SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vizimpro 45 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

4.2 Posology and method of administration

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

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

Posology

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

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 reactions are provided in Table 2 (see sections 4.4 and 4.8).

Table 1. Recommended dose modifications for Vizimpro adverse reactions

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

Table 2. Dose modification and management for Vizimpro adverse reactions

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

	• For Grade 1 exfoliative skin conditions, no dose modification is required. Initiate treatment (e.g., oral antibiotics and topical steroids). • For Grade 2 rash, erythematous or exfoliative skin conditions, no dose modification is required. Initiate treatment or provide additional treatment (e.g., oral antibiotics and topical steroids). • If Grade 2 rash, erythematous or exfoliative skin conditions persist for 72 hours despite treatment, withhold dacomitinib. Upon recovery to Grade ≤ 1, resume dacomitinib at the same dose level or consider a reduction of 1 dose level. • For Grade ≥ 3 rash, erythematous or exfoliative skin conditions, withhold dacomitinib. Initiate or continue treatment and/or provide additional treatment (e.g., broad spectrum oral or intravenous antibiotics and topical steroids). Upon recovery to Grade ≤ 1, resume dacomitinib with a reduction of 1 dose level.
Other	• For Grade 1 or 2 toxicity, no dose modification is required. • For Grade ≥ 3 toxicity, withhold dacomitinib until symptoms resolve to Grade ≤ 2. Upon recovery, resume dacomitinib with a reduction of 1 dose level.

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. The starting dose of Vizimpro should be adjusted to 30 mg once daily in patients with severe (Child-Pugh class C) hepatic impairment. The dose may be increased to 45 mg once daily based on individual safety and tolerability after at least 4 weeks of treatment (see section 5.2).

Renal impairment
No starting dose adjustments are required when administering Vizimpro to patients with mild or moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min). Limited data are available in patients with severe renal impairment (CrCl < 30 mL/min). No data are available in patients requiring haemodialysis. Thus no dosing recommendations can be made for either patient population (see section 5.2).

Elderly population
No starting dose adjustment of Vizimpro in elderly (≥ 65 years of age) patients is required (see section 5.2).

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

Method of administration

Vizimpro is for oral use. The tablets should be swallowed with water and can be taken with or without meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

Interstitial lung disease (ILD)/Pneumonitis

ILD/pneumonitis, which could be fatal, has been reported in patients receiving Vizimpro (see section 4.8). Patients with a history of ILD have not been studied.

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

Diarrhoea

Diarrhoea, including severe diarrhoea, has been very commonly reported during treatment with Vizimpro (see section 4.8). Diarrhoea may result in dehydration with or without renal impairment, which could be fatal if not adequately treated.

Proactive management of diarrhoea should start at the first sign of diarrhoea especially within the first 2 weeks of starting dacomitinib, including adequate hydration combined with anti-diarrhoeal medicinal products and continued until loose bowel movements cease for 12 hours. Anti-diarrhoeal medicinal products (e.g., loperamide) should be used and, if necessary, escalated to the highest recommended approved dose. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib. Patients should maintain adequate oral hydration and patients who become dehydrated may require administration of intravenous fluids and electrolytes (see section 4.2).

Skin-related adverse reactions

Rash, erythematous and exfoliative skin conditions have been reported in patients treated with Vizimpro (see section 4.8).

For prevention of dry skin, initiate treatment with moisturizers, and upon development of rash, initiate treatment with topical antibiotics, emollients, and topical steroids. Start oral antibiotics and topical steroids in patients who develop exfoliative skin conditions. Consider adding broad spectrum oral or intravenous antibiotics if any of these conditions worsen to greater than or equal to Grade 2 severity. Rash, erythematous and exfoliative skin conditions may occur or worsen in areas exposed to the sun. Advise patients to use protective clothing and sunscreen before exposure to the sun. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib (see section 4.2).

Hepatotoxicity and transaminases increased

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) have been reported during treatment with Vizimpro (see section 4.8). Among NSCLC patients treated with dacomitinib 45 mg daily, there have been isolated reports of hepatotoxicity in 4 (1.6%) patients. Across the dacomitinib program, hepatic failure led to a fatal outcome in 1 patient. Therefore, periodic liver function testing is recommended. In patients who develop severe elevations in transaminases while taking dacomitinib, treatment should be interrupted (see section 4.2).

