once, at the maximum CTC grade reported, for each preferred term.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. MedDRA Version 19.1.
b. Any SAE without consideration for the minimum frequency cutoff of 2 patients used in this table.

Table 79: Treatment-related SAEs reported in at least 1% of patients in any race subgroup in Study A7471050

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
MedDRA PT[a]	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
Any treatment-related SAE[b]	5 (8.8)	16 (9.4)	21 (9.3)	2 (4.2)	8 (4.5)	10 (4.5)
Diarrhoea	1 (1.8)	4 (2.4)	5 (2.2)	0	0	0
Abdominal pain	2 (3.5)	0	2 (0.9)	0	0	0
Liver injury	0	2 (1.2)	2 (0.9)	0	1 (0.6)	1 (0.4)
Acute kidney injury	1 (1.8)	0	1 (0.4)	0	0	0
Death	0	1 (0.6)	1 (0.4)	1 (2.1)	0	1 (0.4)
Dehydration	1 (1.8)	0	1 (0.4)	0	0	0
Chronic myeloid leukaemia	1 (1.8)	0	1 (0.4)	0	0	0
Drug-induced liver injury	0	1 (0.6)	1 (0.4)	1 (2.1)	0	1 (0.4)
Hepatic enzyme increased	0	0	0	0	2 (1.1)	2 (0.9)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.2.4; Module 5.3.5.3 NASER Table 14.3.2.4.5.
Abbreviations: CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; PT=preferred term; SAE=serious adverse event.
Note: 1) Patients are counted only once, at the maximum CTC grade reported, for each preferred term.
2) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.
a. MedDRA Version 19.1.
b. Any treatment-related SAE without consideration for the minimum frequency cutoff of 1% patients used in this table.

- *Deaths*

In the non-Asian subgroup of the dacomitinib arm, Grade 5 AEs were reported for 9 (15.8%) patients and the most frequently reported Grade 5 AE (frequency ≥3.0% of patients) was Disease progression (4 [7%]). In the non-Asian subgroup of the dacomitinib arm, Grade 5 AEs were reported for 9 (15.8%) patients and the most frequently reported Grade 5 AE was Disease progression (4 [7%]). The frequency of Grade 5 TRAEs was low and comparable between the non-Asian and Asian subgroups.

- *Adverse Events of Special Interest*

Table 80: AEoSIs by race subgroup, by cluster term in the Phase 3 Study A7471050

	Number (%) of Patients					
	Dacomitinib (N=227)			Gefitinib (N=224)		
Cluster Term[a]	Non-Asian n (%)	Asian n (%)	Total n (%)	Non-Asian n (%)	Asian n (%)	Total n (%)
DIARRHOEA AND ASSOCIATED AEs	44 (77.2)	154 (90.6)	198 (87.2)	25 (52.1)	101 (57.4)	126 (56.3)
RASH/DERMATITIS	41 (71.9)	135 (79.4)	176 (77.5)	22 (45.8)	100 (56.8)	122 (54.5)
OTHER SKIN TOXICITY	42 (73.7)	131 (77.1)	173 (76.2)	11 (22.9)	60 (34.1)	71 (31.7)
STOMATITIS	28 (49.1)	129 (75.9)	157 (69.2)	11 (22.9)	63 (35.8)	74 (33.0)
LIVER-RELATED LABORATORY TESTS	5 (8.8)	62 (36.5)	67 (29.5)	9 (18.8)	86 (48.9)	95 (42.4)
ACUTE RENAL FAILURE	4 (7.0)	7 (4.1)	11 (4.8)	2 (4.2)	11 (6.3)	13 (5.8)
SEVERE SKIN TOXICITY	2 (3.5)	6 (3.5)	8 (3.5)	3 (6.3)	5 (2.8)	8 (3.6)
INTERSTITIAL LUNG DISEASE	1 (1.8)	5 (2.9)	6 (2.6)	0	3 (1.7)	3 (1.3)
HEPATOTOXICITY	0	4 (2.4)	4 (1.8)	2 (4.2)	6 (3.4)	8 (3.6)
KERATITIS	NR	4 (2.4)	4 (1.8)	NR	0	0
QT INTERVAL PROLONGATION	2 (3.5)	1 (0.6)	3 (1.3)	0	0	0
LEFT VENTRICULAR DYSFUNCTION	2 (3.5)	0	2 (0.9)	0	1 (0.6)	1 (0.4)
GASTROINTESTINAL PERFORATIONS	1 (1.8)	0	1 (0.4)	0	1 (0.6)	1 (0.4)

Data source: Module 5.3.5.1 A7471050 CSR Table 14.3.1.2.12.3; Module 5.3.5.3 NASER Table 14.3.1.2.9.2.5.
Abbreviations: CSR=Clinical Study Report; N=number of patients; n=number of patients in each category; NASER=Non-Asian Supplemental Evaluation Report; NR=not reported.
Note: 1) Asian was defined as Mainland Chinese, Japanese and Other East Asian. Non-Asian was defined as Black or White patients.

- *Clinical laboratory evaluations*

Results in the non-Asian and Asian subgroups were consistent with the results in the As-Treated population with anemia as the most frequently reported of the most abnormal postbaseline hematology findings in both the dacomitinib and gefitinib arm and most findings Grade 1 or 2 in severity. In the dacomitinib arm of the As-Treated population, the most frequently reported shift (≥1.0% of patients) from Grade ≤2 at baseline to Grade 3 postbaseline was lymphopenia (13.4% in non-Asian and 2.9% in Asian subgroup).

In the dacomitinib arm, lower frequencies of increased creatinine, hyperglycemia, and hypoalbumenia were observed in the non-Asian subgroup compared to the Asian subgroup. In the gefitinib arm, lower frequencies of increased AST and increased total bilirubin were observed in the non-Asian subgroup.

