Summary Report of Benefit-Risk Assessment

VIZIMPRO FILM-COATED TABLET 15MG, 30MG AND 45MG

NEW DRUG APPLICATIONS

Active Ingredient(s)	Dacomitinib monohydrate
Product Registrant	Pfizer Private Limited
Product Registration Number	SIN15966P, SIN15967P, SIN15965P
Application Route	Abridged evaluation
Date of Approval	25 June 2020

A INTRODUCTION

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 (exon 19 deletion or exon 21 L858R substitution mutations).

The active substance, dacomitinib, is an oral tyrosine kinase inhibitor that irreversibly inhibits the activity of EGFR proteins including EGFR/HER1, HER2 and HER4 and specific EGFR activating mutations, including exon 19 deletion or the exon 21 L858R substitution mutation leading to inhibition of the cell proliferation and induction of apoptosis.

Vizimpro is available as film-coated tablets containing 15 mg, 30 mg and 45 mg of dacomitinib. Other ingredients in the tablet core are microcrystalline cellulose, lactose monohydrate, sodium starch glycolate and magnesium stearate.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, dacomitinib, is manufactured at Pfizer Ireland Pharmaceuticals, Ireland. The drug product, Vizimpro Film-coated Tablet 15mg, 30mg and 45mg, are manufactured at Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Pfizer Ireland Pharmaceuticals, Ireland is adequate to support the approved storage condition and re-test period. The packaging is double polyethylene bags within a high density polyethylene (HDPE) drum, and each bag is sealed with re-sealable ties. The HDPE drum is then sealed with a screw top lid. The drug substance is approved for store at or below 25ºC with a re-test period of 60 months.

Drug product:
The tablet is manufactured using a direct compression approach, followed by film-coating. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 60 months when stored at or below 30 ºC. The container closure system is Oriented Polyamide/Alu/PVC blisters with aluminium foil containing 10 or 30 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of dacomitinib for the first-line treatment of locally advanced or metastatic NSCLC was based primarily on one pivotal Phase III study (Study A7471050), referred to as the ARCHER study, and one supportive study (Study A7471017).

Study A7471017 was a Phase II, open-label, multi-centre trial in subjects with advanced NSCLC who received two starting doses of dacomitinib (30mg or 45 mg per day) as a single agent. The study comprised two cohorts, Cohort A or Cohort B. Only Cohort A was relevant to the proposed indication. The study showed a favourable though non-statistically significant trend to improved progression-free survival (PFS) in those subjects who started treatment at a dose of 45 mg compared to 30 mg, with a median PFS of 12.7 months [95% CI: 9.2 to 16.2 months] versus 9.2 months [95% CI: 4.7 to 16.6 months], respectively. In terms of safety, the 45mg dose was not associated with increased toxicity compared to the 30mg dose, , the 45 mg dose was selected for investigation in the Phase III study.

The ARCHER study was a Phase III, multicentre, open-label, randomised study comparing dacomitinib with gefitinib in first-line treatment of patients with locally advanced or metastatic NSCLC with an EGFR-activating mutation in either exon 19 or 21. Patients were randomised in a 1:1 ratio to receive oral dacomitinib 45 mg once daily or oral gefitinib 250 mg once daily. Patients received treatment for up to 48 months or until the patients experienced disease progression or death or unacceptable toxicity or initiation of a new anti-cancer therapy. Two dose reductions were allowed for dacomitinib in the event of unacceptable toxicity, i.e. to 30 mg and to 15 mg.

For the comparator arm, gefitinib 250 mg once daily was allowed to be reduced to 250 mg every other day. The use of gefitinib as an active comparator was considered acceptable as it is one of the established and locally approved treatment options for first-line treatment of locally advanced or metastatic NSCLC with EGFR activating mutations in exon 19 or 21.