Medicinal products metabolised by cytochrome P450 (CYP)2D6

Vizimpro may increase exposure (or decrease exposure of active metabolites) of other medicinal products metabolised by CYP2D6. Concomitant use of medicinal products predominantly metabolised by CYP2D6 should be avoided unless such products are considered necessary (see section 4.5).

Other forms of interactions

Concomitant use of proton pump inhibitors (PPIs) with dacomitinib should be avoided (see section 4.5).

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.

Sodium

This medicinal product 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

Co-administration 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 24 healthy subjects indicated that co-administration of a single 45 mg dacomitinib dose with the PPI rabeprazole 40 mg once daily for 7 days decreased dacomitinib C_{max}, $AUC_{0\text{-}96h}$ (area under the concentration-time curve from time 0 to 96 hours), and AUC_{inf} (AUC from time 0 to infinity) (n=14) by approximately 51%, 39%, and 29%, respectively, when compared to a single 45 mg dose of dacomitinib administered alone. PPIs should be avoided while receiving treatment with dacomitinib (see section 4.4).

Based on data from observations in 8 patients from Study A7471001, there was no apparent effect of local antacid administration on C_{max} and AUC_{inf} of dacomitinib. Based on pooled data in patients, there was no apparent effect of histamine-2 (H2) receptor antagonists on steady-state trough concentration of dacomitinib (geometric mean ratio of 86% (90% CI: 73; 101). Local antacids and H2 receptor antagonists may be used if needed. Dacomitinib should be administered 2 hours before or at least 10 hours after taking H2 receptor antagonists.

Co-administration of dacomitinib and CYP2D6 substrates

Co-administration of single 45 mg oral dose of dacomitinib increased the mean exposure (AUC_{last} and C_{max}) of dextromethorphan, a probe CYP2D6 substrate, 855% and 874%, respectively, compared with administration of dextromethorphan alone. These results suggest that dacomitinib may increase exposure of other medicinal products (or decrease exposure to active metabolites) primarily metabolised by CYP2D6. Concomitant use of medicinal products predominantly metabolised by CYP2D6 should be avoided (see section 4.4). If concomitant use of such medicinal products is considered necessary, they should follow their respective labels for dose recommendation regarding co-administration with strong CYP2D6 inhibitors.

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).

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential/Contraception

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Vizimpro. Women of childbearing potential who are receiving this medicinal product should use adequate contraceptive methods during therapy and for at least 17 days (5 half-lives) after completing therapy.

Pregnancy

There are no data on the use of dacomitinib in pregnant women. Studies in animals have shown limited effects on reproductive toxicity (lower maternal body weight gain and food consumption in rats and rabbits, and lower foetal body weight and higher incidence of unossified metatarsals in rats only) (see section 5.3). Based on its mechanism of action, dacomitinib may cause foetal harm when administered to a pregnant woman. Dacomitinib should not be used during pregnancy. Female patients taking dacomitinib during pregnancy or who become pregnant while taking dacomitinib should be apprised of the potential hazard to the foetus.

Breast-feeding

It is not known whether dacomitinib and its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk, and because of the potential for serious adverse reactions in breast-fed infants from exposure to dacomitinib, mothers should be advised against breast-feeding while receiving this medicinal product.

Fertility

Fertility studies have not been performed with dacomitinib. Non-clinical safety studies showed reversible epithelial atrophy in the cervix and vagina of rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Vizimpro has minor influence on the ability to drive and use machines. Patients experiencing fatigue or ocular adverse reactions while taking dacomitinib should exercise caution when driving or operating machinery.

4.8 Undesirable effects

Summary of safety profile

The median duration of treatment with Vizimpro across the pooled data set was 66.7 weeks.

The most common (> 20%) adverse reactions in patients receiving dacomitinib were diarrhoea (88.6%), rash (79.2%), stomatitis (71.8%), nail disorder (65.5%), dry skin (33.3%), decreased appetite (31.8%), conjunctivitis (24.7%), weight decreased (24.3%), alopecia (23.1%), pruritus (22.4%), transaminases increased (22.0%), and nausea (20.4%).