In the dacomitinib arm of the As-Treated population, the most frequently reported shifts from Grade ≤2 at baseline to Grade 3 postbaseline (≥2.0% of patients) were observed for hypokalemia (5.7% of patients), hypermagnesemia (3.1%), and hyponatremia (2.2%). Shifts from Grade ≤2 at baseline to Grade 4 postbaseline were observed for no more than 2 (0.9%) patients in the dacomitinib arm. In the gefitinib arm, the most frequently reported shifts from Grade ≤2 at baseline to Grade 3 postbaseline were in ALT (11.6% of patients), AST (6.7%), hypermagnesemia (2.7%), hyperglycemia (2.2%), and hypokalemia (2.2%). Shifts from Grade ≤2 at baseline to Grade 4 postbaseline were observed for no more than 2 (0.9%) patients in the gefitinib arm. The proportions of patients with shifts in ALT and AST from Grade ≤2 at baseline to Grade 3 postbaseline were higher in the gefitinib arm (10.3% and 6.7% of patients, respectively) than in the dacomitinib arm (1.3% and 0.4%, respectively). Results were generally comparable between the non-Asian and Asian subgroups with regards to shifts from Grade ≤2 at baseline to Grade 3 postbaseline in either treatment arm.

- Sex

Table 81: Overview of AEs, by Sex – Pool B and Study 1050

	Pool B (N=1473)		Study A7471050 (N=451)			
			Dacomitinib (N=227)		Gefitinib (N=224)	
Category	Women	Men	Women	Men	Women	Men
Number of patients[a]	707	766	146	81	124	100
Number of AEs[b]	7898	6585	1985	968	1249	963
Patients with AEs, n (%)	705 (99.7)	759 (99.1)	145 (99.3)	81 (100.0)	122 (98.4)	98 (98.0)
Patients with SAEs, n (%)	224 (31.7)	299 (39.0)	38 (26.0)	24 (29.6)	24 (19.4)	26 (26.0)
Patients with Grade 3 AEs, n (%)[c]	321 (45.4)	256 (33.4)	84 (57.5)	32 (39.5)	34 (27.4)	33 (33.0)
Patients with Grade 4 AEs, n (%)[c]	29 (4.1)	29 (3.8)	3 (2.1)	2 (2.5)	2 (1.6)	3 (3.0)
Patients with Grade 5 AEs, n (%)	91 (12.9)	155 (20.2)	12 (8.2)	10 (12.3)	12 (9.7)	8 (8.0)
Patients permanently discontinued treatment due to AEs, n (%)	114 (16.1)	121 (15.8)	29 (19.9)	11 (13.6)	14 (11.3)	13 (13.0)
Patients with dose reduced due to AEs, n (%)	183 (38.7)[d]	93 (17.8)[d]	110 (75.3)	40 (49.4)	10 (8.1)	8 (8.0)
Patients temporarily discontinued treatment due to AEs, n (%)	285 (40.3)	268 (35.0)	88 (60.3)	42 (51.9)	33 (26.6)	27 (27.0)

Data source: SCS Tables 14.3.1.2.1.B.1, 14.3.1.2.11.1.B.1, 14.3.1.2.1.C.1, and 14.3.1.2.11.1.C.1.
Abbreviations: AEs=adverse events; CRF=Case Report Form; CTCAE=Common Terminology Criteria for Adverse Events ; N=total number of patients; n=number of patients meeting prespecified criteria; SCS=Summary of Clinical Safety.
Notes: 1) Definition of Pool B is provided in Section 2.7.4.1.2.1.
2) AE severity was assessed using CTCAE Version 4.03.
a. Patients are counted once per pool in each row.
b. Number of AEs is a sum of unique AEs calculated for each patient.
c. Data for Grade 3 or Grade 4 AEs are summarized by maximum severity.
d. Information on dose reductions associated with AEs in Study A7471011 is not provided for Pool B, as dose reduction field was not available on the Study A7471011 AE CRF page. Therefore, percentages of patients with dose reduced due to AEs in each sex group in Pool B are based on the denominators calculated using the total numbers of treated patients in these sex groups minus the numbers of dacomitinib-treated patients in those sex groups in Study A7471011.

Safety related to drug-drug interactions and other interactions

Based on the analyses in Study A7471050, extensive use of PPIs by Asian, non-Asian patients and Total Arm Patients did not appear to demonstrate relevance to clinical safety or efficacy of dacomitinib in Asian, non-Asian or Total Arm Patients in Study A7471050. In the EGFR-activating mutation subset of Study A7471009 there were no patients with extensive PPI use, therefore an analysis of safety and efficacy of PPI use in this subpopulation was not performed. The current recommendation on the PPI use was based on the pharmacokinetic results from a formal drug-drug interaction study with a PPI (rabeprazole), where rabeprazole (40 mg for 7 days) decreased dacomitinib exposure (AUC 0-96h) by 39%

This decrease in dacomitinib exposure may reduce the clinical efficacy. Therefore, due to the small sample size of the subgroups and the confounding nature of the post-hoc analyses, these results are difficult to interpret and not considered sufficiently reliable to support a change in the currently proposed dose recommendation with PPI.

Discontinuation due to adverse events

Permanent treatment discontinuations associated with AEs

Table 82: AEs associated with permanent treatment discontinuation reported for at least 2 patients in any treatment arm, by MedDRA PT, Phase 3 studies – As-Treated patients