The primary efficacy endpoint was PFS by Independent Radiologic Central (IRC), defined as time from randomisation to documented progressive disease (PD) per RECIST 1.1 or death due to any cause. Key secondary efficacy endpoints were PFS by investigator's assessment, objective response rate (ORR), overall survival (OS) and duration of response (DoR). Tumour assessments were performed using CT scan or MRI at the end of Cycles 1 and 2, then every other cycle (within 7 days of the start of subsequent cycle, including Day 1 of subsequent cycle). The study was a superiority study using hierarchical testing, starting with PFS by IRC, followed by ORR-IRC and OS with a gatekeeping approach maintaining the 1-sided alpha at 0.025.

A total of 452 patients were randomised in the study and were included in the intent-to-treat (ITT) population: 227 patients in the dacomitinib arm and 225 in the gefitinib arm. There was a higher incidence of discontinuation in gefitinib arm (82.7%) compared to dacomitinib arm (70.9%) due to progression or relapse or deaths (46.7% vs 40.1%). The incidence AEs leading to discontinuation were numerically lower in gefitinib arm compared to dacomitinib (12.1% vs 17.6%).

The demographics and baseline characteristics were well balanced across the two arms except for more females (64% vs 55%) and a slightly higher proportion of elderly subjects ≥65 years (41.4% vs 37.8%) in the dacomitinib arm compared to the gefitinib arm. The median age was 62 years (range 28 to 87 years), and 76.5% were Asians. All subjects had either exon 19 deletion or L858R mutation in exon 21, with only two subjects in dacomitinib arm who had concomitant T790M mutation in exon 20 along with L858R mutation in exon 21. There was about 96.5% agreement between local and central testing for the mutations. The median duration since histopathological diagnosis was 0.92 months (range: 0.1 months to 132.6 months) and 0.79 months (range: 0.0 months to 86.8 months), in the dacomitinib and gefitinib arms, respectively. All patients had a histological status of adenocarcinoma. Most of patients 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). Five patients had brain metastasis (4 in gefitinib and 1 in dacomitinib).

