Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

VIZIMPRO (Dacomitinib) 15 mg film-coated tablet
VIZIMPRO (Dacomitinib) 30 mg film-coated tablet
VIZIMPRO (Dacomitinib) 45 mg film-coated tablet

2. Qualitative and quantitative composition

VIZIMPRO 15 mg film-coated tablets
Each film-coated tablet contains dacomitinib monohydrate equivalent to 15 mg dacomitinib.

Excipients with known effect:
Each film-coated tablet contains 40 mg of lactose monohydrate.

VIZIMPRO 30 mg film-coated tablet
Each film-coated tablet contains dacomitinib monohydrate equivalent to 30 mg dacomitinib.

Excipients with known effect:
Each film-coated tablet contains 81 mg of lactose monohydrate.

VIZIMPRO 45 mg film-coated tablets
Each film-coated tablet contains dacomitinib monohydrate equivalent to 45 mg dacomitinib.

Excipients with known effect:
Each film-coated tablet contains 121 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets

VIZIMPRO 15 mg film-coated tablets
Blue film-coated, 6.35 mm, round biconvex tablet, debossed with "Pfizer" on one side and "DCB15" on the other.

VIZIMPRO 30 mg film-coated tablets
Blue film-coated, 7.5 mm, round biconvex tablet, debossed with "Pfizer" on one side and "DCB30" on the other.

VIZIMPRO 45 mg film-coated tablets
Blue film-coated, 9.0 mm, round biconvex tablet, debossed with "Pfizer" on one side and "DCB45" on the other.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

EGFR mutation status should be established prior to initiation of VIZIMPRO therapy.

Posology

The recommended dose of VIZIMPRO is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. VIZIMPRO can be taken with or without food.

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken and the next prescribed dose should be taken at the usual time the next day.

Dose modifications

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 Drug Reactions (ADRs) are provided in Table 2.

No starting dose adjustments are required on the basis of patient age, race, gender, or body weight (see Section 5.2 Pharmacokinetic properties).

Table 1. Recommended Dose Modifications for VIZIMPRO Adverse Drug 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 Drug Reactions

Adverse Drug Reactions	**Dose Modification**
Interstitial lung disease (ILD/Pneumonitis)	• Withhold VIZIMPRO during ILD/Pneumonitis diagnostic evaluation. • Permanently discontinue VIZIMPRO if ILD/Pneumonitis is confirmed.
Diarrhea	• For Grade 1 diarrhea, no dose modification is required. Initiate treatment with anti-diarrheal medications (e.g., loperamide) at first onset of diarrhea. Encourage adequate oral fluid intake during diarrhea. • For Grade 2 diarrhea, if not improved to Grade ≤1 within 24 hours while using anti-diarrheal medications (e.g., loperamide) and adequate oral fluid intake, withhold VIZIMPRO. Upon recovery to Grade ≤1, resume VIZIMPRO at the same dose level or consider a reduction of one dose level. • For Grade >3 diarrhea, withhold VIZIMPRO. Treat with anti-diarrheal medications (e.g., loperamide), and adequate oral fluid intake or intravenous fluids or electrolytes as appropriate. Upon recovery to Grade ≤1, resume VIZIMPRO with a reduction of 1 dose level.
Rash, erythematous and exfoliative skin conditions	• 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 and 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 VIZIMPRO. Upon recovery to Grade ≤1, resume VIZIMPRO at the same dose level or consider a reduction of 1 dose level. • For Grade ≥3 rash, erythematous or exfoliative skin conditions, withhold VIZIMPRO. 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 VIZIMPRO with a reduction of 1 dose level.
Other	• For Grade 1 or 2 toxicity, no dose modification is required. • For Grade ≥3 toxicity, withhold VIZIMPRO until symptoms resolve to Grade ≤2. Upon recovery, resume VIZIMPRO with a reduction of 1 dose level.

Special populations

Hepatic impairment: No starting dose adjustments are required when administering VIZIMPRO to patients with mild (Child-Pugh class A), moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Renal impairment: No starting dose adjustments are required when administering VIZIMPRO to patients with mild or moderate renal impairment (CrCl ≥30 mL/min). Insufficient data are available in patients with severe renal impairment (CrCl <30 mL/min) or requiring hemodialysis to provide dosing recommendations in this patient population. (see Section 5.2 Pharmacokinetic properties)

Elderly population: No starting dose adjustment of VIZIMPRO in elderly (≥65 years of age) patients is required (see Section 5.2 Pharmacokinetic properties).