	Number (%) of Patients					
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)
Any AE[b]	40 (17.6)	27 (12.1)	87 (20.0)	80 (18.3)	53 (11.1)	24 (10.0)
Disease progression	6 (2.6)	1 (0.4)	13 (3.0)	20 (4.6)	0	0
Pneumonia	5 (2.2)	1 (0.4)	6 (1.4)	2 (0.5)	0	0
Dermatitis acneiform	3 (1.3)	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Diarrhoea	2 (0.9)	0	4 (0.9)	1 (0.2)	3 (0.6)	0
Interstitial lung disease	2 (0.9)	1 (0.4)	2 (0.5)	3 (0.7)	0	0
Pneumonitis	2 (0.9)	2 (0.9)	1 (0.2)	0	1 (0.2)	0
Rash maculo-papular	2 (0.9)	0	0	0	0	0
Stomatitis	2 (0.9)	0	3 (0.7)	0	2 (0.4)	0
Death	1 (0.4)	1 (0.4)	4 (0.9)	1 (0.2)	1 (0.2)	0
Lung infection	1 (0.4)	0	0	0	9 (1.9)	1 (0.4)
Rash	1 (0.4)	0	4 (0.9)	3 (0.7)	0	0
Respiratory failure	1 (0.4)	0	0	4 (0.9)	2 (0.4)	0
Acute kidney injury	0	0	2 (0.5)	0	3 (0.6)	0
Acute respiratory failure	0	0	2 (0.5)	0	0	0
Alanine aminotransferase increased	0	4 (1.8)	0	1 (0.2)	0	0
Anaemia	0	0	0	2 (0.5)	0	0
Aspartate aminotransferase increased	0	2 (0.9)	0	0	0	0
Asthenia	0	1 (0.4)	5 (1.1)	1 (0.2)	0	0
Atrial fibrillation	0	0	0	2 (0.5)	0	0
Cerebrovascular accident	0	0	0	0	0	2 (0.8)
Dehydration	0	0	1 (0.2)	0	2 (0.4)	0
Depressed level of consciousness	0	0	0	0	2 (0.4)	0
Dyspnoea	0	2 (0.9)	3 (0.7)	0	2 (0.4)	2 (0.8)
Failure to thrive	0	0	2 (0.5)	0	0	0
Fatigue	0	0	1 (0.2)	2 (0.5)	0	1 (0.4)
General physical health deterioration	0	1 (0.4)	2 (0.5)	6 (1.4)	0	0
Hepatic enzyme increased	0	2 (0.9)	0	0	0	0
Hip fracture	0	0	0	0	2 (0.4)	0
Hypoxia	0	0	0	0	2 (0.4)	0
Non-small cell lung cancer	0	0	0	1 (0.2)	23 (4.8)	14 (5.9)
Sepsis	0	0	1 (0.2)	2 (0.5)	1 (0.2)	0
Vomiting	0	2 (0.9)	1 (0.2)	0	1 (0.2)	1 (0.4)
Weight decreased	0	0	2 (0.5)	0	0	1 (0.4)

Data source: A7471050 CSR Table 14.3.1.1.1.1; A7471009 SCS Tables 14.3.1.1.2.1.D and 14.3.1.1.2.1.E.
Abbreviations: AE=adverse event; CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term.
a. MedDRA Version 19.1.
b. Any AE without consideration for the minimum 2-patient frequency cutoff used in this table.

Table 83: Treatment related AEs associated with permanent treatment discontinuation reported for at least 2 patients in any treatment arm, by MedDRA PT, Phase 3 studies – As-Treated patients

	Number (%) of Patients					
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)
Any TRAE[b]	22 (9.7)	15 (6.7)	34 (7.8)	20 (4.6)	13 (2.7)	0
Dermatitis acneiform	3 (1.3)	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Diarrhoea	2 (0.9)	0	4 (0.9)	1 (0.2)	3 (0.6)	0
Interstitial lung disease	2 (0.9)	1 (0.4)	2 (0.5)	3 (0.7)	0	0
Pneumonia	2 (0.9)	1 (0.4)	2 (0.5)	0	0	0
Rash maculo-papular	2 (0.9)	0	0	0	0	0
Stomatitis	2 (0.9)	0	3 (0.7)	0	2 (0.4)	0
Pneumonitis	1 (0.4)	2 (0.9)	1 (0.2)	0	1 (0.2)	0
Rash	1 (0.4)	0	4 (0.9)	3 (0.7)	0	0
Acute kidney injury	0	0	2 (0.5)	0	3 (0.6)	0
Alanine aminotransferase increased	0	4 (1.8)	0	1 (0.2)	0	0
Aspartate aminotransferase increased	0	2 (0.9)	0	0	0	0
Asthenia	0	0	5 (1.1)	1 (0.2)	0	0
Atrial fibrillation	0	0	0	2 (0.5)	0	0
Fatigue	0	0	0	2 (0.5)	0	0
Hepatic enzyme increased	0	2 (0.9)	0	0	0	0

Data source: A7471050 CSR Table 14.3.1.1.1.1.2; A7471009 SCS Tables 14.3.1.1.3.1.D and 14.3.1.1.3.1.E.
Abbreviations: CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; TRAE=treatment-related adverse event.
a. MedDRA Version 19.1.
b. Any TRAE without consideration for the minimum 2-patient frequency cutoff used in this table.

Treatment modifications associated with AEs

Dose reductions owing to AEs were reported for 26.8%, 55.9%, and 62.4% of patients in Pool B, Pool A, and the First-Line Pool, respectively. The most frequently reported AEs associated with a dose reduction (frequency ≥2% of patients) were Dermatitis acneiform (6.1%, 15.8%, and 18.4%, respectively), Paronychia (5.5%, 12.9%, and 15.3%, respectively), and Diarrhoea (1.9%, 7.7%, and 7.5%, respectively). Dose reductions were reported more frequently in the dacomitinib arm of Study 1050 than in the gefitinib arm, and the pattern of AEs reported was similar than that of the pooled populations.

Temporary treatment discontinuations were reported in the pooled populations for 29.9%, 42.6%, and 53.3% of patients in Pool B, Pool A, and the First-Line Pool, respectively. The most frequently reported AEs associated with temporary treatment discontinuation (frequency ≥3% of patients) were Diarrhoea (11.2%, 9.9%, and 9.8%, respectively), Dermatitis acneiform (5.0%, 9.0%, and 13.1%, respectively), and Paronychia (3.7%, 8.9%, and 11.8%, respectively). A summary of AEs associated with temporary treatment discontinuation reported in the Phase 3 Studies is provided below.

Table 84: AEs associated with dose reduction reported for at least 2 patients in any treatment arm, by MedDRA PT in the dacomitinib arm of Study A7471050 - Phase 3 Studies – As-Treated Patients