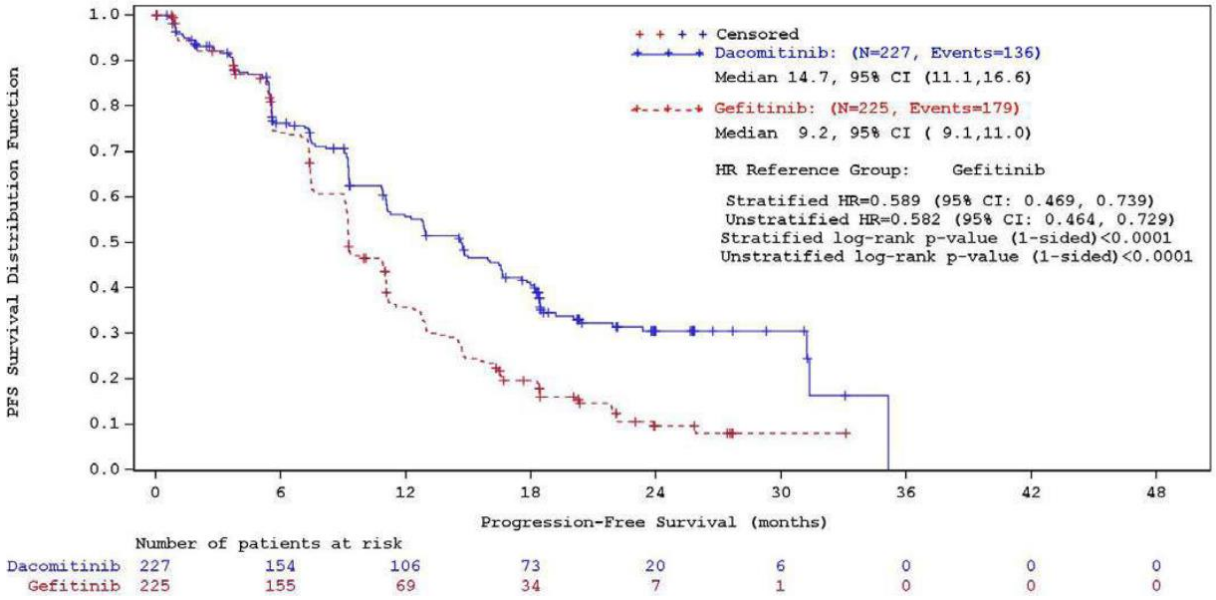
Summary of key efficacy results

	Dacomitinib	**Gefitinib**
Primary endpoint		
PFS per IRC, n	227	225
PFS events, n (%)	136 (59.9)	179 (79.6)
Median PFS (months) (95% CI)	14.7 (11.1,16.6)	9.2 (9.1,11)
Stratified HR (95% CI)	0.589 (0.469, 0.739)	
Stratified log-rank 1-sided p-value	<0.0001	
Secondary endpoints		
PFS per Investigator assessment, n	227	225
PFS events, n(%)	140 (61.7%)	177 (78.7%)
Median PFS (months) (95% CI)	16.6 (12.9, 18.4)	11.0 (9.4, 12.1)
Stratified HR (95% CI)	0.622 (0.497, 0.779)	
Stratified log-rank 1-sided p-value	< 0.0001	
ORR-IRC, n	227	225
Confirmed ORR (95% CI)	74.9% (68.7, 80.4)	71.6% (65.2, 77.4)
Stratified CMH p-value	0.1942	
OS (ITT), n	227	225

OS events, n (%)	103 (45.5%)	117 (52.0%)
Median OS (months) (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
Stratified HR (95% CI)	0.760 (0.582, 0.993)	
Stratified log-rank p-value	0.0219	

Treatment with dacomitinib resulted in a statistically significant improvement in PFS per IRC, with a 42% risk reduction of progression or death with dacomitinib [HR: 0.589 (95% CI: 0.469, 0.739; 1-sided p<0.0001)] and lower events in dacomitinib arm (59.9%) compared to gefitinib arm (79.6%), respectively. The Kaplan-Meier (KM) curves started to separate at about 6 months in favour of dacomitinib and the median PFS was 14.7 months (95% CI: 11.1, 16.6) for the dacomitinib arm versus 9.2 months (95% CI: 9.1, 11.0) for the gefitinib arm (the median follow-up duration was 22.1 months). The probability of being event-free at 24 months was 30.6% (95% CI: 23.8, 37.5) in the dacomitinib arm and 9.6% (95% CI: 5.6, 15.0) in the gefitinib arm.

Kaplan-Meier curves of PFS per IRC (ITT-PFS population)