Pediatric population: The safety and efficacy of VIZIMPRO in children (<18 years of age) have not been established.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

The warnings and precautions listed below are based on pooled data from 255 patients who received VIZIMPRO 45 mg once daily for first-line treatment of NSCLC with EGFR-activating mutations across clinical studies.

Interstitial lung disease (ILD)/Pneumonitis

ILD/pneumonitis, including a fatal event, has been reported in patients receiving VIZIMPRO (see Section 4.8 Undesirable effects – ILD).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (e.g., dyspnea, cough, fever) should be performed to exclude ILD/pneumonitis. Treatment with VIZIMPRO should be withheld pending investigation of these symptoms. If ILD/pneumonitis is confirmed, VIZIMPRO should be permanently discontinued and appropriate treatment instituted as necessary (see Section 4.2 Posology and method of administration – Table 2).

Diarrhea

Diarrhea has been reported during treatment with VIZIMPRO. Across the clinical experience of 255 patients, there was one case (0.4%) of diarrhea which was not adequately treated and was fatal (see Section 4.8 Undesirable effects – Diarrhea).

Proactive management of diarrhea should start at the first sign of diarrhea especially within the first 2 weeks of starting VIZIMPRO, including adequate hydration combined with anti-diarrheal medications and continued until loose bowel movements cease for 12 hours. Anti-diarrheal medications (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 VIZIMPRO. Patients should maintain adequate oral hydration and patients who become dehydrated may require administration of intravenous fluids and electrolytes (see Section 4.2 Posology and method of administration- Table 2).

Rash, erythematous and exfoliative skin conditions
Rash, erythematous and exfoliative skin conditions have been reported in patients treated with VIZIMPRO (see Section 4.8 Undesirable effects- Rash, erythematous and exfoliative skin conditions).

Rash, erythematous and exfoliative skin conditions may occur or worsen in areas exposed to the sun. For patients who are exposed to the sun, protective clothing and use of sunscreen is advisable. Early intervention is advisable. Patients may require dosing interruption and/or dose reduction of therapy with VIZIMPRO and additional treatment as warranted (e.g., antibiotics, topical steroids, and emollients) (see Section 4.2 Posology and method of administration- Table 2).

Drugs metabolized by CYP2D6

VIZIMPRO may increase exposure (or decrease exposure of active metabolites) of other drugs metabolized by CYP2D6. CYP2D6 substrates with a narrow therapeutic index should be avoided (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Lactose
VIZIMPRO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Sodium
VIZIMPRO contains < 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of cytochrome P450 (CYP)2D6 inhibitors on dacomitinib

Coadministration of dacomitinib with strong inhibitors of CYP2D6 did not result in clinically relevant changes in exposure of dacomitinib. Dose adjustment of VIZIMPRO is not required in patients taking a strong CYP2D6 inhibitor.

Effect of VIZIMPRO on drugs metabolized by CYP2D6

Dacomitinib is a strong inhibitor of CYP2D6 (see Section 5.2 Pharmacokinetic properties). Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP2D6, including but not limited to amitriptyline, atomoxetine, desipramine, dextromethorphan, doxepin, fluvoxamine, methoxyphenamine, metoprolol, or nebivolol. Coadministration of VIZIMPRO with CYP2D6 substrates with a narrow therapeutic index, including to but not limited to procainamide, pimozide, and thioridazine, should be avoided. Drugs with active metabolites formed via CYP2D6, such as codeine and tramadol, should be replaced by an alternative within the therapeutic class as their exposure with the coadministration of dacomitinib may be subtherapeutic.

Coadministration with medicinal products that increase gastric pH

The aqueous solubility of dacomitinib is pH dependent, with low (acidic) pH resulting in higher solubility. Proton pump inhibitors (PPIs) should be avoided while receiving treatment with VIZIMPRO.

Local antacids may be used if needed. If the use of a histamine-2 (H2) receptor antagonist is needed, VIZIMPRO should be administered 2 hours before or at least 10 hours after taking a H2 receptor antagonist (see Section 5.2 Pharmacokinetic properties).

4.6 Fertility, pregnancy, and lactation

Fertility
Fertility studies have not been performed with VIZIMPRO. Nonclinical safety studies showed reversible epithelial atrophy in the cervix and vagina of rats and no effects on reproductive organs of male rats or dogs (see Section 5.3 Preclinical safety data).