	Number (%) of Patients			
	A7471050 (N=451)		A7471009 (N=872)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)
Any AE[b]	150 (66.1)	18 (8.0)	41 (9.4)	21 (4.8)
Dermatitis acneiform	46 (20.3)	3 (1.3)	2 (0.5)	2 (0.5)
Paronychia	38 (16.7)	2 (0.9)	7 (1.6)	0
Diarrhoea	19 (8.4)	3 (1.3)	12 (2.8)	2 (0.5)
Rash maculo-papular	11 (4.8)	0	2 (0.5)	0
Rash	10 (4.4)	0	12 (2.8)	6 (1.4)
Rash pustular	9 (4.0)	0	0	1 (0.2)
Dermatitis	7 (3.1)	0	0	0
Dry skin	7 (3.1)	0	2 (0.5)	0
Stomatitis	6 (2.6)	0	3 (0.7)	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	5 (2.2)	0	0	0
Acne	4 (1.8)	0	2 (0.5)	1 (0.2)
Asthenia	3 (1.3)	0	5 (1.1)	0
Erythema	3 (1.3)	0	0	0
Pruritus	3 (1.3)	1 (0.4)	0	1 (0.2)
Conjunctivitis	2 (0.9)	0	0	0
Decreased appetite	2 (0.9)	0	2 (0.5)	1 (0.2)
Drug eruption	2 (0.9)	0	0	0
Mouth ulceration	2 (0.9)	0	0	0
Nausea	2 (0.9)	0	0	2 (0.5)
Rash papular	2 (0.9)	0	0	0
Skin fissures	2 (0.9)	0	0	0
Skin toxicity	2 (0.9)	0	0	1 (0.2)
Alanine aminotransferase increased	0	6 (2.7)	0	0
Aspartate aminotransferase increased	0	5 (2.2)	0	0
Hepatic function abnormal	0	3 (1.3)	0	0
Gamma-glutamyltransferase increased	0	2 (0.9)	0	0

Data source: SCS Tables 14.3.1.2.9.6.1.C and 14.3.1.2.9.6.1.D.
Abbreviations: AE=adverse event CRF=Case report Form; CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety.
Note: Information on dose reductions associated with AEs in Study A7471011 is not provided, as dose reduction field was not available on the AE CRF page.
a. MedDRA Version 19.1.
b. Any AE without consideration for the minimum 2-patient frequency cutoff used in this table.

Table 85: AEs associated with temporary treatment discontinuation for at least 1% of patients in any treatment arm, by MedDRA PT, in Study A7471050 - Phase 3 Studies – As-Treated Patients

	Number (%) of Patients					
	A7471050 (N=451)		A7471009 (N=872)		A7471011 (N=716)	
MedDRA PT[a]	Dacomitinib (N=227)	Gefitinib (N=224)	Dacomitinib (N=436)	Erlotinib (N=436)	Dacomitinib (N=477)	Placebo (N=239)
Any AE[b]	130 (57.3)	60 (26.8)	213 (48.9)	145 (33.3)	65 (13.6)	22 (9.2)
Dermatitis acneiform	32 (14.1)	4 (1.8)	12 (2.8)	10 (2.3)	2 (0.4)	0
Paronychia	28 (12.3)	2 (0.9)	16 (3.7)	3 (0.7)	0	0
Diarrhoea	22 (9.7)	1 (0.4)	87 (20.0)	21 (4.8)	11 (2.3)	1 (0.4)
Rash	11 (4.8)	1 (0.4)	34 (7.8)	22 (5.0)	0	0
Stomatitis	10 (4.4)	0	15 (3.4)	2 (0.5)	3 (0.6)	0
Rash maculo-papular	9 (4.0)	2 (0.9)	5 (1.1)	3 (0.7)	0	0
Decreased appetite	6 (2.6)	0	12 (2.8)	13 (3.0)	0	0
Dermatitis	6 (2.6)	1 (0.4)	0	1 (0.2)	0	0
Rash pustular	6 (2.6)	0	4 (0.9)	1 (0.2)	0	0
Acne	5 (2.2)	0	4 (0.9)	1 (0.2)	0	0
Asthenia	5 (2.2)	2 (0.9)	9 (2.1)	9 (2.1)	0	0
Dry skin	5 (2.2)	0	7 (1.6)	0	0	0
Mucosal inflammation	5 (2.2)	0	7 (1.6)	0	0	0
Pruritus	5 (2.2)	2 (0.9)	6 (1.4)	2 (0.5)	0	0
Vomiting	5 (2.2)	1 (0.4)	11 (2.5)	10 (2.3)	4 (0.8)	1 (0.4)
Abdominal pain	4 (1.8)	0	2 (0.5)	1 (0.2)	1 (0.2)	1 (0.4)
Bronchitis	3 (1.3)	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Conjunctivitis	3 (1.3)	0	3 (0.7)	1 (0.2)	0	0
Hypokalaemia	3 (1.3)	0	3 (0.7)	1 (0.2)	0	0
Lung infection	3 (1.3)	0	0	1 (0.2)	9 (1.9)	6 (2.5)
Nausea	3 (1.3)	0	11 (2.5)	8 (1.8)	1 (0.2)	0
Alanine aminotransferase increased	2 (0.9)	19 (8.5)	0	5 (1.1)	0	0
Pneumonia	2 (0.9)	2 (0.9)	8 (1.8)	6 (1.4)	0	0
Aspartate aminotransferase increased	1 (0.4)	14 (6.3)	0	4 (0.9)	0	0
Dehydration	1 (0.4)	0	10 (2.3)	3 (0.7)	10 (2.1)	0
Liver injury	1 (0.4)	3 (1.3)	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0.4)	0	6 (1.4)	0	0	0
Pyrexia	1 (0.4)	1 (0.4)	2 (0.5)	5 (1.1)	2 (0.4)	0
Dyspnoea	2 (0.9)	1 (0.4)	3 (0.7)	2 (0.5)	12 (2.5)	8 (3.3)
Fatigue	0	0	11 (2.5)	11 (2.5)	2 (0.4)	0
General physical health deterioration	0	0	3 (0.7)	5 (1.1)	0	0
Hepatic function abnormal	0	5 (2.2)	0	2 (0.5)	0	0
Pulmonary haemorrhage	0	0	0	0	3 (0.6)	3 (1.3)

Data source: SCS Tables 14.3.1.2.9.5.1.C, 14.3.1.2.9.5.1.D, and 14.3.1.2.9.4.1.E.
Abbreviations: AE=adverse event CSR=Clinical Study Report; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; PT=Preferred Term; SCS=Summary of Clinical Safety.
a. MedDRA Version 19.1.
b. Any AE without consideration for the minimum 1% frequency cutoff used in this table.

2.6.1. Discussion on clinical safety

The clinical safety for dacomitinib has been evaluated in a clinical program including 26 clinical studies. Safety data have been pooled across studies to obtain a broader perspective of the safety profile. This assessment focused on Phase 3 Pivotal study A7471050 (Study 1050) and Pool B. Pool B represents 1473 previously treated or first-line patients with NSCLC who received single-agent dacomitinib at a starting dose of 45 mg QD independent of the presence or absence of EGFR-activating mutations.