Serious adverse reactions were reported in 6.7% of patients treated with dacomitinib. The most frequently (≥ 1%) reported serious adverse reactions in patients receiving dacomitinib were diarrhoea (2.0%), interstitial lung disease (1.2%), rash (1.2%), and decreased appetite (1.2%).

Adverse reactions leading to dose reductions were reported in 52.2% of patients treated with dacomitinib. The most frequently reported (> 5%) reasons for dose reductions due to any adverse reactions in patients receiving dacomitinib were rash (32.2%), nail disorder (16.5%), and diarrhoea (7.5%).

Adverse reactions leading to permanent discontinuation were reported in 6.7% of patients treated with dacomitinib. The most common (> 0.5%) reasons for permanent discontinuations associated with adverse reactions in patients receiving dacomitinib were: rash (2.4%), interstitial lung disease (2.0%), and diarrhoea (0.8%).

Tabulated list of adverse reactions

Table 3 presents adverse reactions for Vizimpro. Adverse reactions are listed according to system organ class (SOC). Within each SOC, the adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions reported in dacomitinib clinical studies (N=255)

System organ class	Very common	Common
Metabolism and nutrition disorders	Decreased appetite Hypokalaemia[a]	Dehydration
Nervous system disorders		Dysgeusia
Eye disorders	Conjunctivitis[b]	Keratitis
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease*[c]
Gastrointestinal disorders	Diarrhoea* Stomatitis[d] Vomiting Nausea	
Skin and subcutaneous tissue disorders	Rash[e] Palmar-plantar erythrodysaesthesia syndrome Skin fissures Dry skin[f] Pruritus[g] Nail disorder[h] Alopecia	Skin exfoliation[i] Hypertrichosis
General disorders and administration site conditions	Fatigue Asthenia	
Investigations	Transaminases increased[j] Weight decreased	

Data based on pool of 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.

* Fatal events were reported.

[a] Hypokalaemia includes the following preferred terms (PTs): Blood potassium decreased, Hypokalaemia.

[b] Conjunctivitis includes the following PTs: Blepharitis, Conjunctivitis, Dry eye, 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, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular.

[f] Dry skin includes the following PTs: Dry skin, Xerosis.

[g] Pruritus includes the following PTs: Pruritus, Rash pruritic.

[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.

[i] Skin exfoliation (also referred to as Exfoliative skin conditions) includes the following PTs: Exfoliative rash, Skin exfoliation.

[j] Transaminases increased includes the following PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased.

Description of selected adverse reactions

Very common adverse reactions in patients occurring in at least 10% of patients in Study ARCHER 1050 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 4.

Table 4. Very common adverse reactions in Phase 3 Study ARCHER 1050 (N=451)

	Dacomitinib (N=227)			**Gefitinib (N=224)**		
Adverse Reactions[a]	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Metabolism and nutrition disorders						
Decreased appetite	30.8	3.1	0.0	25.0	0.4	0.0
Hypokalaemia[b]	10.1	4.0	0.9	5.8	1.8	0.0
Eye disorders						
Conjunctivitis[c]	23.3	0.0	0.0	8.9	0.0	0.0
Gastrointestinal disorders						
Diarrhoea[d]	87.2	8.4	0.0	55.8	0.9	0.0
Stomatitis[e]	69.6	4.4	0.4	33.5	0.4	0.0
Nausea	18.9	1.3	0.0	21.9	0.4	0.0
Skin and subcutaneous tissue disorders						
Rash[f]	77.1	24.2	0.0	57.6	0.9	0.0
Palmar-plantar erythrodysaesthesia syndrome	14.5	0.9	0.0	3.1	0.0	0.0
Dry skin[g]	29.5	1.8	0.0	18.8	0.4	0.0
Pruritus[h]	20.3	0.9	0.0	14.3	1.3	0.0
Nail disorder[i]	65.6	7.9	0.0	21.4	1.3	0.0
Alopecia	23.3	0.4	0.0	12.5	0.0	0.0
General disorders and administration site conditions						
Asthenia	12.8	2.2	0.0	12.5	1.3	0.0
Investigations						
Transaminases increased[j]	23.8	0.9	0.0	40.2	9.8	0.0
Weight decreased	25.6	2.2	0.0	16.5	0.4	0.0