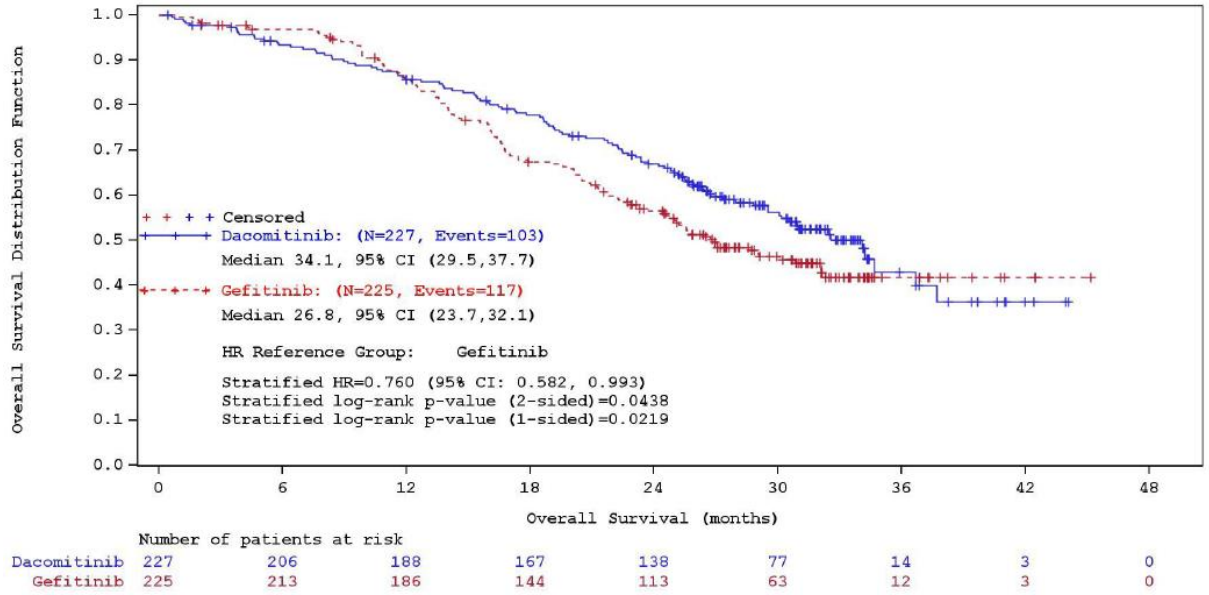


There was no statistically significant difference in the ORR between the dacomitinib and gefitinib arms, 74.9% vs 71.6%, respectively (p=0.1942). However, the duration of response in responders was significantly longer with dacomitinib compared to gefitinib (14.8 months (95% CI: 12.0, 17.4) vs 8.3 months (95% CI: 7.4, 9.2)), which might have driven the PFS improvement in the dacomitinib arm. In addition, 5.3% of subjects who received dacomitinib achieved complete responses, compared to 1.8% of subjects in the gefitinib arm. There were approximately 69% of partial responders in both arms.

The median OS was 34.1 months (95% CI: 29.5, 37.7) in the dacomitinib arm and 26.8 months (95% CI: 23.7, 32.1) in the gefitinib arm, which corresponded to an improvement of 7.3 months. While the final readout of OS was statistically significant (HR:0.760; 95% CI: 0.582, 0.993; p-value=0.0219) when assessed on its own, due to the pre-planned hierarchical testing the final OS analysis could not be considered statistically significant as the ORR (per blinded IRC review) was not statistically significant The separation between the KM curves in favour of dacomitinib was evident between 12 months and 36 months. Although the KM curves were in favour of gefitinib in the first 12 months, the number of deaths were comparable between the

two arms. The censoring post 30 months with cross-over explained the crossing of the curves at 36 months, however the long-term extended follow-up (median duration of 47.9 months), showed a separation of the curves beyond 36 months.

Kaplan Meier curves of OS (ITT-OS population)



Subgroup analyses based on age, gender or ECOG status demonstrated a consistent PFS benefit from dacomitinib treatment. Patients with both types of activating mutations (exon 19 deletion and Leu858Arg mutation in exon 20) showed statistically significant PFS improvement with dacomitinib compared to gefitinib. There was no statistically significant difference in PFS between the treatment arms for the non-Asian subgroup (68.42% with dacomitinib vs 79.59% with gefitinib). However, OS in the non-Asian subgroup numerically favoured the dacomitinib arm (29.5 months vs 20.6 months).

Overall, the study demonstrated superiority with a 42% reduction risk of progression/deaths and a 6.5-month improvement in median PFS favouring the dacomitinib arm in locally advanced/metastatic NSCLC patients with sensitising EGFR mutations. ORR was comparable between the two treatment groups (74.9% for dacomitinib vs 71.6%) with no statistically significant difference but a longer duration of response was observed in dacomitinib arm. A numerical improvement of 7.3 months was demonstrated for OS for dacomitinib (34.1 months) versus gefitinib (26.8 months) with 24.0% lower risk of death in the dacomitinib arm than in the gefitinib.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of dacomitinib for first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations comprised a total of 451 patients (227 patients in the dacomitinib arm and 224 patients in the gefitinib arm) enrolled in the ARCHER study. The median number of cycles started was higher in the dacomitinib arm (17.0 cycles; range: 1 to 41 cycles) compared to gefitinib arm (13.0 cycles; range: 1 to 38 cycles). The median treatment duration was longer in the dacomitinib arm (66.6 weeks; range: 0.3 to 162.7 weeks) than in the gefitinib arm (52.1 weeks; range: 0.3 to 148.3 weeks). A higher

proportion of patients in the dacomitinib arm (78.0%) had at least 1 dose interruption compared with patients in the gefitinib arm (53.6%).