Pregnancy
VIZIMPRO may cause fetal harm when administered to a pregnant woman based on its mechanism of action. In pregnant rats or rabbits, effects were limited to lower maternal body weight gain and food

consumption in rats and rabbits, and lower fetal body weights in rats only (see Section 5.3 Preclinical safety data).

There are no adequate and well-controlled studies in pregnant women using VIZIMPRO. Women of childbearing potential should be advised to avoid becoming pregnant while receiving VIZIMPRO. Women of childbearing potential who are receiving this drug should use adequate contraceptive methods during therapy and for at least 17 days (5 half-lives) after completing therapy.

Female patients taking VIZIMPRO during pregnancy or who become pregnant while taking VIZIMPRO should be apprised of the potential hazard to the fetus.

Lactation

It is not known whether dacomitinib and its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious ADRs in breastfed infants from exposure to dacomitinib, mothers should be advised against breastfeeding while receiving VIZIMPRO.

4.7 Effects on ability to drive and use machines.

No studies on the effects of VIZIMPRO on the ability to drive or operate machinery have been conducted. However, patients experiencing fatigue while taking VIZIMPRO should exercise caution when driving or operating machinery.

4.8 Undesirable effects

The ADRs described in this section are based on pooled data from 255 patients who received VIZIMPRO 45 mg once daily as starting dose for first-line treatment of NSCLC with EGFR- activating mutations across clinical studies as defined in Table 3 footnotes [a] through [h]. The median duration of treatment with VIZIMPRO across the pooled data set was 66.7 weeks.

The most common (>20%) ADRs in patients receiving VIZIMPRO were diarrhea (88.6%), rash (82.4%), stomatitis (71.8%), nail disorder (65.5%), dry skin (33.3%), decreased appetite (31.8%), conjunctivitis (25.5%), weight decreased (24.3%), alopecia (23.1%), and nausea (20.4%). Serious ADRs were reported in 6.7% of patients treated with VIZIMPRO. The most frequently (≥1%) reported serious ADRs in patients receiving VIZIMPRO were diarrhea (2.0%), interstitial lung disease (1.2%), rash (1.2%), and decreased appetite (1.2%).

ADRs leading to dose reduction were reported in 52.2% of patients treated with VIZIMPRO. The most frequently reported (>5%) reasons for

dose reductions due to any ADRs in patients receiving VIZIMPRO were rash (32.9%), nail disorder (16.5%), and diarrhea (7.5%).

ADRs leading to permanent discontinuation were reported in 6.7% of patients treated with VIZIMPRO. The most common (>0.5%) reasons for permanent discontinuations associated with ADRs in patients receiving VIZIMPRO were rash (2.4%), interstitial lung disease (2.0%), and diarrhea (0.8%).

Tabulated list of adverse drug reactions

Table 3 presents adverse drug reactions for VIZIMPRO within each system organ class (SOC) presented by decreasing medical seriousness within each SOC.

Table 3. Adverse Drug Reactions Reported in Patients with EGFR-Activating Mutations Who Received VIZIMPRO 45 mg as First-Line Therapy

System Organ Class	Adverse Drug Reactions
Metabolism and nutrition disorders	Decreased appetite Dehydration Hypokalaemia[a]
Nervous system disorders	Dysgeusia
Eye disorders	Conjunctivitis[b]
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[*c]
Gastrointestinal disorders	Diarrhoea[*] Stomatitis[d] Vomiting Nausea
Skin and subcutaneous tissue disorders	Rash[e] Skin exfoliation[f] Skin fissures Dry skin[g] Nail disorder[h] Hypertrichosis Alopecia
General disorders and administration site conditions	Fatigue Asthenia
Investigations	Weight decreased

Adverse drug reactions include treatment-emergent all-causality events that occurred after the start of study treatment and within 28 days after the final dose of study treatment.
Preferred terms (PTs) were retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
[*]. Fatal events

[a] Hypokalaemia includes the following PTs: Blood potassium decreased, Hypokalaemia
[b] Conjunctivitis includes the following PTs: Conjunctivitis, Dry eye, Blepharitis, Keratitis, Noninfective conjunctivitis.
[c] Interstitial lung disease includes the following PTs: Interstitial lung disease, Pneumonitis.
[d] Stomatitis includes the following PTs: Aphthous ulcer, Cheilitis, Dry mouth, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, Stomatitis.
[e] Rash (also referred to as Rash and Erythematous skin conditions) includes the following PTs: Acne, Dermatitis acneiform, Erythema, Erythema multiforme, Palmar-plantar erythrodysaesthesia syndrome, Pruritus, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic.
[f] Skin exfoliation (also referred to as Exfoliative skin conditions) includes the following PTs: Exfoliative rash, Skin exfoliation.
[g] Dry skin includes the following PTs: Dry skin, Xerosis.
[h] Nail disorder includes the following PTs: Ingrowing nail, Nail bed bleeding, Nail bed inflammation, Nail discolouration, Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia.