[a] Only adverse reactions with ≥ 10% incidence in the dacomitinib arm are included.
[b] Hypokalaemia includes the following preferred terms (PTs): Blood potassium decreased, Hypokalaemia.
[c] Conjunctivitis includes the following PTs: Blepharitis, Conjunctivitis, Dry eye, Noninfective conjunctivitis.
[d] 1 fatal event was reported in the dacomitinib arm.
[e] Stomatitis includes the following PTs: Aphthous ulcer, Cheilitis, Dry mouth, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, Stomatitis.
[f] Rash includes the following PTs: Acne, Dermatitis acneiform, Erythema, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular.
[g] Dry skin includes the following PTs: Dry skin, Xerosis.
[h] Pruritus includes the following PTs: Pruritus, Rash pruritic.

Table 4. Very common adverse reactions in Phase 3 Study ARCHER 1050 (N=451)

	Dacomitinib (N=227)			Gefitinib (N=224)		
Adverse Reactions[a]	**All Grades %**	**Grade 3 %**	**Grade 4** %	**All Grades %**	**Grade 3 %**	**Grade 4** %

[i] Nail disorder includes the following PTs: Ingrowing nail, Nail discolouration, Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia.

[j] Transaminases increased includes the following PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased.

Interstitial lung disease (ILD)/Pneumonitis
ILD/pneumonitis adverse reactions were reported in 2.7% of patients receiving Vizimpro, and Grade ≥ 3 ILD/pneumonitis adverse reactions were reported in 0.8%, including a fatal event (0.4%) (see section 4.4).

The median time to the first episode of any grade ILD/pneumonitis was 16 weeks and the median time to the worst episode of ILD/pneumonitis was 16 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 ILD/pneumonitis was 13 weeks and 1.5 weeks, respectively (see section 4.4).

Diarrhoea
Diarrhoea was the most frequently reported adverse reaction in patients receiving Vizimpro (88.6%) and Grade ≥ 3 diarrhoea adverse reactions were reported in 9.4% of patients. In a clinical study, one patient (0.4%) had a fatal outcome (see section 4.4).

The median time to the first episode of any grade diarrhoea was 1 week and the median time to the worst episode of diarrhoea was 2 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 diarrhoea was 20 weeks and 1 week, respectively (see section 4.4).

Skin-related adverse reactions
Rash, erythematous and exfoliative skin condition adverse reactions were reported in 79.2% and 5.5%, respectively, of patients receiving Vizimpro. Skin-related adverse reactions were Grades 1 to 3. Grade 3 rash and erythematous skin condition adverse reactions were the most frequently reported Grade 3 adverse reactions (25.5%). Grade 3 exfoliative skin conditions were reported in 0.8% of patients (see section 4.4).

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 dacomitinib. The median duration of any grade and Grade ≥ 3 rash and erythematous skin conditions was 53 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.

Transaminases increased
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%) (see section 4.4).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple
App Store.

4.9 Overdose

The adverse reactions observed at doses greater than 45 mg once daily were primarily gastrointestinal, dermatological, and constitutional (e.g., fatigue, malaise, and weight loss).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic 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 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.

Clinical efficacy

Vizimpro in first-line treatment of NSCLC patients with EGFR-activating mutations (ARCHER 1050)
The efficacy and safety of Vizimpro was studied in a Phase 3 study (ARCHER 1050) conducted in patients with locally advanced, not amenable to curative surgery or radiotherapy, or metastatic NSCLC harbouring activating mutations of EGFR, to demonstrate the superiority of dacomitinib versus gefitinib. A total of 452 patients were randomised 1:1 to dacomitinib or gefitinib in a multicentre, multinational, randomised, 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 randomisation 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 standardised and commercially available test kit.

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), and overall survival (OS).

The demographic characteristics of the overall study population were 60% female; median age at enrolment was 62 years with 10.8% being ≥ 75 years old. Thirty percent had baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 and 70% had ECOG PS 1; 59% had an exon 19 deletion, and 41% had a L858R mutation in exon 21. Race was 23% White, 77% Asian, and < 1% Black. Patients with brain metastases or leptomeningeal disease or ECOG PS ≥ 2 were excluded from the study.