Dacomitinib starting dose was 45 mg once a day, although dose modifications (dose reductions and/or dose interruptions) were allowed to manage adverse events.

The median exposure to dacomitinib in the pivotal study A1050 was 66.7 weeks (range: 0.3-162.7), which was longer than the median exposure to gefitinib (52.1 weeks [range: 0.3-148.3]). Median exposure to dacomitinib is considered acceptable. Nevertheless, median relative dose intensity (RDI) was 72.5% and only in 67 (29.5%) patients RDI was > 90-100%. This is in line with the high rates of dose modifications reported in patients treated with dacomitinib. In the dacomitinib arm of study A1050, 66.1% of patients reported at least one dose reduction and 78.0% required temporary treatment discontinuation, compared to 8% and 53.6%, respectively, in the gefitinib arm. The most common AEs leading to dose reductions or treatment interruptions in patients treated with dacomitinib were dermatitis acneiform, paronychia and diarrhoea. Additionally, permanent treatment discontinuations associated with AEs were reported for 17.6% of patients in the dacomitinib arm and 12.1% of patients in the gefitinib arm. The most frequently reported AEs associated with permanent treatment

discontinuation in the dacomitinib arm other than disease progression (2.6%), were Pneumonia (2.2%) and Dermatitis acneiform (1.3%).

In Pool B, median treatment duration was 12.0 weeks (RDI: 97.5 %). In the Asian subgroup, longer median treatment duration was reported compared to the non-Asian subgroup (77.9 weeks vs. 52.7 weeks).

Overall, the clinical safety results for patients treated with dacomitinib in Study 1050 were consistent with those observed in Pool B.

The most common (> 20%) adverse reactions in patients receiving dacomitinib were diarrhoea (88.6%), rash (79.2%), stomatitis (71.8%), nail disorder (65.5%), dry skin (33.3%), decreased appetite (31.8%), conjunctivitis (24.7%), weight decreased (24.3%), alopecia (23.1%), pruritus (22.4%), transaminases increased (22.0%), and nausea (20.4%).

Serious adverse reactions were reported in 6.7% of patients treated with dacomitinib. The most frequently (≥ 1%) reported serious adverse reactions in patients receiving dacomitinib were diarrhoea (2.0%), interstitial lung disease (1.2%), rash (1.2%), and decreased appetite (1.2%).

Adverse reactions leading to dose reductions were reported in 52.2% of patients treated with dacomitinib. The most frequently reported (> 5%) reasons for dose reductions due to any adverse reactions in patients receiving dacomitinib were rash (32.2%), nail disorder (16.5%), and diarrhoea (7.5%).

Adverse reactions leading to permanent discontinuation were reported in 6.7% of patients treated with dacomitinib. The most common (> 0.5%) reasons for permanent discontinuations associated with adverse reactions in patients receiving dacomitinib were rash (2.4%), interstitial lung disease (2.0%), and diarrhoea (0.8%).

Diarrhoea, including severe diarrhoea, has been very commonly reported during treatment with dacomitinib. Diarrhoea may result in dehydration with or without renal impairment, which could be fatal if not adequately treated.

Proactive management of diarrhoea should start at the first sign of diarrhoea especially within the first 2 weeks of starting dacomitinib, including adequate hydration combined with anti-diarrhoeal medicinal products and continued until loose bowel movements cease for 12 hours. Anti-diarrhoeal medicinal products (e.g., loperamide) should be used and, if necessary, escalated to the highest recommended approved dose. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib. Patients should maintain adequate oral hydration and patients who become dehydrated may require administration of intravenous fluids and electrolytes (see sections 4.2, 4.4 and 4.8 of the SmPC).

Rash, erythematous and exfoliative skin conditions have been reported in patients treated with Vizimpro. For prevention of dry skin, initiate treatment with moisturizers, and upon development of rash, initiate treatment with topical antibiotics, emollients, and topical steroids. Start oral antibiotics and topical steroids in patients who develop exfoliative skin conditions. Consider adding broad spectrum oral or intravenous antibiotics if any of these conditions worsen to greater than or equal to Grade 2 severity. Rash, erythematous and exfoliative skin conditions may occur or worsen in areas exposed to the sun. Advise patients to use protective clothing and sunscreen before exposure to the sun. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib (see sections 4.2, 4.4 and 4.8 of the SmPC).

Overall, the incidence of acute renal failure cluster was low in patient treated with dacomitinib across trials. In the study A1050 it was reported in 11/227 patients (4.8%). The majority of events were grade 1 or grade 2.

Grade 3 events were reported in 1 patient (anuria). Additionally, one patient reported an AE grade 4 of acute kidney injury, which was considered secondary to grade 5 AE of diarrhoea.

In the pooled population 1 patient reported grade 5 renal failure which was not considered by the investigator related to study drug.

Interstitial lung disease(ILD)/pneumonitis, which could be fatal, has been reported in patients receiving dacomitinib. Patients with a history of ILD have not been studied.

Careful assessment of all patients with an acute onset or unexplained worsening of pulmonary symptoms (e.g., dyspnoea, cough, fever) should be performed to exclude ILD/pneumonitis. Treatment with dacomitinib should be withheld pending investigation of these symptoms. If ILD/pneumonitis is confirmed, dacomitinib should be permanently discontinued and appropriate treatment instituted as necessary (see sections 4.2, 4.4 and 4.8).

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) have been reported during treatment with dacomitinib. Among NSCLC patients treated with dacomitinib 45 mg daily, there have been isolated reports of hepatotoxicity in 4 (1.6%) patients. Across the dacomitinib program, hepatic failure led to a fatal outcome in 1 patient. Therefore, periodic liver function testing is recommended. In patients who develop severe elevations in transaminases while taking dacomitinib, treatment should be interrupted (see sections 4.2, 4.4 and 4.8 of the SmPC and RMP).

Prevalence of AEoSIs reported for at least 10% of patients up to Cycle 39 in Pool B was summarized by cycle interval. The frequencies of these AEoSIs were highest during Cycles 1 to 6 and then decreased gradually over Cycles 7 to 39.