Description of selected adverse drug reactions

Interstitial lung disease (ILD)/ Pneumonitis

ILD/Pneumonitis adverse drug reactions were reported in 2.7% of patients receiving VIZIMPRO, and Grade ≥3 ILD/pneumonitis adverse drug reactions were reported in 0.8%, including a fatal event (0.4%) (see Section 4.4 Special warnings and precautions for use).

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 VIZIMPRO. The median duration of any grade and Grade ≥3 ILD/pneumonitis was 13 weeks. and 1.5 weeks, respectively (see Section 4.4 Special warnings and precautions for use).

Diarrhea

Diarrhea was the most frequently reported adverse drug reaction in patients receiving VIZIMPRO (88.6%) and Grade ≥3 diarrhea adverse reactions were reported in 9.4% of patients. In a clinical study, one patient (0.4%) was inadequately treated and had a fatal outcome (see Section 4.4 Special warnings and precautions for use).

The median time to the first episode of any grade diarrhea was 1 week and the median time to the worst episode of diarrhea was 2 weeks in

patients receiving VIZIMPRO. The median duration of any grade and Grade ≥3 diarrhea was 20 weeks and 1 week, respectively (see Section 4.4 Special warnings and precautions for use).

Rash, erythematous and exfoliative skin conditions

Rash, erythematous and exfoliative skin condition ADRs were reported in 82.4% and 5.5%, respectively, of patients receiving VIZIMPRO. Grade 3 rash and erythematous skin condition ADRs were the most frequently reported Grade 3 adverse reactions (26.3%). Grade 3 exfoliative skin conditions were reported in 0.8% of patients. There were no Grade 4 or 5 rash, erythematous, and exfoliative skin conditions ADRs reported (see Section 4.4 Special warnings and precautions for use).

The median time to the first episode of any grade rash and erythematous skin conditions was approximately 2 weeks and the median time to the worst episode of rash and erythematous skin conditions was 7 weeks in patients receiving VIZIMPRO. The median duration of any grade and Grade ≥3 rash and erythematous skin conditions was 58 weeks and 2 weeks, respectively. The median time to the first episode of any grade exfoliative skin conditions was 6 weeks and the median time to the worst episode of exfoliative skin conditions was 6 weeks. The median duration of any grade and Grade ≥3 exfoliative skin conditions was 10 weeks and approximately 2 weeks, respectively (see Section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions ND PQMPs to https://pv.pharmacyboardkenya.org

4.9 Overdose

The highest dose of dacomitinib studied in a limited number of patients was 105 mg (6 doses every 12 hours every 14 days). The adverse drug reactions observed at doses greater than 45 mg once a day were primarily gastrointestinal, dermatological, and constitutional (e.g., fatigue, malaise, and weight loss). There were no overdoses reported in the dacomitinib clinical trials.

There is no known antidote for dacomitinib. The treatment of VIZIMPRO overdose should consist of symptomatic treatment and general supportive measures.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EB07

Mechanism of action

Dacomitinib is a pan-human epidermal growth factor receptor (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with clinical 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. Dacomitinib demonstrates dose-dependent target inhibition and antitumor efficacy in mice bearing human tumor xenografts driven by HER family targets including mutated EGFR.

Dacomitinib distributes to the brain in mice, with brain and plasma average concentrations approximately equal following oral dosing. Dacomitinib exhibits target inhibition and antitumor efficacy in orally-dosed dacomitinib- versus control-treated mice bearing intracranial human tumor xenografts driven by EGFR.