A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomised to dacomitinib compared with those randomised to gefitinib, see Table 5 and Figure 1. Subgroup analyses of PFS per IRC review based on baseline characteristics were consistent with those from the primary analysis of PFS. In particular, the hazard ratios (HRs) for PFS per IRC review in Asian and non-Asian patients were 0.509 (95% CI: 0.391, 0. 662) and 0.889 (95% CI: 0.568, 1.391), respectively. In Asian patients, median PFS was 16.5 months for dacomitinib arm and 9.3 months for gefitinib arm. In non-Asian patients, median PFS was 9.3 months for dacomitinib arm and 9.2 months for gefitinib arm.

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.

Table 5. 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	
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	

Data based on data cut-off date of 29 July 2016.

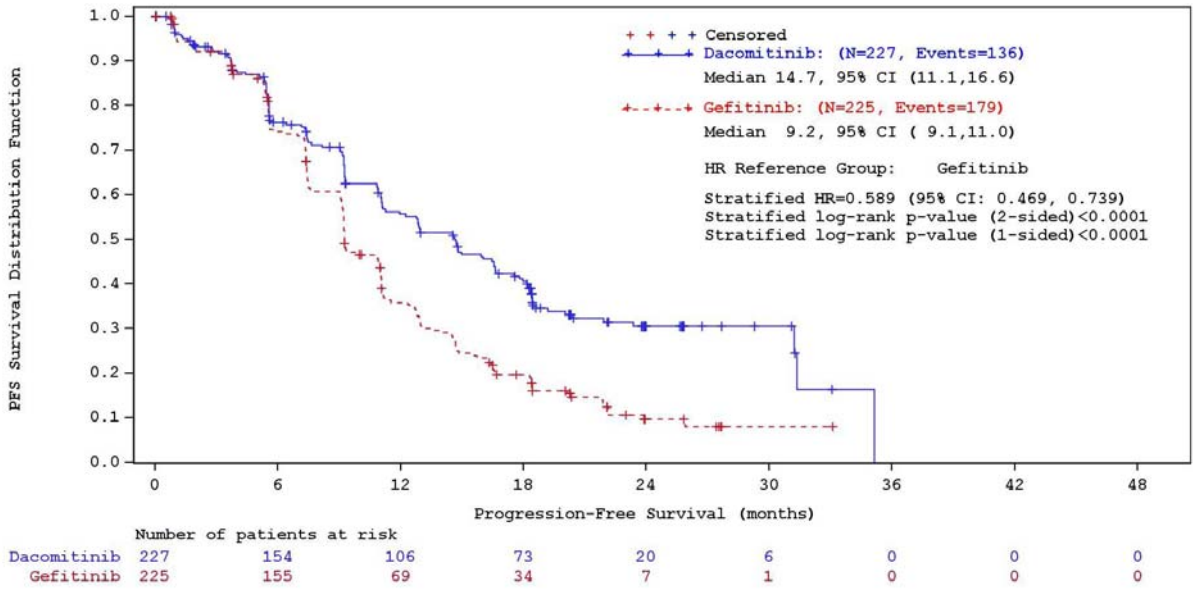
Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; IRC=independent radiologic central; ITT=Intent-to-treat; IWRS=interactive web response system; N/n=total number; NSCLC=non-small cell lung cancer; PFS=progression-free survival; DoR=Duration of Response.

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

b. Based on the stratified log-rank test. The stratification factors were Race (Japanese vs mainland Chinese and other East Asian vs non-East Asian) and EGFR mutation status (exon 19 deletion vs the L858R mutation in exon 21) at randomisation per IWRS.

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

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with dacomitinib in all subsets of the paediatric population in NSCLC indication (see section 4.2 for information on paediatric use).

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% (range: 65% to 100%) 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 is a substrate for the membrane transport proteins P-gp and BCRP. However, based on the oral bioavailability of 80%, these membrane transport proteins are unlikely to have any impact on dacomitinib absorption.

Distribution

Dacomitinib is extensively distributed throughout the body with a mean steady-state volume of distribution of 27 L/kg (patient of 70 kg) [coefficient of variation (CV%): 18%] following intravenous administration. In plasma, dacomitinib binds to albumin and α_1-acid glycoprotein and the fraction unbound is approximately 2% *in vitro* and *ex vivo* in healthy volunteers.