Overall, the proportion of deaths in study A1050 was lower in the dacomitinib arm than in the gefitinib arm (76 [33.5%] vs. 91 [40.6%], respectively). The majority of deaths were related to disease under study in both treatment arms (68 [30.0%] dacomitinib vs. 85 [37.9%] gefitinib). In the dacomitinib arm 2 (0.9%) deaths were related to study treatment toxicity (1 diarrhoea and 1 death of unknown cause in a patient who had reported an AE of grade 3 of drug-liver injury). Both deaths occurred prior to or on 28 days after last dose. Additionally, there were 4 deaths due to other reasons (bronchopulmonary aspergillosis, pneumonia, diazepam overdose, and lung infection) and 2 deaths reported as "unknown".

Administration of EGFR TKIs have been shown to increase the risk of all-grade infections (Wang et al., 2017). However, no association between administration of EGFR TKI and high grade (severe/life threatening) infections was made.

SAEs were more frequent in patients treated with dacomitinib compared to gefitinib (27.3% vs. 22.3%) and treatment-related SAEs were twice as common in the dacomitinib arm of Study 1050 than in the gefitinib arm (21 [9.3%] vs. 10 [4.5%]). The most frequent treatment-related SAE reported in the dacomitinib arm were diarrhoea, (5 [2.2%]), abdominal pain and liver injury (2 [0.9%], each).

Other common treatment-related SAEs (≥ 1%) reported in dacomitinib clinical trials were dehydration and vomiting.

According to safety data on 157 patients ≥75 years from the NSCLC Pool B, tolerability of dacomitinib appears to be worse in this population compared to patients <75 years, according to the higher rates of SAEs, grade 3 AEs and discontinuations (permanent and temporary) reported in this population of very elderly patients.

Regarding dacomitinib safety profile by race (Non-Asian vs. Asian), overall incidence of AEs was similar between groups, however SAEs, grade 3 and grade 5 AEs as well as permanent and temporary treatment discontinuations were more frequent in Non-Asian patients. This difference between groups was less evident in

the gefitinib arm of the study. No major differences were observed between Non-Asian and Asian patients in the overall incidence of TRAEs, serious TRAEs and treatment discontinuations and modifications. However, treatment-related grade 3 AEs were more frequent in Non-Asian patients treated with dacomitinib. These differences may be explained by a more elderly non-Asian population.

Grade 3 AEs and dose reductions were reported more frequently in women. More women than men were permanently discontinued from treatment due to AEs in the dacomitinib arm while in the gefitinib arm the numbers were similar.

Based on the analyses in Study A7471050, concomitant PPI use by Asian, non-Asian patients and all patients did not show clinically relevant effect on dacomitinib in these subgroups of patients. However, due to the small sample size of the subgroups and the confounding nature of the post-hoc analyses, these results are difficult to interpret and not considered sufficiently reliable. Based on the pharmacokinetic results from a formal drug-drug interaction study with rabeprazole, PPIs should be avoided while receiving treatment with dacomitinib (see section 4.5 of the SmPC).
Anaemia and lymphopenia were the most frequently reported abnormal postbaseline haematology findings in patients treated with dacomitinib. The majority were grade 1 or grade 2. In the dacomitinib arm, the most frequently reported shift (≥1.0% of patients) from Grade ≤ 2 at baseline to Grade 3 postbaseline was also lymphopenia.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Vizimpro. Women of childbearing potential who are receiving this medicinal product should use adequate contraceptive methods during therapy and for at least 17 days (5 half-lives) after completing therapy. There are no data on the use of dacomitinib in pregnant women. Based on its mechanism of action, dacomitinib may cause foetal harm when administered to a pregnant woman. Dacomitinib should not be used during pregnancy. Female patients taking dacomitinib during pregnancy or who become pregnant while taking dacomitinib should be apprised of the potential hazard to the foetus (see section 4.6 of the SmPC).

It is not known whether dacomitinib and its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk, and because of the potential for serious adverse reactions in breast-fed infants from exposure to dacomitinib, mothers should be advised against breast-feeding while receiving this medicinal product.

Dacomitinib has minor influence on the ability to drive and use machines. Patients experiencing fatigue or ocular adverse reactions while taking dacomitinib should exercise caution when driving or operating machinery.

The adverse reactions observed at doses greater than 45 mg once daily were primarily gastrointestinal, dermatological, and constitutional (e.g., fatigue, malaise, and weight loss).

There is no known antidote for dacomitinib. The treatment of dacomitinib overdose should consist of symptomatic treatment and general supportive measures.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of dacomitinib in the proposed indication is in line with the expected safety profile for a tyrosine kinase inhibitor, and generally consistent with that of the irreversible EGFR inhibitor afatinib.

The most commonly reported adverse events related to dacomitinib were gastrointestinal (diarrhoea and stomatitis), skin related (dermatitis acneiform, dry skin rash, pruritus), nail-related (paronychia), and decreased appetite.

Other adverse events of special interest reported in clinical trials were acute renal failure, interstitial lung disease, keratitis, hepatotoxicity, QT prolongation and left ventricular dysfunction. Reproductive and developmental toxicity has been identified as a potential risk in non-clinical trials.

The toxicity profile of dacomitinib overall seems worse than that of gefitinib, according to the higher rates of treatment related AEs, grade 3 TRAEs, treatment related SAEs and discontinuations.

2.7. Risk Management Plan

Safety concerns

Important Identified Risks	Interstitial lung disease Diarrhoea
Important Potential Risks	Hepatotoxicity Reproductive and developmental toxicity
Missing Information	Patients with severe renal impairment Patients with severe hepatic impairment

Pharmacovigilance plan

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 **– Required additional pharmacovigilance activities**				
A7571058 Phase 1, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Plasma PK and Safety of Dacomitinib in Participants with Severely Impaired Hepatic Function relative to Participants with Normal Hepatic Function.	To evaluate the effect of severe hepatic impairment on the single-dose plasma PK of dacomitinib when compared to participants with normal hepatic function	Patients with severe hepatic impairment	Final report submission	31 March 2022

Risk minimisation measures

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
Interstitial Lung Disease	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Diarrhoea	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Important Potential Risks		
Hepatotoxicity	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 (transaminases increased) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Reproductive and developmental toxicity	Routine risk minimisation measures: SmPC Sections 4.6, 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Safety in Patients with Severe Renal Impairment	Routine risk minimisation measures: SmPC sections 4.2, 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in Patients with Severe Hepatic Impairment	Routine risk minimisation measures: SmPC sections 4.2, 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Study A7471058

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant has requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of dacomitinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers dacomitinib to be a new active substance as it is not a

constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vizimpro (dacomitinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Dacomitinib is a pan-HER (EGFR/HER1, HER2/erythroblastosis oncogene B [ERBB]2, and HER4/ERBB4) inhibitor, with clinical activity against mutated EGFR with del exon 19 or L858R.