Clinical efficacy

VIZIMPRO in first-line treatment of NSCLC patients with EGFR-activating mutations (ARCHER 1050)

The efficacy and safety of VIZIMPRO was demonstrated in a Phase 3 study (ARCHER 1050) conducted in patients with locally advanced or metastatic NSCLC harboring activating mutations of EGFR. A total of 452 patients were randomized 1:1 to VIZIMPRO or gefitinib in a multicenter, multinational, randomized, open-label Phase 3 study. Treatment was administered orally on a continuous daily basis until disease progression, institution of new anticancer therapy, intolerable toxicity, withdrawal of consent, death, or investigator decision dictated by protocol compliance, whichever occurred first. Stratification factors at randomization were race (Japanese versus mainland Chinese versus other East Asian versus non-East Asian, as stated by the patient) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21). EGFR mutation status was determined by a standardized and commercially available test kit (e.g., therascreen®, Cobas®).

The primary endpoint of the study was progression-free survival (PFS) as determined by blinded Independent Radiology Central (IRC) review. Key secondary endpoints included Objective Response Rate (ORR), Duration of Response (DoR), Overall Survival (OS), and patient-reported outcomes (PROs).

The demographic characteristics of the overall study population were 60% female, median age at enrollment of 62 years, baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 (30%), or 1 (70%), 59% with exon 19 deletion, and 41% with L858R mutation in exon 21; 23% White, 77% Asian, and less than 1% Black.

A statistically significant and clinically meaningful improvement in PFS as determined by the IRC was demonstrated for patients randomized to VIZIMPRO compared with those randomized to gefitinib, see Table 4 and Figure 1.

Subgroup analyses of PFS per IRC review based on baseline characteristics were consistent with those from the primary analysis of PFS.

The pre-specified final analysis of OS demonstrated that dacomitinib resulted in a significant improvement in OS versus gefitinib, see Table 4 and Figure 2.

Table 4. Efficacy Results From ARCHER 1050 in Patients With Previously Untreated NSCLC With EGFR-activating Mutations – ITT Population*

	Dacomitinib N=227	**Gefitinib N=225**
Progression-Free Survival (per IRC)		
Number of patients with event, n (%)	136 (59.9%)	179(79.6%)
Median PFS in months (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)[a]	0.589 (0.469, 0.739)	
2-sided p-value[b]	<0.0001	
Progression-Free Survival (per Investigator assessment)		
Number of patients with event, n (%)	140 (61.7%)	177 (78.7%)
Median PFS in months (95% CI)	16.6 (12.9, 18.4)	11.0 (9.4, 12.1)
HR (95% CI)[a]	0.622 (0.497, 0.779)	
2-sided p-value[b]	<0.0001	
Overall Survival		
Number of patients with event, n (%)	103 (45.4)	117 (52.0)
Median OS in months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)[a]	0.760 (0.582, 0.993)	
2-sided p-value[b]	0.0438	
Objective Response Rate (per IRC)		
Objective Response Rate % (95% CI)	74.9% (68.7, 80.4)	71.6% (65.2, 77.4)
2-sided p-value[c]	0.3883	
Duration of Response in Responders (per IRC)		
Number of responders per IRC review, n (%)	170 (74.9)	161 (71.6)
Median DoR in months (95% CI)	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)
HR (95% CI)[a]	0.403 (0.307, 0.529)	
2-sided p-value[b]	<0.0001	
Duration of Response[d] (per IRC)		
Median DoR in months (95% CI)	9.3 (8.2, 12.0)	6.4 (4.6, 6.5)
HR (95% CI)[a]	0.530 (0.426, 0.659)	
2-sided p-value[b]	<0.0001	

* Data based on data cut-off date of 29 July 2016 except for pre-specified final OS analysis which is based on the data cut-off date of 17 February 2017.

Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; IRC=independent radiologic central; ITT= intent-to-treat; IWRS= interactive web response system; N/n=total number; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; DoR=duration of response.