Biotransformation

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 faeces, dacomitinib, O-desmethyl dacomitinib, a cysteine conjugate of dacomitinib, and a mono-oxygenated metabolite of dacomitinib were the major drug-related components. *In vitro* studies indicated that CYP2D6 was the major CYP isozyme involved in the formation of O-desmethyl dacomitinib, while CYP3A4 contributed to the formation of other minor oxidative metabolites. O-desmethyl dacomitinib accounted for 16% of human plasma radioactivity and is formed mainly by CYP2D6 and to a lesser extent CYP2C9. The inhibition of CYP2D6 translated into approximately a 90% reduction in metabolite exposure and an approximate 37% increase in dacomitinib exposure.

Other information on drug-drug interactions

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. *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, OCT2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3, but may inhibit the activity of P-gp (in the 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.

Elimination

The plasma half-life of dacomitinib ranges from 54 to 80 hours. Dacomitinib showed a clearance of 20.0 L/hr with an inter-individual variability of 32% (CV%). In 6 healthy male subjects given a single-oral dose of [^{14}C] radiolabeled dacomitinib, a median of 82% of the total administered radioactivity was recovered in 552 hours; faeces (79% of dose) was the major route of excretion, with 3% of the dose recovered in urine, of which < 1% of the administered dose was unchanged dacomitinib.

Special populations

Age, race, gender, body weight
Based on population pharmacokinetic analyses, patient age, race (Asian and non-Asian), gender, and body weight do not have a clinically relevant effect on predicted steady-state exposure of dacomitinib. Approximately 90% of patients included in this analysis were Asian or White.

Hepatic impairment
In a dedicated hepatic impairment study, following a single-oral dose of 30 mg Vizimpro, dacomitinib exposure (AUC_{inf} 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 study, following a single oral dose of 30 mg Vizimpro, dacomitinib exposure was unchanged for AUC_{inf} and increased by 31% for C_{max} in subjects 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.

Renal impairment
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. Limited pharmacokinetic data are available in patients with severe renal impairment (CrCl < 30 mL/min) (N=4). The pharmacokinetics in patients requiring haemodialysis have not been studied.

Exposure response relationships
No clear relationship between dacomitinib exposure and efficacy could be characterised over the exposure range studied. Significant exposure-safety relationship was defined for Grade ≥ 3 rash/dermatitis acneiform, other skin toxicities, diarrhoea and Grade ≥ 1 stomatitis.

5.3 Preclinical safety data

Repeated-dose toxicity

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

Genotoxicity

Dacomitinib was tested using a series of genetic toxicology assays. Dacomitinib was not mutagenic in a bacterial reverse mutation (Ames) assay, and not clastogenic or aneugenic in the *in vivo* bone marrow micronucleus assay in male and female rats. Dacomitinib was clastogenic in the *in vitro* human lymphocyte chromosome aberration assay at cytotoxic concentrations. Dacomitinib is not directly reactive toward DNA as evidenced by the negative response in the bacterial reverse mutation assay and did not induce chromosome damage in a bone marrow micronucleus assay at concentrations up to approximately 60-70 times the unbound AUC or C_{max} at the recommended human dose. Thus, dacomitinib is not expected to be genotoxic at clinically relevant exposure concentrations.

Carcinogenicity

Carcinogenicity studies have not been performed with dacomitinib.

Impairment of fertility

Fertility studies have not been performed with dacomitinib. In repeat-dose toxicity studies with dacomitinib, effects on reproductive organs were observed in female rats given approximately 0.3 times the unbound AUC at the recommended human dose (for 6 months) and were limited to reversible epithelial atrophy in the cervix and vagina. There was no effect on reproductive organs in male rats given $\leq$ 2 mg/kg/day for 6 months (approximately 1.1 times the unbound AUC at the recommended human dose), or in dogs given $\leq$ 1 mg/kg/day for 9 months (approximately 0.3 times the unbound AUC at the recommended human dose).

Developmental toxicity

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

Phototoxicity

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

Environmental risk assessment

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

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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

Dacomitinib has the potential to be a very persistent, bioaccumulative and toxic substance (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1678

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

07/12/2023