The claimed indication is for first-line treatment of patients with locally advanced or metastatic NSCLC with epidermal growth factor receptor (EGFR)-activating mutations.

3.1.1. Disease or condition

Lung cancer is the leading cause of cancer-related death in men and the leading cause of cancer related death in women in developed countries, and it is the second leading cause of cancer-related death in less developed countries. Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancers, and the majority of patients present with locally advanced or metastatic disease.

The developments in molecular testing techniques and targeted therapies have changed the diagnosis and treatment paradigms for patients with NSCLC. Research by the Lung Cancer Mutation Consortium has demonstrated that overall survival (OS) is longer for patients who have NSCLC with oncogenic driver mutations who were treated with molecularly targeted therapies in their treatment paradigm. The discovery of mutations in the adenosine triphosphate (ATP) cleft within the epidermal growth factor receptor (EGFR) tyrosine kinase domain has better defined which patients would derive clinical benefit from the targeted treatment of these driver mutations. It also has furthered understanding of the development of resistance to treatment.

3.1.2. Available therapies and unmet medical need

EGFR-activating mutations occur in about 10% to 20% of White patients and in about 30% to 50% in East Asian patients with NSCLC out of the approximately 1.6 million patients worldwide diagnosed with NSCLC annually. EGFR-activating mutations are more common in tumours of non-squamous than of squamous histology, in women than in men, in Asians than in non-Asians, and in never-smokers than in prior or current smokers. The presence of EGFR-activating mutations is less well studied in some populations such as Black/African American, Hispanic/Latino, and Pacific Islanders.

Currently, first-generation (gefitinib and erlotinib) and second-generation (afatinib) EGFR TKIs are approved globally for the treatment of patients with NSCLC with EGFR-activating mutations. Osimertinib is a third-generation EGFR TKI that is approved in the US for the treatment of patients with EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy34, and is approved in the EU for the indication of treatment of adult patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC. Recently, the CHMP adopted a positive opinion for osimertinib in the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

3.1.3. Main clinical studies

This application is mainly based on data from 452 patients included in the pivotal study A1050, a phase III open label study comparing dacomitinib versus gefitinib as first line treatment in patients newly diagnosed stage IIIB/IV or recurrent NSCLC harbouring EGRF-activating mutations. Additionally, data on 45 patients with locally advanced or metastatic NSCLC with EGFR-activating mutations from Cohort A of study A1017 have been provided and are considered supportive.

The applicant has also provided data on other 3 studies of dacomitinib in patients with locally advanced or metastatic NSCLC in later lines of therapy: two phase III, double-blind, randomized studies (Study A1009, erlotinib-controlled and Study 1011, placebo-controlled) and an open label, randomized phase II study (Study A1028, erlotinib-controlled).

3.2. Favourable effects

Study A1050 met its primary objective showing a statistically significant and clinically meaningful improvement in terms of PFS at the time of primary analysis (DCO: 29 July 2016; IRC; 59.9% of events in the dacomitinib arm vs. 79.6% of events in gefitinib arm), with dacomitinib compared to gefitinib (HR 0.589 [95% CI: 0.469, 0.739]). Treatment with dacomitinib resulted in a 5.5-month improvement in median PFS compared to control arm (14.7 months [95% CI: 11.1, 16.6] vs. 9.2 months [95% CI: 9.1, 11.0]).

PFS results according to investigator assessment (HR: 0.45 (95% CI: 0.36, 0.57; p-value <0.0001) as different sensitivity analyses also support robustness of results.

Subgroup analyses for PFS showed consistent results in most subgroups analysed except for patients >75 years and non-Asian patients.

Despite there was no difference in terms of ORR (74.9% [95% CI: 68.7, 80.4] in the dacomitinib arm and 71.6% [95% CI: 65.2, 77.4] in the gefitinib arm with 12 CR vs. 4 CR respectively) responses were longer in the dacomitinib arm than in gefitinib (median 14.8 months vs. 8.3 months).

3.3. Uncertainties and limitations about favourable effects

Final OS results (DCO: 17 Feb 2017) showed an overall HR :0.760 (95% CI: 0.582, 0.993) in favour of dacomitinib. While the final readout of OS was statistically significant when assessed on its own, since the gate-keeping procedure stopped at the testing of ORR (per IRC review) as ORR was not statistically significant, the statistical significance of OS improvement could not be formally assessed.

Importantly, OS curves crossed and started to separate after 12 months in favour of dacomitinib.

Overall, the superiority of dacomitinib over gefitinib shown in the ITT population has not been observed in the subset of non-Asian population. Nevertheless, a literature review indicated that there is no consistent pattern that would suggest that non-Asian patients respond differently from Asian patients to this class of drug. Furthermore, the provided PK/PD data do not suggest a biological sharp distinction between Asians and non-Asians that can explain the observed difference in the estimated treatment effect between these subgroups. Although the efficacy appears less favourable in the non-Asian than in the Asian patients, this could be a chance finding.

There are no data for dacomitinib in patients with activating mutations other than exon 19 deletions or exon 21 (L858R). Other potentially relevant populations such as patients with brain metastases have been excluded from the confirmatory trial in spite of the fact that non-clinical data suggest activity in CNS. These uncertainties have been reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

The safety profile of dacomitinib is based mainly on data from the pivotal phase III study A1050 and additional data from 28 patients from study A1017 Cohort A, with a median exposure of 66.7 weeks.

The most commonly adverse events with dacomitinib (vs. gefitinib) were diarrhoea (87.2% vs. 55.8%), paronychia (61.7% vs. 20.1%), dermatitis acneiform (48.9% vs. 28.6%), stomatitis (43.6% vs. 17.9%), decreased appetite (30.8% vs. 24.6%), dry skin (27.8% vs. 17.0%), weight decreased (25.6% vs. 16.5%) and alopecia (23.3% vs. 12.5%).

Grade 3 adverse events were reported in 51.1% of patients and grade 4 in 2.2% (hypokalaemia and mucosal inflammation) [29.9% and 2.2% in the gefitinib arm, respectively). The most common grade 3 AEs in the dacomitinib arms (vs. gefitinib) were dermatitis acneiform (13.7% vs. 0), diarrhoea (8.4% vs. 0.9%), paronychia (7.5% vs. 1.3%), rash (4.4% vs. 0) and rash maculo-papular (4.4% vs. 0.4%).

Two deaths (0.2%) were related to study drug toxicity (1 event of diarrhoea and a death of unknown cause in a patient who had previously reported an AE of grade 3 of drug-liver injury).

The most frequent treatment-related SAE reported in the dacomitinib arm were diarrhoea, (5 [2.2%]), abdominal pain and liver injury (2 [0.9%], each).

Adverse events of special interest are: diarrhoea (87.2%), stomatitis (43.6%), hepatotoxicity (1.8%), severe skin toxicity (3.5%), acute renal failure (4.8%), interstitial lung disease (2.6%), QT interval prolongation (1.3%), keratitis (1.8%), left ventricular dysfunction (0.9%), rash/dermatitis acneiform (77.5%) and other skin toxicity (76.2%).

Discontinuation of dacomitinib due to adverse events was reported in 17.6% of patients compared to 12.1% in the gefitinib arm. Of these, 9.7% in the datomitinib arm and 6.7% in the gefitinib arm were considered to be

related to study drug, being the most frequently reported with dacomitinib dermatitis acneiform, diarrhoea, ILD, pneumonia, rash macula-papular and stomatitis.

Dose modifications (dose reductions and/or treatment interruptions) were frequent in patients treated wih dacomitinib; 66.1% of patients reported at least one dose reduction and 78.0% required temporary treatment discontinuation. The main AEs leading to dose reductions or treatment interruption were dermatitis acneiform, paronychia and diarrhoea.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties on the safety profile that require specific investigation or follow-up post authorisation beyond routine pharmacovigilance.

3.6. Effects Table

Table 86: Effects Table for dacomitinib in EGFR-activating mutations NSCLC -1st line-(data cut-off: 29 Jul 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (IRC)	Progression free survival	Median (months)	14.7	9.2	HR (stratified) 0.589 (CI 95%: 0.469, 0.739) P-value (1-sided) < 0.0001	Efficacy section of ARs
ORR (IRC)	Anti-tumour activity (CR+PR)	%	74.9	71.6	P-value (1-sided) = 0.1942	
DoR	Duration of the response	Median (months)	14.8	8.3	HR (stratified) 0.403 (CI 95%: 0.307, 0.529) P-value (1-sided) < 0.0001	
TTF (IRC)	Time to treatment failure	Median (months)	11.1	9.2	HR (stratified) 0.670 (CI 95%: 0.543, 0.826) P-value (1-sided) < 0.0001	
OS*	Overall survival	Median (months)	34.1	26.8	HR (stratified) 0.760 (CI 95%: 0.582, 0.993) P-value (1-sided) < 0.0219	
Unfavourable Effects						
AEs grade ⩾3	Adverse events grade 3-4 regardless causality	n (%)	53.3	32.1		
SAEs	Serious AEs regardless causality	n (%)	27.3	22.3		
Deaths	Number of deaths related to Grade 5 AEs regardless causality	n (%)	22 (9.7)	20 (8.9)		
Diarrhoea	AE most commonly reported	%	87.2	55.8		
Paronychia	AE most commonly reported	%	61.7	20.1		
Dermatitis acneiform	AE most commonly reported	%	48.9	28.6		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Stomatitis	AE most commonly reported	%	43.6	17.9		
Dry skin	AE most commonly reported	%	27.8	17.0		
Weight decreased	AE most commonly reported	%	25.6	16.5		
Alopecia	AE most commonly reported	%	23.3	12.5		
ILD	AEoSI	%	2.6	1.3		
Hepatotoxicity	AEoSI	%	1.8	3.6		
Keratitis	AEoSI	%	1.8	0		

Abbreviations: AE (adverse event); AeoSI (adverse event of special interest); AR (assessment report); IRC (independent review committee); CR (complete response); DoR (duration of the response); ILD (Interstitial lung disease);; ORR (objective response rate); OS (overal survival); PFS (progression free survival); PR (partial response); TTF (time to treatment failure)

Notes: Efficacy and safety data included in this table are taken from the pivotal phase III study (A1050). * Overal survival analysis was exploratory (Data cutoff: 17 Feb 2017)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The delay in the tumour progression offered by dacomitinib is considered clinically meaningful. An increased survival has been observed although the data are considered exploratory. The outcomes from the pivotal trial are especially valuable as the comparator is one of the SoC (gefitinib) commonly used in the clinical practice.

The safety profile of dacomitinib is inferior to the safety profile of gefitinib, which is reflected in the SmPC, it is however considered manageable.

3.7.2. Balance of benefits and risks

In the overall population of first line NSCLC patients with either exon 19 deletions or exon 21 mutation (L858R), a median gain of 5.5 months PFS with dacomitinib compared to gefitinib outweighs the increase in diarrhoea and skin toxicities observed with dacomitinib as well as Grade 3 and serious adverse events.

In conclusion, the efficacy as demonstrated in the pivotal trial against an effective comparator, is considered clinically relevant for Asian and non-Asian patients. Information about the observed differences in PFS results between the key subgroups is considered of importance for the prescriber, and reflected in the SmPC.

The safety profile of dacomitinib is inferior to the safety profile of gefitinib, which is reflected in the SmPC. Non-Asian patients seem to have a higher frequency and severity grade of AEs compared to Asians which may be explained by a more elderly non-Asian population. The findings in the overall population can be extrapolated also to the subgroup of non-Asian patients.

3.8. Conclusions

The overall B/R of Vizimpro for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR activating mutations is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vizimpro is favourable in the following indication:

Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that dacomitinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.