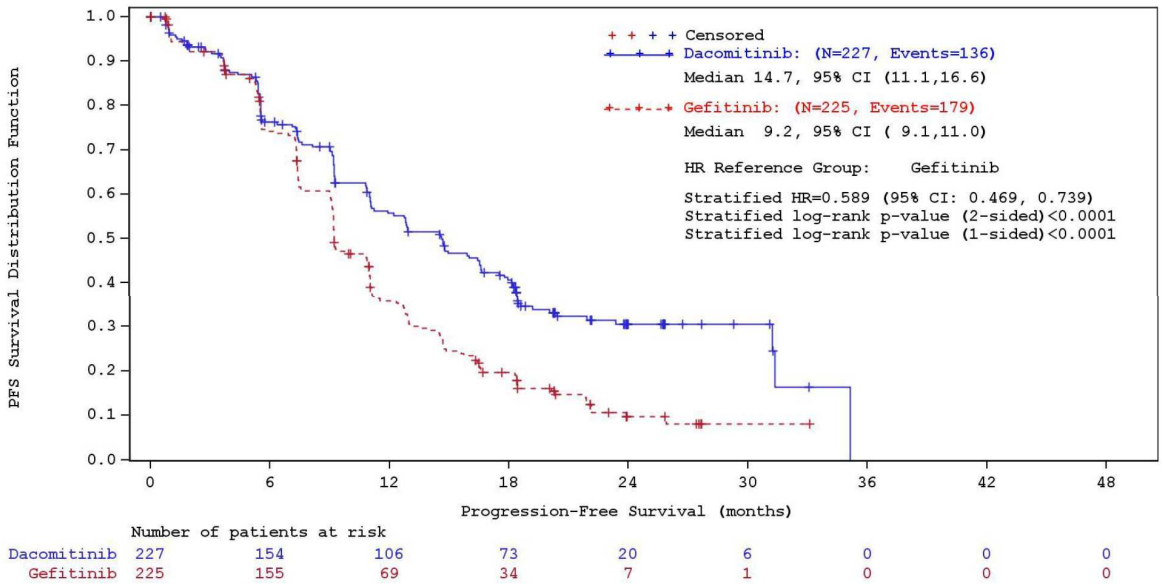
a.From stratified Cox Regression. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21) at randomization per IWRS.

b. Basedonthestratifiedlog-rank test. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R
mutation in exon 21) at randomization per IWRS.

c. Based on the stratified Cochran-Mantel-Haenszel test. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21) at randomization per IWRS.

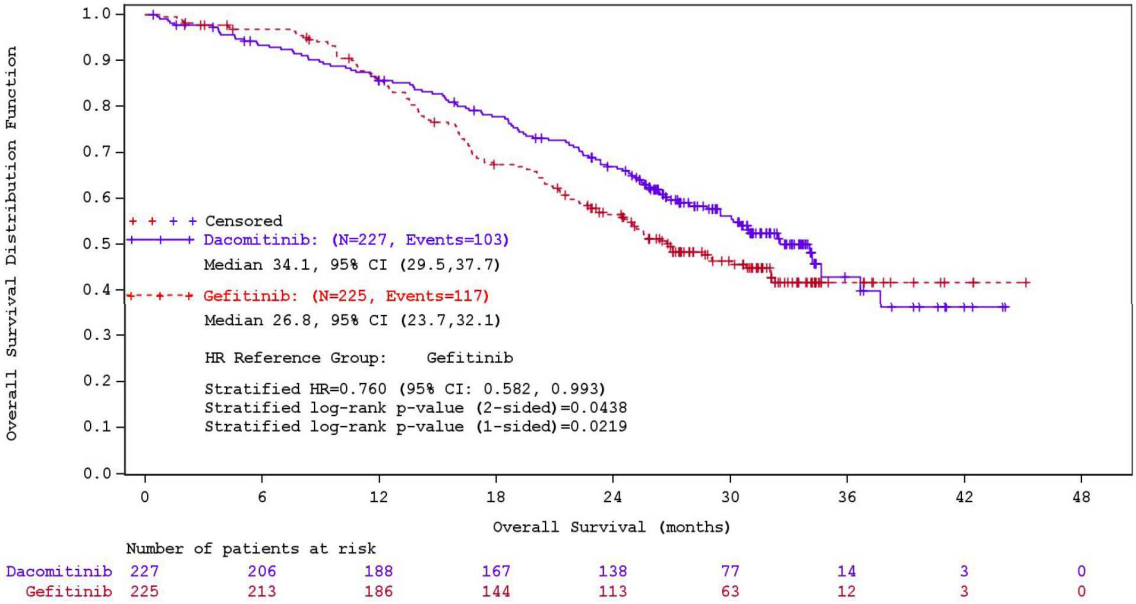
d. Analysis was based on the ITT population with patients without response being given a duration of zero and considered an event.

Figure 1. ARCHER 1050 - Kaplan-Meier Curve for PFS per IRC Review – ITT Population



Abbreviations: CI=confidence interval; HR=hazard ratio; IRC=independent radiologic central; ITT=Intent-To-Treat; N=total number; PFS=progression-free survival.

Figure 2. ARCHER 1050 - Kaplan-Meier Curve for OS – ITT Population



Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=Intent-To-Treat; N=total number; OS=overall survival.