Overview of safety profile

AE n (%)	Dacomitinib (N=227)	Gefitinib (N=224)
Any TEAE	226 (99.6%)	220(98.2%)
Treatment-related TEAE	220 (96.9%)	213 (95.1%)
SAE	62 (27.3%)	50 (22.3%)
Treatment-related SAE	21 (9.3 %)	10 (4.5 %)
Discontinuations due to TEAE	40 (17.6 %)	27 (12.1%)
Deaths from all causes	76 (33.5%)	91 (40.6%)

n: number of patients meeting prespecified criteria; TEAE: treatment-emergent adverse event; SAE: serious adverse event

The most frequently reported treatment-related TEAEs (frequency ≥20% of patients) in the dacomitinib and gefitinib arms were diarrhoea (85% vs 51.3%), paronychia(61.7% vs 20.1%), dermatitis acneiform (48.9% vs 28.6%), stomatitis(41% vs 15.2%), dry skin (27.3% vs 16.1%), decreased appetite (25.1% vs 15.2%), and alopecia (20.3% vs 8.5%). Other AEs which were higher frequency in the dacomitinib arm than the gefitinib arm included mouth ulceration (12.3% vs 5.8%), pruritis (19.4% vs 12.9%), rash (17.2% vs 10.3%), Palmar-plantar erythrodysaestheisa syndrome (14.5% vs 3.1%), dermatitis (10.6% vs 3.1%), conjunctivitis (16.7% vs 2.7%) and decreased weight (10.6% vs 2.2%).

These AEs were consistent with that seen with other EGFR TKIs and mainly related to gastrointestinal disorders, skin disorders and nail disorders. There were 4 cases of keratitis in dacomitinib arm compared to 0 in gefitinib arm (mostly Grade 1 or Grade 2 in severity and 2 cases of Grade 3 keratitis). No incidence of ulcerative keratitis (Grade 4) observed in this study. Due to the more potent and irreversible inhibition of EGFR by dacomitinib, keratitis incidence was higher and longer lasting than that with the reversible inhibitor gefitinib which has a shorter half-life. AEs were generally managed by dacomitinib dose reduction and/or temporary treatment discontinuation with standard concomitant medical therapy.

Treatment-related SAEs were reported for 21 patients (9.3%) in the dacomitinib arm and 10 patients (4.5%) in the gefitinib arm. Treatment-related SAEs reported for more than 1 patient in the dacomitinib arm were diarrhoea (5 patients [2.2%]), abdominal pain (2 patients [0.9%]), and liver injury (2 patients [0.9%]); while the only treatment-related SAE reported for more than 1 patient in the gefitinib arm was hepatic enzyme increased (2 patients [0.9%]). The overall frequency of TEAEs associated with temporary treatment discontinuation was higher in the dacomitinib arm (57.3%) than in the gefitinib arm (26.8%). The common reasons for treatment discontinuations in the dacomitinib arm were dermatitis, rash, paronychia, diarrhoea, stomatitis. The most common cause of death was disease progression and there were two AEs in dacomitinib arm which resulted in deaths probably related to study drug (acute kidney injury secondary to diarrhoea; Grade 3 drug induced liver injury).

The most commonly reported AEs of special interest were gastrointestinal (diarrhoea and associated AEs and stomatitis) and dermatologic (rash/dermatitis acneiform and their skin toxicities). These AEs are complications of EGFR tyrosine kinase inhibitor (TKI) therapy. These AEs were mostly Grade 1 or Grade 2 in severity and the frequency of permanent treatment discontinuations associated with these AEs was less than 2%.

Overall, the most commonly reported AEs were gastrointestinal, skin and nail-related and respiratory in nature. The majority of AEs were Grade 1 to Grade 3 in severity and managed using temporary dosing interruption or dose reduction with standard concomitant medical therapy. Overall, the safety profile was similar to that known for EGFR inhibitors, however, some were of higher frequency and lasted longer than gefitinib, probably due to higher potency and irreversible binding which resulted in a longer duration of action.

E ASSESSMENT OF BENEFIT-RISK PROFILE

NSCLC is one of the most common cancers in Singapore in both men and women.. The efficacy of dacomitinib, which is a novel TKI, in the target patient population was adequately supported by the pivotal study, which demonstrated that treatment with dacomitinib statistically significantly improved PFS by 5.5 months over gefitinib, as assessed by blinded IRC. This resulted in a 41.1% lower risk of disease progression or death in the dacomitinib arm than in the gefitinib arm. PFS benefit was consistent across all prespecified subgroups and supported by significant improvements in the secondary endpoints of PFS, DoR and OS endpoints.

Dacomitinib therapy was associated with higher incidences of SAE, treatment-related SAE and discontinuation due to TEAE compared to gefinitib. However, the safety profile was overall typical of patients with NSCLC treated with an EGFR TKI and the higher incidences observed with dacomitinib were not unexpected due to its potency.. The most notable safety concerns were gastrointestinal (diarrhoea and associated AEs and stomatitis) and dermatologic (rash/dermatitis acneiform and their skin toxicities). These risks have been adequately addressed in the package insert via the provision of relevant warnings and precautions, as well as dose adjustment recommendations in the event of toxicities.

Overall, the benefit-risk profile of dacomitinib was considered favourable for the first-line treatment of with locally advanced or metastatic NSCLC with EGFR-activating mutations (exon 19 deletion, L858R exon 21 substitution).

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk profile of dacomitinib for the first-line treatment of with locally advanced or metastatic NSCLC with EGFR-activating mutations (exon 19 deletion, L858R exon 21 substitution) was deemed favourable and approval of the product registration was granted on 25 June 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

VIZIMPRO FILM-COATED TABLETS

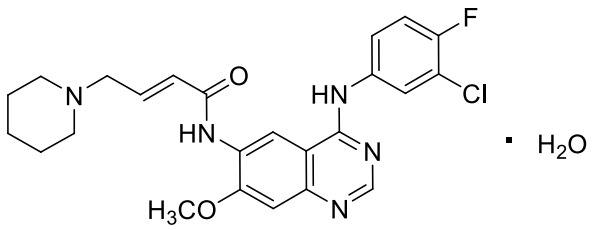
Dacomitinib

1. NAME OF THE MEDICINAL PRODUCT

VIZIMPRO 15 mg film-coated tablets
VIZIMPRO 30 mg film-coated tablets
VIZIMPRO 45 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dacomitinib monohydrate is a kinase inhibitor with a molecular formula of $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$ and a molecular weight of 487.95 Daltons (or 469.94 Daltons as dacomitinib anhydrate). The chemical structure of dacomitinib monohydrate is**:**



Dacomitinib is a white to pale yellow powder with pKa values of 5.0 and 8.5.

Each film-coated tablet contains dacomitinib monohydrate equivalent to 15 mg or 30 mg or 45 mg of dacomitinib. For the full list of excipients, see section 6.1 (List of excipients).

3. PHARMACEUTICAL FORM

Film-coated tablets.

VIZIMPRO 15 mg film-coated tablets
Tablet size of 6.35 mm with de-bossing of ‘Pfizer’ on one side and ‘DCB 15’ on the opposite side.

VIZIMPRO 30 mg film-coated tablets
Tablet size of 7.5 mm with de-bossing of ‘Pfizer’ on one side and ‘DCB 30’ on the opposite side.

VIZIMPRO 45 mg film-coated tablets
Tablet size of 9.0 mm with de-bossing of ‘Pfizer’ on one side and ‘DCB 45’ on the opposite side.

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 (exon 19 deletion or exon 21 L858R substitution 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) or moderate (Child-Pugh class B) hepatic impairment. VIZIMPRO has not been studied in patients with 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

Hypersensitivity to the active substance or to any of the excipients.

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). Patients with a history of ILD have not been studied.

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. Concomitant use of medicinal products predominantly metabolised by CYP2D6 should be avoided unless such products are considered necessary (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Assessment of EGFR mutation status

When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Concomitant use with proton pump inhibitors (PPIs)

Concomitant use of proton pump inhibitors (PPIs) with dacomitinib should be avoided.

Eye

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with VIZIMPRO should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

VIZIMPRO should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also known to be an independent risk factor for keratitis and ulceration.

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. Concomitant use of medicinal products predominantly metabolised by CYP2D6 should be avoided (see Section 4.4 Special warnings and precautions for use). If concomitant use of such medicinal products is considered necessary, they should follow their respective labels for dose recommendation regarding coadministration with strong CYP2D6 inhibitors. 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. The impact of histamine-2 receptor (H2) antagonists on dacomitinib pharmacokinetics has not been studied. Dacomitinib may be administered 2 hours before or at least 10 hours after taking H2 receptor antagonists (see Section 5.2 Pharmacokinetic properties).

Effect of dacomitinib on drug transporters

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 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.

VIZIMPRO should not be used during pregnancy. 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 for SmPC by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC reported in patients with EGFR-activating mutations who received VIZIMPRO 45 mg as first-line therapy

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10
Metabolism and nutrition disorders	Decreased appetite Hypokalaemia[a]	Dehydration
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 fissures Dry skin[f] Nail disorder[g] Alopecia	Skin exfoliation[h] Hypertrichosis
General disorders and administration site conditions	Fatigue Asthenia	
Investigations	Weight decreased	

Abbreviations: CIOMS=Council for International Organizations of Medical Sciences; SOC=System Organ Class.

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.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000)

*. Fatal event.

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. Dry skin includes the following PTs: Dry skin, Xerosis.

g. 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.
h. Skin exfoliation (also referred to as Exfoliative skin conditions) includes the following PTs: Exfoliative rash, Skin exfoliation.

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).

Hepatotoxicity and transaminases increased

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) have been reported during treatment with VIZIMPRO. 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.

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) were reported in 22.0% of patients receiving VIZIMPRO and were Grades 1 to 3, with the majority Grade 1 (18.4%). 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.

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

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.

OS results from the final analysis (data cut-off date of 17-Feb-2017) when 48.7% of events had occurred showed a HR of 0.760 (95% CI: 0.582, 0.993) and a gain of 7.3 months in median OS (median OS: 34.1 months [95% CI: 29.5, 37.7] and 26.8 months [95% CI: 23.7, 32.1] in the dacomitinib and gefitinib arm, respectively). However, according to the hierarchical testing approach, the analysis was stopped with the testing of ORR as the statistical significance was not reached. Therefore, the statistical significance of OS improvement could not be formally assessed, 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	**Gefitinib**

	N=227	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.

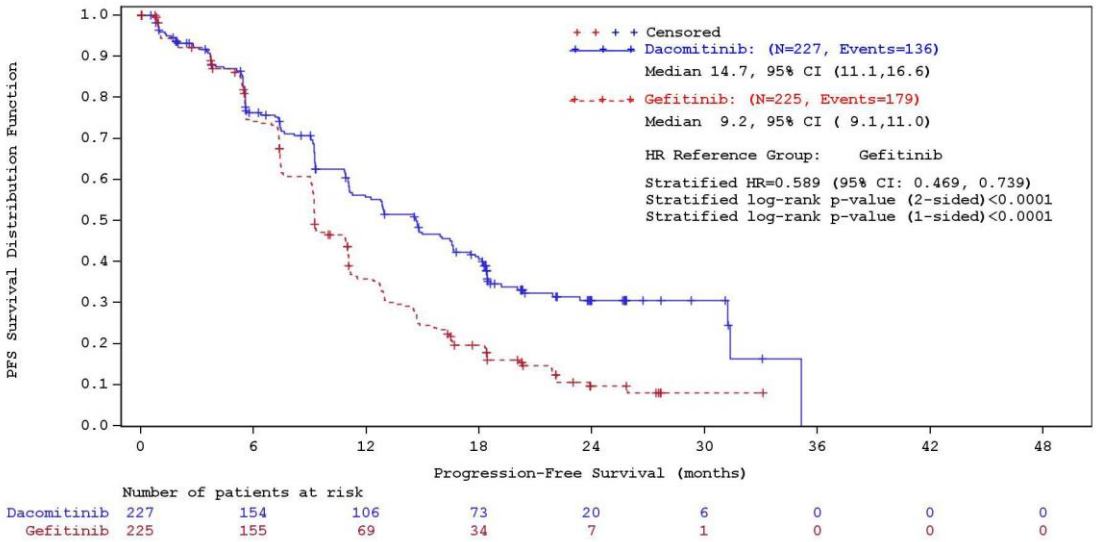
a. From stratified Cox Regression. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21) at randomization per IWRS.

b. Based on the stratified log-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.

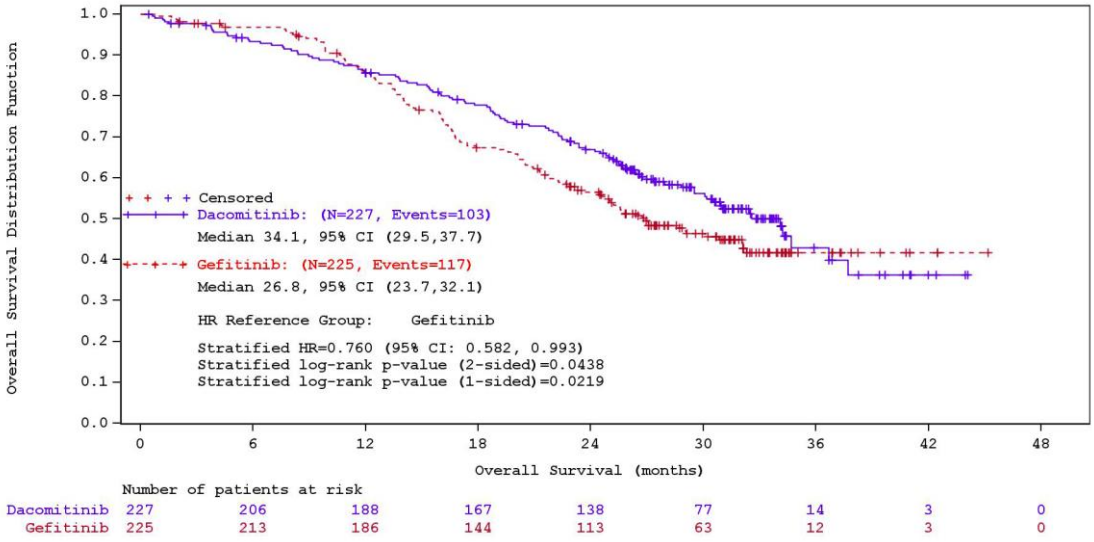
d. Analysis was based on the ITT population with patients without response being given a duration of zero and considered an event.

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 patients, there was no apparent effect of local antacid administration on C_{max} and AUC_{inf} of dacomitinib. Local antacids may be used if needed. The impact of histamine-2 (H2) receptor antagonists on dacomitinib pharmacokinetics has not been studied. Dacomitinib may be administered 2 hours before or at least 10 hours after taking H2 receptor antagonists.

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 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.

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
Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate

Film coating

Opadry II Blue 85F30716 containing:
Polyvinyl alcohol – part hydrolysed (E1203), Talc (E553b), Titanium dioxide (E171), Macrogol/PEG 3350 (E1521), FD&C Blue #2/Indigo Carmine Aluminium Lake (E132)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Refer to Expiry date on outer carton

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

Aluminium/aluminium blister containing 10 film-coated tablets. Each pack may contain 10 or 30 film-coated tablets.

Not all pack sizes are marketed.

6.6. Special precautions for disposal and other handling

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

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street

New York 10017, USA

8. DATE OF REVISION OF THE TEXT

VIM-SIN-1118/1
Date of last revision: March 2020