Patient-reported outcomes were collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (items) (EORTC-QLQ-C30) and its lung cancer module European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer module 13 (items) (EORTC-QLQ-LC13). Dacomitinib resulted in an improvement in the disease-related symptom of pain in chest (p=0.0235) compared to gefitinib. The improvement from baseline was clinically meaningful (≥10 point change from baseline) in pain in chest in the dacomitinib arm.

There was a clinically meaningful improvement from baseline (≥10 point change from baseline) in disease-related symptom of cough in the dacomitinib arm which was similar to the gefitinib arm (p=0.3440).

Improvements from baseline that were not statistically different between the dacomitinib arm and the gefitinib arm were seen in the disease related symptoms of dyspnea (p=0.9411), fatigue (p=0.5490), pain in arm or shoulder (p=0.2854), and pain in other parts (p=0.3288).

5.2 Pharmacokinetic properties

Absorption

Following the administration of a single 45 mg dose of dacomitinib tablets, the mean oral bioavailability of dacomitinib is 80% 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. Food does not alter bioavailability to a clinically meaningful extent. Dacomitinib can be administered with or without food. Dacomitinib is a substrate for the membrane transport proteins P-glycoprotein (P-gp) and Breast Cancer Resistant Protein (BCRP). However, based on the oral bioavailability of 80% these membrane transport proteins are unlikely to have any impact on dacomitinib absorption.

Distribution

Dacomitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1889 L following intravenous administration. In vitro binding of dacomitinib to human plasma proteins is approximately 98% and is independent of drug concentrations.

Metabolism

In humans, dacomitinib undergoes oxidation and glutathione conjugation as the major metabolic pathways. Following oral administration of a single 45 mg dose of [^{14}C] dacomitinib, 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 feces, 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.

Elimination

The plasma half-life of dacomitinib ranges from 54 to 80 hours. In six 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; feces (79% of dose) was the major route of excretion, with 3% of the dose recovered in urine.

Drug interactions

Coadministration of dacomitinib and CYP2D6 inhibitors

Coadministration of a single 45 mg oral dose of dacomitinib in the presence of paroxetine (30 mg), a potent CYP2D6 inhibitor, resulted in a 37% increase in dacomitinib exposures (AUC). The change in dacomitinib disposition due to paroxetine coadministration is unlikely to be clinically relevant and dose adjustment of dacomitinib is not required upon concomitant administration with a CYP2D6 inhibitor.

Coadministration of dacomitinib and CYP2D6 substrates

Coadministration of single 45 mg oral dose of dacomitinib increased the mean exposure (AUC and C_{max}) of dextromethorphan, a probe CYP2D6 substrate, 855% and 874%, respectively, compared with administration of dextromethorphan alone. These results suggest that dacomitinib may increase exposure of other drugs (or decrease exposure to active metabolites) primarily metabolized by CYP2D6. Administration of drugs which are highly dependent on CYP2D6 metabolism may require dose adjustment, or substitution with an alternative medication. Clinical monitoring for exaggerated or decreased drug effects is also recommended.

Coadministration of dacomitinib with agents that increase gastric pH

The aqueous solubility of dacomitinib is pH dependent, with low (acidic) pH resulting in higher solubility. Data from a study in healthy subjects indicated that coadministration of a single 45 mg dacomitinib dose with multiple doses of the PPI rabeprazole 40 mg decreased dacomitinib C_{max} and AUC_{inf} (area under the concentration-time curve from time 0 to infinity) by approximately 51% and 30%, respectively when compared to a single 45 mg dose of VIZIMPRO administered alone. PPIs should be avoided while receiving treatment with VIZIMPRO.

Based on data from observations in 8 cancer patients from Study A7471001, there was no apparent effect of local antacid administration on C_{max} and AUC_{inf} of dacomitinib. Based on data from 16 cancer patients across multiple studies, there was no apparent effect of H2 receptor antagonists on steady-state trough concentrations of dacomitinib.

Effect of dacomitinib and O-desmethyl dacomitinib on CYP enzymes

In vitro, dacomitinib and its metabolite O-desmethyl dacomitinib have a low potential to inhibit the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 at clinically relevant concentrations, but they may inhibit the activity of CYP2D6.
In vitro, dacomitinib has a low potential to induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Effect of dacomitinib on drug transporters

In vitro, dacomitinib has a low potential to inhibit the activities of drug transporters P-gp (systemically), organic anion transporters (OAT)1 and OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3, but may inhibit the activity of P-gp (in the gastrointestinal [GI] tract), BCRP (systemically and GI tract), and OCT1 at clinically relevant concentrations.

Effect of dacomitinib on UGT enzymes

In vitro, dacomitinib has a low potential to inhibit uridine-diphosphate glucuronosyltransferase (UGT)1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, but may inhibit UGT1A1 at clinically relevant concentrations.

Special populations

Age, race, gender, body weight
Based on population pharmacokinetic analyses, patient age, race, gender, and body weight do not have a clinically relevant effect on predicted steady state trough concentration of dacomitinib.

Patients with hepatic impairment

In a dedicated hepatic impairment trial, following a single-oral dose of 30 mg VIZIMPRO, dacomitinib exposure (AUC and C_{max}) was unchanged in mild hepatic impairment (Child-Pugh class A; N=8) and decreased by 15% and 20%, respectively in moderate hepatic impairment (Child-Pugh class B; N=9) when compared to subjects with normal hepatic function (N=8). In a second dedicated hepatic impairment trial, following a single oral dose of 30 mg VIZIMPRO, dacomitinib exposure was unchanged for AUC_{inf} and increased by 31% for C_{max} in subject with severe hepatic impairment (Child-Pugh class C; N=8), when compared to subjects with normal hepatic function (N=8). 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.

Patients with renal impairment

Approximately 3% of a single [^{14}C] 45 mg dose was excreted in the urine. No clinical studies have been conducted in patients with impaired renal function. 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. From the small number of patients with severe renal impairment (CrCl <30 mL/min; N=4), there is no evidence for a change in dacomitinib pharmacokinetics. The pharmacokinetics of dacomitinib have not been studied in patients requiring hemodialysis.

Cardiac electrophysiology

The effect of dacomitinib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 32 patients with advanced NSCLC. Dacomitinib did not prolong QTc to any clinically relevant extent at therapeutic maximum concentrations expected following 45 mg once daily.

5.3 Preclinical safety data

Genotoxicity

Dacomitinib was tested using a series of genetic toxicology assays. Dacomitinib is 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. Thus, dacomitinib is not expected to be genotoxic at clinically relevant exposure concentrations.

Carcinogenicity
Carcinogenicity studies have not been performed with VIZIMPRO.

Impairment of fertility
Fertility studies have not been performed with VIZIMPRO. In repeat-dose toxicity studies with VIZIMPRO, effects on reproductive organs were observed in female rats given ≥0.5 mg/kg/day for 6 months (approximately 0.3 times the unbound AUC at the recommended human dose) 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
In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 5 mg/kg/day and 4 mg/kg/day dacomitinib, respectively, during the period of organogenesis. Maternal body weight gain and food intake were lower at 5 mg/kg/day and 4 mg/kg/day in pregnant rats and rabbits, respectively. The maternally toxic dose of 5 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At the maternally toxic dose of 4 mg/kg/day in rabbits, there was no evidence of developmental toxicity. At 5 mg/kg/day in rats and 4 mg/kg/day in rabbits, the maternal systemic exposures were approximately 2.4 and 0.3 times, respectively, the unbound AUC at the recommended human dose.

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

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate

Film coating

Opadry II Blue 85F30716 containing:
Polyvinyl alcohol – partially hydrolysed (E1203) Talc (E553b)
Titanium dioxide (E171)
Macrogol (E1521)
Indigo Carmine Aluminium Lake (E132)

Do not use VIZIMPRO after the expiry date which is stated on the Carton/Blister label after EXP:. The expiry date refers to the last day of that month.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months.

6.4 Special precautions for storage:
Store below 30℃

6.5 Nature and contents of container

Aluminium/aluminium blister containing 10 film-coated tablets. Each pack contains 30 film- coated tablets.

6.6 Special precautions for disposal and other handling:

Any unused product or waste should be disposed in accordance with local requirements.

Keep out of the sight and reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Pfizer Laboratories Limited
Address: P.O. BOX 18244-00500
Country: Kenya

Manufacturing site address:
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

8. Marketing authorization number
VIZIMPRO 15 mg Tablet: CTD9773
VIZIMPRO 30 mg Tablet: CTD9774
VIZIMPRO 45 mg Tablet: CTD9768

9. Date of first registration
09/09/2022

10. Date of revision of the text:
14/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable