NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	ARIA: Real-world utilization and outcomes with dacomitinib first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer among Asian patients – A multi-center chart review
Protocol number	A7471067
Protocol version identifier	3.0
Date	10 Jan 2022
EU Post Authorization Study (PAS) register number	EUPAS44543
Active substance	Protein kinase inhibitor (ATC code: L01XE), Dacomitinib (ATC code: L01XE47)
Medicinal product	Dacomitinib (VIZIMPRO®)
Research question and objectives	The overall objective is to describe the clinical and disease characteristics, therapeutic patterns of dacomitinib utilization and outcomes in an Asian advanced non-small cell lung cancer (NSCLC) epidermal growth factor receptor (EGFR) mutation-positive population treated with dacomitinib as a first-line treatment.
Author	PPD **, PhD** PPD , Pfizer Emerging Market Email: PPD PPD **, MA** PPD , Pfizer Patient Health and Impact

	PPD , **PhD** PPD , IQVIA PPD , **MBBS, PhD** PPD , IQVIA

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
AIDS	acquired immune deficiency syndrome
ARCHER 1050	Randomised, open-label, phase 3 trial of dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer
ARIA	Advanced NSCLC Real World Study of DacomItinib in Asian patients
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
ATP	adenosine triphosphate
CDE	Center for Drug Evaluation
CI	confidence interval
CNS	central nervous system
CRF	case report form
CSA	clinical study agreement
DCT	data collection tool
DMP	data management plan
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ErbB	Erb-b2 receptor tyrosine kinases
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
ICD	informed consent document

Abbreviation	Definition
IEC	Independent Ethics Committee
IQR	interquartile range
IRB	Institutional Review Board
IV	intravenous
LAR	legally acceptable representative
NA	not applicable
NI	non-interventional
NCCN	National Comprehensive Cancer Network
NIS	Non-interventional study
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
OH (CCO)	Ontario Health (Cancer Care Ontario)
OS	overall survival
PAC	Post-Approval Commitment
PASS	Post-Authorization Safety Study
PFS	progression-free survival
RECIST	Response Evaluation Criteria In Solid Tumors
SAP	statistical analysis plan
SCLC	small cell lung cancer
SDV	source data verification
STD	standard deviation
SMP	study monitoring plan
TKI	tyrosine kinase inhibitor
TNM	Tumor, Node and Metastasis
TTF	time-to-treatment failure
U.S.	United States
WHO	World Health Organization
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Wong, Chew Hooi, PhD	Scientific Expert, Lung Cancer, Pfizer Emerging Market	Pfizer (Sponsor)	80 Pasir Panjang Road, #16-81/82, MapleTree Business City, Singapore 117372
Ivanova, Jasmina, MA	Director, Global Health Economics and Outcomes Research, Pfizer Patient Health and Impact	Pfizer (Sponsor)	235 E 42nd St, New York, NY 10017, United States
Yeo, See-Hwee, PhD	Consultant, Real World Solutions	IQVIA	79 Anson Road #19-01, Singapore 079906
Foo, Chee Yoong, MBBS, PhD	Senior Consultant, Real World Solutions	IQVIA	301, Level 3, Uptown 1, 1, Jalan SS21/58, Damansara Uptown, 47400 Petaling Jaya, Malaysia

4. ABSTRACT

Title: ARIA: Real-world utilization and outcomes with dacomitinib first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer among Asian patients – A multi-center chart review

Version (date) of protocol: 3.0 (10 Jan 2022)

Name (affiliation) of main authors: PPD (Pfizer); PPD (Pfizer) PPD (IQVIA); PPD (IQVIA)

Rationale and background

Dacomitinib, a second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), was approved by the United States (U.S.) Food and Drug Administration (FDA) as treatment for advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. In the ARCHER 1050 randomized trial, a statistically significant improvement in progression-free survival (PFS) was observed with dacomitinib compared to gefitinib.

There is currently a paucity of information on the real-world utilization of dacomitinib and associated clinical outcomes among Asian patients with EGFR mutation-positive advanced NSCLC. Understanding the characteristics, drug utilization and outcomes of these patients prescribed with dacomitinib represents an important step towards addressing the existing knowledge gaps.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the National Medical Products Administration (NMPA)'s Center for Drug Evaluation (CDE) of China.

Research objectives

The primary objectives are:

1. To describe demographics, as well as clinical and disease characteristics of patients on first-line dacomitinib therapy for treatment of EGFR mutation-positive advanced NSCLC.

2. To describe starting dose of dacomitinib as first-line therapy, dose modification (if any), related timing and reason for dose modification, interruption or discontinuation.

3. To describe duration of dacomitinib therapy and time-to-treatment failure (TTF).

The secondary objectives are:

4. To describe real-world PFS of patients.

5. To characterize all adverse events (AEs) for patients treated with dacomitinib.

6. To describe TTF, PFS, overall survival (OS) and AEs, as well as starting dose and dose modification of dacomitinib in a subgroup of patients with common EGFR mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China.

The exploratory objectives are:

7. To describe real-world OS of patients on first-line dacomitinib therapy.

8. To describe best tumor response to dacomitinib therapy.

9. To describe prevalence of T790M mutation emergence at disease progression to dacomitinib.

10. To describe subsequent treatments after permanent discontinuation of dacomitinib and the associated treatment durations.

Study design

This is a longitudinal, multi-center cohort study with mixed prospective and retrospective data collection. Data will be collected from eligible adults with EGFR mutation-positive advanced NSCLC treated with dacomitinib as first-line therapy from the date of advanced NSCLC diagnosis to the date of death, lost to follow-up, withdrawal of consent or end of study, whichever occurs first.

Population and setting

Approximately fifteen tertiary cancer-treating hospitals in China, India and Malaysia are planned as participating sites.

Inclusion criteria for study population:

1. Adults (aged ≥18 years) with histology-confirmed advanced NSCLC (TNM stage IIIB-IV);

2. Presence of any EGFR-activating mutation (exon 19 deletion or exon 21 L858R substitution) or other uncommon EGFR mutations prior to anti-cancer treatment;

3. Initiating dacomitinib as first-line treatment for advanced NSCLC after confirmation of EGFR-mutation status (ie, no prior treatment with other EGFR TKI or systemic therapy);

4. Received dacomitinib after the following dates (which mark the marketing authorization date in China, or initiation of the compassionate use program in Malaysia and India);

- Patients from China: 01 July 2019;
- Patients from Malaysia and India: 01 August 2018;

5. Initiated dacomitinib no later than 20 months before end of data collection (to allow minimum of 20 months follow-up from dacomitinib initiation);

6. Had at least one follow-up visit after dacomitinib initiation unless there is a documented death in the patient records before a follow-up visit.

For prospective and mixed patients, there should be evidence of a personally signed and dated informed consent document (ICD) indicating that the patient (or a legally acceptable representative, LAR) has been informed of all pertinent aspects of the study.

Exclusion criteria:

1. Enrolled in any interventional clinical study or trial at time of study inclusion (however, patients enrolled in non-interventional, real world study may still be included).

Variables

Demographic and patient characteristics of interest include age, sex, ethnicity, country, weight, height, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, date of initial and advanced NSCLC diagnosis, NSCLC histopathological subtype, NSCLC staging (based on Tumor, Node and Metastasis, TNM), presence and location of metastasis, date of EGFR mutation test, type of EGFR mutation and NSCLC assessment.

Treatment variables of interest include dacomitinib dosing regimen (at initiation and after dose modification), duration of dacomitinib treatment, dates of dose modification, interruption or permanent discontinuation, concomitant treatment while on dacomitinib, as well as subsequent treatment and associated duration after permanent dacomitinib discontinuation.

Outcomes of interest include real-world OS, real-world PFS, T790 mutation status at progression, adverse events, reasons (including adverse events) resulting in dose modification, interruption or discontinuation, tumor response to dacomitinib (based on the Response Evaluation Criteria In Solid Tumors [RECIST] and/or clinician's judgement) and TTF for dacomitinib.

Data sources

Unstructured retrospective and/or prospective data from patients' hospital medical records will be abstracted manually by a trained research associate. Data will subsequently be

entered into a study-specific electronic data capture system (EDC) via a standardized electronic case report form (eCRF).

Study size

The total target number of patients is 300 from China, India and Malaysia. For China, the target number is at least 200 patients with a maximum number of 290 patients. As this is a descriptive cohort study with no a priori hypothesis, a power calculation was not performed.

Data analysis

There will be no hypothesis testing in this study. All statistical analyses will be descriptive and no *P*-values will be reported in this study.

Results will be presented using appropriate summary statistics. Categorical variables will be summarized using frequencies (counts) and percentages. Continuous variables will be summarized using means, standard deviations, medians and IQRs. Time-to-event data such as real-world OS, real-world PFS and TTF will be analyzed using the Kaplan-Meier method.

Outcomes including TTF, PFS, OS and AEs, as well as starting dose and dose modification of dacomitinib will be described for a subgroup of patients with common mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China. If data permits (depending on sample size), further subgroup analyses by starting dacomitinib dose, EGFR mutation subtype at baseline and country will be conducted for all patients.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	08 April 2021	• Addition of secondary objectives (Section 8) • Revision of inclusion criteria (Section 9.2.1)	• Added subgroup analysis for patients with common mutations enrolled in China • Added characterization of all adverse events • Allow inclusion of patients who died after dacomitinib initiation but before a follow-up visit	The protocol is amended to satisfy the requirements of the China regulatory agency as a post-approval commitment (PAC) for dacomitinib. This is not a PAC for India and there is no dacomitinib PAC requirement for Malaysia.
3.0	10 Jan 2022 2021	• Revision of Setting (Section 9.2) • Revision of Study Size (Section 9.5)	• Added a clause to state that the maximum number of patients from China is 290 • Added a clause to state that the maximum number of patients from China is 290	Due to the delay in study start-up in India and lower than expected recruitment rate in Malaysia, the maximum number of patients in China is increased to 290.

6. MILESTONES

Milestone	Planned date
Start of data collection	31 May 2021
End of data collection	28 Feb 2024 *
Final study report	31 Oct 2024 *

* Dates may change depending on study progress.

7. RATIONALE AND BACKGROUND

Lung cancer is the most prevalent cancer worldwide, accounting for about 2.1 million new cases (11.6% of all cancer cases) and 1.76 million deaths (18.4% of all cancer deaths) in 2018.[1] Lung cancer can be classified into two broad categories, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of all lung cancers cases.[2] The most common histological subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.

EGFR is an important driver oncogene in NSCLC, with mutations such as in the exon 19 or 21 tyrosine kinase domains commonly found in patients with this cancer.[3] Based on a recent systematic review and meta-analysis which includes 456 studies and 115,815 NSCLC patients, the overall pooled prevalence for EGFR mutations was 32.3% (95% confidence interval: 30.9-33.7%).[4] The prevalence is higher in Asia (38.4%), compared with 24.4% in America (North and South) and 14.1% in Europe.[4]

Recent clinical guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend all patients with advanced or metastatic NSCLC to receive EGFR mutation testing.[5,6] Based on a recent update in the NCCN guidelines, plasma-based testing for the T790M mutation should be considered at disease progression for patients on EGFR TKIs.[6] If plasma-based testing is negative, tissue-based testing with re-biopsy is strongly recommended. Hence, practitioners should consider scheduling the biopsy concurrently with plasma testing referral.

The approval of TKIs to selectively target tumors with EGFR activating mutations marked a revolutionary milestone in the management of NSCLC and signaled the dawn of precision medicine use in lung cancer. EGFR TKI therapy is now considered a standard-of-care first-line treatment for EGFR mutation-positive advanced NSCLC.[5,6]

First-generation EGFR TKIs (eg, gefitinib and erlotinib) reported improvements in PFS, over classical platinum doublet chemotherapy by inhibiting EGFR through competitive binding with ATP.[7,8] In comparison, second-generation TKIs (eg, afatinib and dacomitinib) have two key advantages: firstly, higher potency due to irreversible inhibition of EGFR and secondly, inhibition of the entire ErbB (EGFR, ERBB2, ERBB3, ERBB4) family of tyrosine kinases.[7,9] Dacomitinib, a second-generation irreversible EGFR TKI inhibitor, has shown efficacy in clinical studies among patients with NSCLC.[11] A phase 3 randomized open-label study (ARCHER 1050) conducted in seven countries directly compared dacomitinib with a first-generation EGFR TKI (gefitinib) as treatment for EGFR mutation-positive advanced NSCLC. In this study, dacomitinib (45 mg once daily orally) was reported to be superior to gefitinib (250 mg once daily orally) in improving both PFS and OS when given as first-line therapy.[11] Dacomitinib showed significantly longer median PFS over gefitinib (14.7 vs. 9.2 months).[11] In addition, patients achieved a median OS of 34.1 months when on dacomitinib, a marked improvement compared with gefitinib (26.8 months).[12-14]

Mutation emergence during EGFR TKI treatment inevitably results in drug resistance. Although numerous resistance mechanisms have been identified, the most common is an acquired missense mutation in exon 20 of EGFR (T790M).[15-17] Previous studies have estimated that T790M mutation is present in about half of the cases who acquired resistance to first-generation EGFR TKIs and afatinib.[18-20] In an open-label phase 2 trial of first-line dacomitinib (ARCHER 1017), among 15 (of 31) patients with detectable plasma EGFR mutations at the end of treatment, 8 (53%) were also T790M mutation-positive.[21]

Therapies targeted for EGFR are nonetheless playing an increasingly significant role in the treatment of advanced NSCLC. Dacomitinib is first approved by the U.S. FDA in September 2018, and subsequently by China's Center for Drug Evaluation (CDE) as first-line treatment for patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations in May 2019.[22] Dacomitinib has also obtained marketing approval in various other countries including Japan (January 2019), Hong Kong (October 2019), India (March 2020), Taiwan (January 2020), Korea (March 2020), Singapore (April 2020) and Malaysia (July 2020).

Currently, there is a paucity of information on the real-world utilization of dacomitinib and associated clinical outcomes among advanced NSCLC with EGFR-positive mutations in Asian patients. Based on favorable efficacy data on dacomitinib from clinical trials, this study is designed to collect complementary information on utilization of dacomitinib in an EGFR mutation-positive advanced NSCLC Asian population. In addition, this study will also describe disease characteristics and clinical outcomes of these patients. Findings from the study will help in addressing the knowledge gaps of dacomitinib.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the National Medical Products Administration (NMPA)'s CDE of China.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective is to describe the clinical and disease characteristics, therapeutic patterns of dacomitinib use and outcomes in Asian advanced NSCLC EGFR mutation-positive populations treated with dacomitinib as a first-line treatment.

The primary objectives are:

1. To describe demographics, as well as clinical and disease characteristics of patients on first-line dacomitinib therapy for treatment of EGFR mutation-positive advanced NSCLC.

2. To describe starting dose of dacomitinib as first-line therapy, dose modification (if any), related timing and reason for dose modification, interruption or discontinuation.

3. To describe duration of dacomitinib therapy and time-to-treatment failure (TTF).

The secondary objectives are:

4. To describe real-world PFS of patients.

5. To characterize all adverse events (AEs) for patients treated with dacomitinib.

6. To describe TTF, PFS, overall survival (OS) and AEs, as well as starting dose and dose modification of dacomitinib in a subgroup of patients with common EGFR mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China.

The exploratory objectives are:

7. To describe real-world OS of patients on first-line dacomitinib therapy.

8. To describe best tumor response to dacomitinib therapy.

9. To describe prevalence of T790M mutation emergence at disease progression to dacomitinib.

10. To describe subsequent treatments after permanent discontinuation of dacomitinib and the associated treatment durations.

9. RESEARCH METHODS

9.1. Study design

This is a longitudinal, multi-center cohort study with mixed prospective and retrospective data collection (Figure 1). As this is an observational real-world study, no investigative drug or intervention will be administered as part of study participation. Physicians will provide treatment based on their routine practices and in the best interests of the patients under their care.

A study patient is defined as an adult (aged ≥18 years) with EGFR mutation-positive advanced NSCLC treated with dacomitinib as first-line therapy within the study observation period (from January 2017 to June 2021). Patients could be given dacomitinib treatment during the pre-marketing authorization compassionate use program in India (from Dec 2018 to March 2020) and Malaysia (from Aug 2018 to July 2020) and/ after it is commercially available in China, India and Malaysia.

All patients with a documented diagnosis of NSCLC or a record of dacomitinib use will be screened for study eligibility. Data will be collected from the eligible patients from the date of advanced NSCLC diagnosis to the study endpoint (eg, date of death), lost to follow-up, withdrawal of consent or end of study (observation period), whichever occurs first.

Clinical data including characteristics, treatment and outcomes will be collected. Prospective patient identification will start from the study initiation date to the end of the enrollment period. After the end of enrollment period, only follow-up data will be collected and there will be no new identification of new prospective patients. The enrollment period may be shortened or extended depending on whether the target number of patients can be included into the study within the stipulated time. Retrospective patient identification and retrospective data collection will cover the observation period from January 2017 to study initiation date.

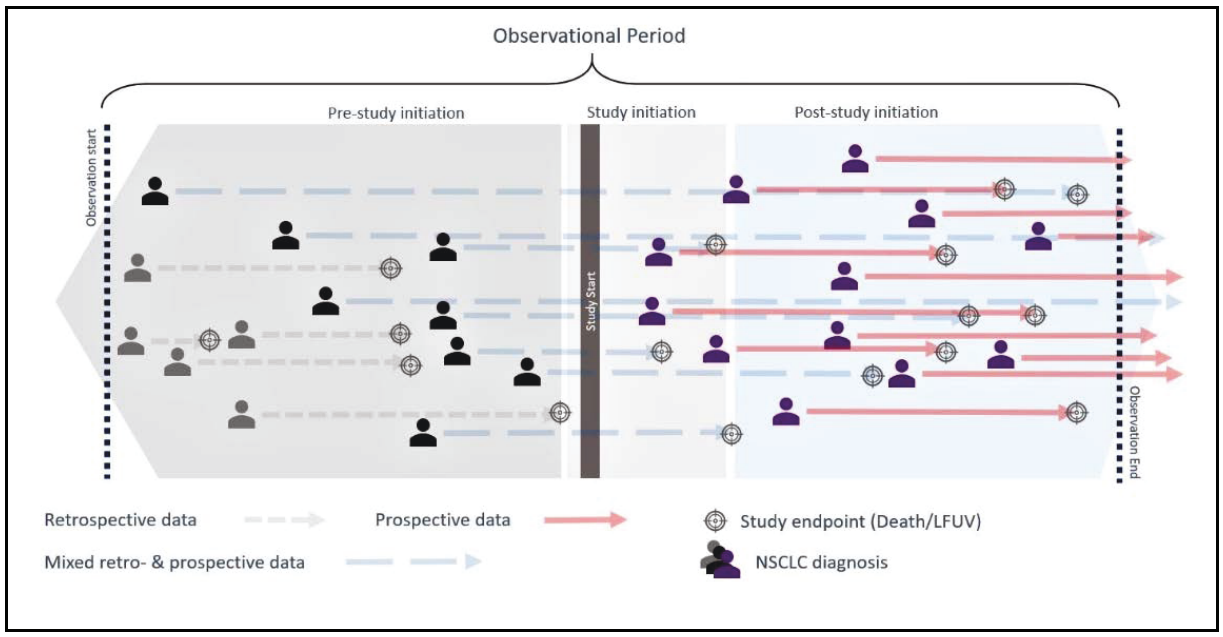
Three different approaches of data collection are further described below:

- For eligible patients who met the study inclusion and exclusion criteria before the study initiation date and have reached any of the study endpoints at or prior to the study initiation date (eg, died), their data will be retrospectively collected from the medical records (thereafter, these patients will be referred to as "retrospective patients").

- For eligible patients who met the study inclusion and exclusion criteria before the study initiation date and are continued to be followed up after the study initiation date, their data will be collected via a mix of retrospective chart abstraction and prospective data collection (thereafter, these patients will be referred to as "mixed patients").

- For eligible patients who met the study inclusion and exclusion criteria at or after the study initiation date, their data will be collected prospectively (thereafter, these patients will be referred to as "prospective patients"). Information will still be from existing healthcare data collection infrastructures within the participating sites.

Figure 1. Schematic Diagram of the Study Design and Planned Data Collection Approaches



9.2. Setting

Approximately fifteen tertiary cancer-treating hospitals in China, India and Malaysia are anticipated to be participating in this study. The total target number of NSCLC study patients is 300 for this study. For China, the target number is at least 200 patients with a maximum number of 290 patients. The inclusion and exclusion criteria for study participation are described in Sections 9.2.1 and 9.2.2.

Site selection criteria:

- Tertiary center providing lung cancer diagnosis and treatment;
- Center is able to provide access of dacomitinib to eligible NSCLC patients via commercial route or compassionate use program (Malaysia only);
- Availability of study resources to execute the study protocol;
- Interest in study participation.

Basic site information (eg, site size, investigator specialty, site type) will be collected via a site qualification survey.

Patient screening process for study eligibility will be performed as per below (Figure 2):

- For potential retrospective and mixed patients: All patients with advanced NSCLC and history of dacomitinib use (based on the inclusion criteria) during the retrospective observation period will be screened.

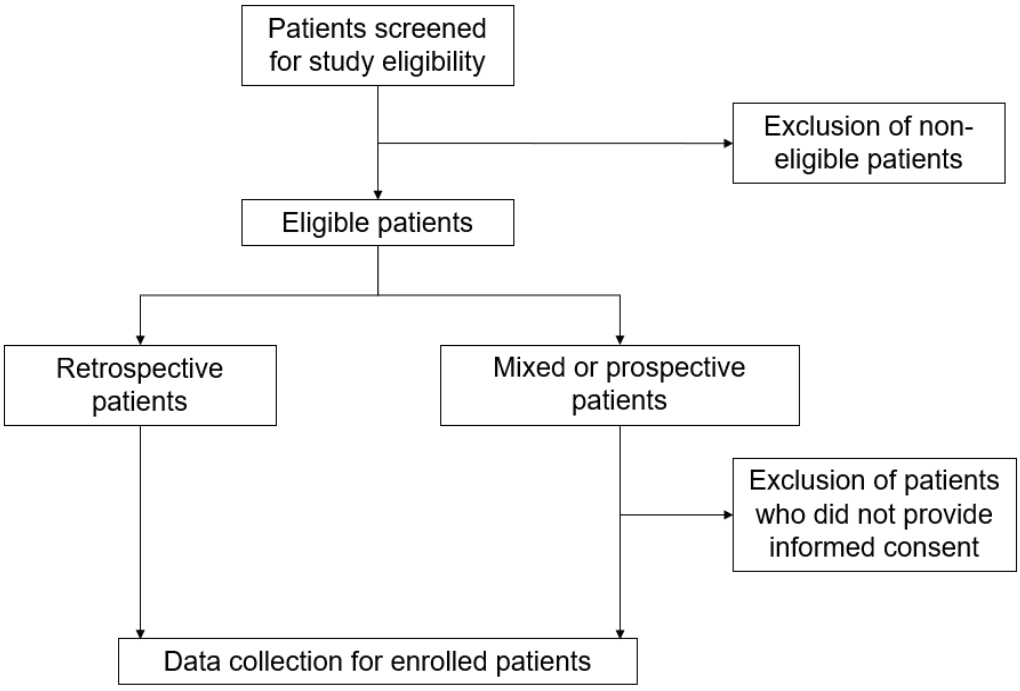
- For potential prospective patients: All patients with advanced NSCLC initiated with dacomitinib during the enrolment period (after study initiation date) will be screened.

- An informed consent waiver will be requested from the local Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for retrospective patients to allow data collection that contain no identifiable patient data. Mixed and prospective patients deemed eligible will be invited to participate in the study. An informed consent process will be carried out before data collection is conducted.

If informed consent waiver from IRB/IEC cannot be obtained for the potential retrospective patients and it is not possible to obtain consent from them (eg, patients have died), the enrolment period may need to be extended for enrolment of more prospective members to meet the target number of patients for this study.

A standardized screening form will be used. Screening of patients will be performed by either the site investigator(s) or a delegated clinical personnel assigned by the investigator. A screening log will be kept on all screened patients. Aggregated, non-identifiable/re-identifiable summary of the screening data will be provided to the study team.

Figure 2. Diagram for Patient Screening Process



9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Adult (aged ≥18 years) with histology-confirmed advanced NSCLC (TNM stage IIIB-IV);

2. Presence of any EGFR-activating mutation (exon 19 deletion or exon 21 L858R substitution) or other uncommon EGFR mutations prior to anti-cancer treatment;

3. Initiating dacomitinib as first-line treatment for advanced NSCLC after confirmation of EGFR-mutation status (ie, no prior treatment with other EGFR TKI or systemic therapy);

4. Received dacomitinib after the following dates (which mark the marketing authorization date in China, or initiation of the compassionate use program in Malaysia and India);

    - Patients from China: 1 July 2019;

    - Patients from Malaysia and India: 1 August 2018;

5. Initiated dacomitinib no later than 20 months before end of data collection (to allow minimum of 20 months follow-up from dacomitinib initiation);

6. Had at least one follow-up visit after dacomitinib initiation unless there was a documented death in the patient records before a follow-up visit.

In addition, for prospective and mixed patients, there should be evidence of a personally signed and dated informed consent document (ICD) indicating that the patient (or a legally acceptable representative, LAR) has been informed of all pertinent aspects of the study. This is subjected to obtaining an informed consent waiver for retrospective patients from the relevant IRB/IEC.

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Enrolled in any interventional clinical study or trial at time of study inclusion (however, patients enrolled in non-interventional, real world study may still be included).

9.3. Variables

All included patientswill be treated with dacomitinib. There will not be a control group. Variables for demographic and characteristics, treatment and outcomes are presented in Table 1. Baseline refers to the date of advanced NSCLC diagnosis.

Table 1. Key Variables of Interest and Data Collection Timepoints

Role	Variable	Baseline	Initiation of dacomitinib	Subsequent follow-up visits
Demographic and patient characteristics	• Date of birth (age).	X		
	• Sex.	X		
	• Ethnicity.	X		
	• Country.	X		
	• Body weight.	X		
	• Height.	X		
	• Smoking status (current smoker, former smoker, never smoker).	X		
	• Eastern Cooperative Oncology Group performance status (0 to 5).[a]	X	X	X
	• Comorbidities (based on Charlson Comorbidity Index).[b]	X		
	• Date of initial non-small cell lung cancer (NSCLC) diagnosis.	X		
	• Date of advanced NSCLC (TNM stage IIIB-IV) diagnosis.	X		
	• NSCLC	X		

Role	Variable	Baseline	Initiation of dacomitinib	Subsequent follow-up visits
	histopathological subtype.			
	• Clinical NSCLC staging (based on Tumor, Node and Metastasis, TNM).[c]	X	X	
	• Presence and location of metastasis (including central nervous system, CNS) at initial diagnosis and dacomitinib initiation.	X	X	
	• Date of epidermal growth factor receptor (EGFR) mutation test.	X		X
	• Method of EGFR testing.	X		X
	• Type of EGFR mutation detected.	X		X
	• NSCLC assessment based on the Response Evaluation Criteria In Solid Tumors (RECIST) and/or clinician's judgement.	X	X	X
Treatment	• Dacomitinib (first-line) initiation date.		X	
	• Dacomitinib initial dose and frequency.		X	
	• Dacomitinib (first/second) dose modification date.			X

Role	Variable	Baseline	Initiation of dacomitinib	Subsequent follow-up visits
	• Dacomitinib dose and frequency after (first/second) dose modification.			X
	• Dacomitinib (first/second) dosing interruption date			X
	• Dacomitinib permanent discontinuation date.			X
	• Second-line treatment after dacomitinib discontinuation.			X
	• Second-line treatment start and end dates.			X
	• Third-line treatment after dacomitinib discontinuation.			X
	• Third-line treatment start and end dates.			X
	• Fourth-line treatment after dacomitinib discontinuation.			X
	• Fourth-line treatment start and end dates.			X
	• Dacomitinib duration, last dose and frequency (if not permanently discontinued).			X
	• Concomitant treatment with dacomitinib (surgery, radiotherapy, chemotherapy).		X	X
Outcomes	• Real-world overall survival (OS).	X	X	X
	• Real-world progression-free survival (PFS).		X	X

Role	Variable	Baseline	Initiation of dacomitinib	Subsequent follow-up visits
	• Adverse events	X	X	X
	• T790M mutation status at progression (among those tested).			X
	• Reasons (including adverse events) resulting in dosing modification, interruption or permanent discontinuation of dacomitinib.			X
	• Time-to-treatment failure (TTF) for dacomitinib.		X	X
	• Tumor response to dacomitinib based on RECIST and/or clinician's judgment.		X	X

Abbreviations: CNS, central nervous system; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TNM, Tumor Node Metastasis; TTF, time-to-treatment failure.

a. See Annex 2A for more information.
b. See Annex 2B for more information.
c. See Annexes 2C and 2D for more information.

Operational definitions for outcomes are described in Table 2.

Table 2. Operational Definitions for Study Real-world Outcomes

Outcome	Definition
Real-world overall survival (OS)	• Measured from the date of dacomitinib initiation to the date of death from any cause. • The OS of patients who are still alive at the end of the follow-up period or who have dropped out from the follow-up with the treating center will be treated as censored survival events.
Real-world progression-free survival	• Defined as the date from first-line dacomitinib treatment start to disease progression or death from any cause,

Outcome	Definition
(PFS)	whichever comes first (first progression). • The PFS of patients who do not have disease progression or who have dropped out from the follow-up with the treating center will be treated as censored PFS events. • Progression will be based on radiologist's interpretation of the imaging and/or clinician's note/interpretation taking into consideration all patient records including diagnostic and laboratory test results. • The date of NSCLC progression will be the earliest reported date of a progression event based on the available sources of documentation. • The date of the second (or subsequent progression) will be documented after initiation of the second-line (or subsequent line) treatment.
T790M mutation emergence at disease progression	• Defined as whether a T790M mutation is detected at the time of disease progression among those who were tested.
Adverse events	• Defined as the presence of any adverse event with or without a documented evidence of dacomitinib dose modification, dosing interruption or permanent discontinuation, including but not limited to the below:[11] • Diarrhea; • Nausea or vomiting; • Constipation; • Stomatitis; • Mouth ulceration; • Rash or dermatitis (including dermatitis acneiform, rash and maculopapular rash); • Dry skin; • Pruritus; • Palmar-plantar erythrodysesthesia syndrome; • Paronychia; • Alopecia; • Decreased appetite; • Decreased weight;

Outcome	Definition
	• Cough; • Nasal mucosal disorder (including epistaxis, nasal inflammation, nasal mucosal ulcer and rhinitis); • Dyspnoea; • Upper respiratory tract infection; • Chest pain; • Pleural effusion; • Interstitial lung disease; • Conjunctivitis; • Pain in extremity; • Musculoskeletal pain; • Asthenia; • Insomnia; • Hematological abnormalities (including anemia and lymphopenia); • Electrolyte abnormalities; • Transaminitis or other hepatic abnormalities. • Dose modification is defined as any dose change (increase or decrease) from prior dacomitinib treatment regimen. • Dosing interruption is defined as dacomitinib treatment being temporarily stopped and subsequently restarted. • Dosing permanent discontinuation is defined as when there is no more dacomitinib treatment after stopping dacomitinib treatment.
Time-to-treatment failure (TTF) for dacomitinib	• Defined as time from dacomitinib initiation to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. • Patients who are lost to follow-up will be censored based on the last known contact/visit date.
Tumor response to dacomitinib	• Defined as the best response recorded from initiation of dacomitinib until disease progression measured using the Response Evaluation Criteria In Solid Tumors (RECIST) and/or based on clinician's judgement. • For RECIST, there must be at least one tumor which can be measured via radiology scans.

Outcome	Definition
	• The types of responses a patient may have are complete response, partial response, progressive disease or stable disease.

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time-to-treatment failure.

9.4. Data sources

Study data will be collected both prospectively and retrospectively from each participating site.

Retrospective data will be available in an unstructured form. Unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. Unstructured data will be abstracted manually by a trained research associate into a set of pre-specified data tables by completing a CRF and subsequently entered into a study-specific EDC via a standardized eCRF interface. The rules of abstraction will be detailed in the (to be developed) abstraction manual.

For prospective patients, investigators will be provided with a point of care data collection toolkit known as the source template. A source template is the paper CRF provided to assist the investigators in collecting high quality study data while focusing on attending to the patients' clinical needs under real-world settings. A study investigator will record the required study data into the source template during a patient's visit. An assigned and supervised research personnel (eg, a clinical research associate) will later assist the study investigator to transfer the recorded data from the source template to the eCRF. The filled source template will remain as part of the clinical document of the investigator and participating center.

Depending on the CRF design, structure and complexity, it may also be feasible for the investigator to enter the data directly into the eCRF. Programming of edit checks to identify discrepant data entered and to check for accuracy will be performed.

9.5. Study size

The number of study patients is expected to be 300 from approximately 15 sites in China, India and Malaysia according to the initial feasibility assessment (Table 3). It is expected that at least 200 patients with a maximum number of 290 patients will be from China.

As this is a descriptive cohort study with no a priori hypothesis, calculation of sample size and statistical power are not relevant.

Table 3. Expected Number of Sites in Each Country

Country	Number of planned sites
China	9
India	3
Malaysia	3
Total	15

9.6. Data management

A data management plan (DMP) will be developed during the database development phase and before data collection begins. The DMP will describe all functions, processes, and specifications for data collection, cleaning and validation.

All data collected for this study will be verified for their completeness and accuracy. High data quality standards will be maintained and processes/procedures utilized to ensure that the data are as clean and accurate as possible for analysis. Ambiguous data will be queried and resolved by communication with the respective study site and/or investigator. The eCRF will include programmed data quality checks to automatically detect if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters described in the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution. 10% of the critical data fields will be reviewed for 100% of the subjects.

Database will be locked after the completion of data cleaning and query resolution procedures. After database lock, any subsequent request for data change(s) will require the activation of the database unlock protocol. The unlock protocol will be described in the DMP.

Changes to the DMP will be documented in written protocol amendments. Major (ie, substantial or significant) amendments will usually require submission to the relevant IRB/IEC for approval. The amendments will be implemented only after approval has been obtained. Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will only be submitted to the relevant IRB/IEC if required by country regulations. Any amendment that could have an impact on the patient's agreement to participate in the study will require patient re-consenting (for prospective patients) before continuing with study participation.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these patients, data collected on the CRFs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless IQVIA and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP) which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. An interim analysis is planned at approximately 4 months after end of enrolment period, with feasibility depending on study progress and enrollment. A final study report will be prepared after completion and finalization of planned analyses.

There will be no hypothesis testing in this study. All statistical analyses performed will be descriptive and no *P*-values will be reported in this study.

Demographic and patient characteristics, treatment patterns and outcomes of EGFR mutation-positive advanced NSCLC patients initiated on dacomitinib will be described (Table 4).

Continuous variables will be summarized using means, standard deviations, medians and IQRs. Categorical variables will be summarized using frequencies (counts) and percentages. Time-to-event data such as real-world OS, PFS and TTF will be analyzed using the Kaplan-Meier method. Patients who are lost to follow-up or without the date of event occurrence will be censored. The numbers and reasons for censored data will be described.

Missing data will be minimized by:

- Ensuring key variables of interest are those routinely collected in actual clinical care and are available in the medical charts and notes;
- Collecting only important data variables aligned with study objectives to minimize site and patient burden;
- Including "Not applicable (NA)" or "Missing/Unknown" as options on CRF so missing values can be differentiated from those which are not applicable;
- Training of sites and data abstractors regarding data collection, as well as setting reporting time windows around target timepoints;
- Planning an interim analysis to characterize drop-outs or those lost to follow-up;
- Checking for patterns of missingness and addressing any issues encountered promptly.

The number of patients with missing data for each variable will be reported. No imputation is planned to address missing data in this study.

Outcomes including TTF, PFS, OS and AEs, as well as starting dose and dose modification of dacomitinib will be described for a subgroup of patients with common mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China. In addition, subgroup analysis may be conducted (only for OS, PFS and TTF) for all patients who tested positive with T790M mutation at disease progression and subsequently received any approved third-generation EGFR TKI, such as osimertinib or almonertinib.

If data permits (depending on sample size), further subgroup analyses by the below variables will be conducted for all patients:

- Starting dose of dacomitinib (15mg, 30mg or 45mg once daily);
- Last dose of dacomitinib (15mg, 30mg or 45mg once daily);
- Presence of metastasis at baseline (Yes or No);
- EGFR mutation subtypes at baseline.
  - Exon 19 deletion.
  - Exon 21 L858R substitution.
  - Other uncommon EGFR mutations.
- Country (China, India or Malaysia).

Subgroup analysis for retrospective patients and mixed/prospective patients may be conducted if the data quality and completeness varies significantly between retrospective and mix/prospective patients.

Table 4. Planned Analyses for Key Variables

Role	Variable	Analysis
Demographic and patient characteristics	• Date of birth.	• Age will be calculated from date of birth. • Use of mean/median and standard deviation (STD)/interquartile range (IQR).
	• Sex.	• Use of count and percentage.
	• Ethnicity.	• Use of counts and percentages.
	• Country.	• Use of counts and percentages.
	• Body weight.	• Body mass index will be calculated from weight and height.
	• Height.	

Role	Variable	Analysis
		• Use of mean/median and STD/IQR.
	• Smoking status (current smoker, former smoker, never smoker).	• Use of counts and percentages.
	• Eastern Cooperative Oncology Group (ECOG) performance status (0 to 5).[a]	• Counts and percentages of patients with different ECOG Grades.
	• Comorbidities (based on Charlson Comorbidity Index).[b]	• Use of count and percentage for each comorbidity.
	• Dates of initial and advanced non-small cell lung cancer (NSCLC) diagnosis and histopathological subtype.	• Counts and percentages of patients with different NSCLC histologic subtypes.
	• NSCLC staging (based on Tumor, Node and Metastasis, TNM).[c]	• Counts and percentages of patients at different NSCLC stages.
	• Presence and location of metastasis (including central nervous system, CNS).	• Count and percentage of patients with metastasis. • Counts and percentages for sites of metastasis.
	• Date of epidermal growth factor receptor (EGFR) mutation test.	• Count and percentage of patients tested for T790M mutation at disease progression.
	• Method of EGFR testing.	• Counts and percentages for methods of EGFR testing performed.
	• Type of EGFR mutation detected.	• Counts and percentages of the EGFR mutation subtypes at baseline and at disease progression.
	• NSCLC assessment based on the Response Evaluation Criteria In Solid Tumors (RECIST) and/or clinician's judgment.	• Counts and percentages of patients with different treatment responses.
Treatment	• Dacomitinib (first-line) initiation date.	• Mean ± STD and median (IQR) of time-to-dacomitinib initiation from NSCLC confirmation and from EGFR status confirmation.
	• Dacomitinib initial dose and	• Counts and percentages of

Role	Variable	Analysis
	frequency.	different doses of dacomitinib.
	• Dacomitinib dose and frequency after (first/second) dosing modification.	• Counts and percentages of different doses of dacomitinib. • Count and percentage of patients with at least one dose reduction.
	• Dacomitinib (first/second) dosing interruption date.	• Count and percentage of patients with at least one dosing interruption.
	• Dacomitinib permanent discontinuation date.	• Count and percentage of patients with dacomitinib permanent discontinuation. • Mean ± STD and median (IQR) of duration of first-line dacomitinib treatment from initiation to permanent discontinuation.
	• Second-line treatment start and end dates.	• Mean ± STD and median (IQR) of time to second-line treatment after dacomitinib discontinuation. • Mean ± STD and median (IQR) of duration of second-line treatment.
	• Second-line treatment after dacomitinib permanent discontinuation.	• Counts and percentages of second-line treatments after dacomitinib discontinuation.
	• Third-line treatment start and end dates.	• Mean ± STD and median (IQR) of time to third-line treatment after dacomitinib discontinuation. • Mean ± STD and median (IQR) of duration of third-line treatment.
	• Third-line treatment after dacomitinib permanent discontinuation.	• Counts and percentages of third-line treatments after dacomitinib discontinuation.
	• Fourth-line treatment start and end dates.	• Mean ± STD and median (IQR) of time to fourth-line treatment after dacomitinib discontinuation. • Mean ± STD and median (IQR) of duration of fourth-line treatment.
	• Fourth-line treatment after dacomitinib permanent discontinuation.	• Counts and percentages of fourth-line treatments after dacomitinib discontinuation.
	• Dacomitinib duration, last dose and frequency (if not discontinued).	• Mean ± STD and median (IQR) of duration of first-line dacomitinib treatment.

Role	Variable	Analysis
		• Counts and percentages of different doses of dacomitinib.
	• Concomitant treatment (surgery, radiotherapy, chemotherapy) with dacomitinib.	• Counts and percentages of patients with concomitant treatment started after initiation of dacomitinib. • Counts and percentages of patients with concomitant treatment just before permanent discontinuation of dacomitinib.
Outcomes	• Real-world overall survival (OS).	• Median (IQR), 95% CI for median of OS. • Counts and percentages of patients who survived at specific timepoints (6, 12, 18 and 24 months) after dacomitinib initiation. • Use of Kaplan-Meier curve.
	• Real-world progression-free survival (PFS).	• Median (IQR), 95% CI for median of PFS. • Counts and percentages of patients who were progression-free at specific timepoints (6, 12, 18 and 24 months) after dacomitinib initiation. • Use of Kaplan-Meier curve.
	• T790M mutation status at progression (among those tested).	• Count and percentage of patients with acquired T790M mutation at post-disease progression among those tested.
	• Reasons (including adverse events) resulting in dose modification, interruption or permanent discontinuation of dacomitinib.	• Counts and percentages of adverse events. • Counts and percentages of the reasons for dacomitinib dose modification. • Counts and percentages of the reasons for dacomitinib dosing interruption. • Counts and percentages of the reasons for dacomitinib permanent discontinuation.
	• Time-to-treatment failure (TTF) for dacomitinib.	• Median (IQR), 95% CI for median of TTF.

Role	Variable	Analysis
		• Counts and percentages of patients who remained on dacomitinib at specific timepoints (6, 12, 18 and 24 months) after dacomitinib initiation. • Use of Kaplan-Meier curve.
	• Tumor response to dacomitinib based on the RECIST and/or clinician's judgment.	• Counts and percentages of tumor responses to dacomitinib.

Abbreviations: CI, confidence interval; CNS, central nervous system; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; STD, standard deviation; TNM, Tumor Node Metastasis; TTF, time-to-treatment failure.

a. See Annex 2A for more information.

b. See Annex 2B for more information.

c. See Annexes 2C and 2D for more information.

9.8. Quality control

A study monitoring plan (SMP) will be developed after protocol finalization and implemented accordingly. Data quality control (site monitoring and/or phone quality control) will be performed at site level by trained and designated personnel.

During the site initiation visit, the study monitor will provide training on the conduct of the study to the investigators and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Site monitoring will be performed by either IQVIA clinical research associates or Pfizer representatives to examine compliance with the protocol, adherence to the data collection procedures, assess accuracy and completeness of submitted clinical data, as well as to verify that records and documents are being properly maintained for the entire study duration. The monitor will perform source data verification (SDV) by review of original patient records. 100% SDV will be conducted on 10% of the critical data items which will be listed in the SMP. The data management team will be tracking the SDV status at regular time intervals and will flag any identified issues.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in the SMP. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of Pfizer quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the

site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.9. Limitations of the research methods

Several potential limitations for this study include:

1. As this is a real-world study, there will likely be issues with missing data and data quality. Some information (such as death date, reason for dacomitinib's interruption or discontinuation) may not be routinely recorded by clinicians, are recorded inconsistently or missing due to lost to follow-up. This will impact the study outcomes and findings. To address loss to follow-up, censoring will be performed based on last contact date for patients with unknown status.

2. This study is planned to be descriptive in nature. Drawing of causal associations (eg, effects of dacomitinib vs. other treatments on outcomes) is not possible as there is no defined control group (eg, patients initiated on another treatment). However, study findings are expected to provide insights on the outcomes of dacomitinib-treated patients.

3. In this study, we will evaluate Asian patients with advanced NSCLC and EGFR-positive mutations using dacomitinib as first-line therapy. Hence, findings from the study may not be generalizable to other populations (eg, Caucasians or patients with early stage NSCLC with EGFR-positive mutations). Even in the countries where patients were enrolled, patients in the participating sites may not be representative of the advanced NSCLC population in the respective country.

4. The possibility of selection bias cannot be excluded as patients with more severe condition may refuse participation or investigators may select patients who they think may benefit more from dacomitinib or study participation based on their clinical judgement.

5. To reduce immortal time bias, patients who died after dacomitinib initiation but before a follow-up visit will be included. However, due to missing information (eg, death date), it is conceivable that there may be some patients who died but are considered as loss to follow-up and hence excluded from the study. As a result, immortal time bias cannot be completely eliminated.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

10.2.1. Retrospective patients

For Malaysia:

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer may not be required. In the case where the local IRB/IEC determines that informed consent from patients:

(a) is required, clause 10.2.2 will apply; or

(b) is not required, all relevant approvals and consents must be obtained from the respective parties, including within limitation an informed consent waiver from local IRB/IEC for retrospective data collection that contain no identifiable patient data, consent from the owner of the data to use the data in the current trial, and consent from the investigator of the previous trial to use the data in the current trial.

For India and China:

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer may not be required. An informed consent waiver will be requested and approved by local IRB/IEC, in accordance with applicable laws and regulations, for retrospective data collection that contain no identifiable patient data.

10.2.2. Prospective or mixed patients

An ICD must be signed by the patient (or the patient's LAR) before his or her participation in the study. LAR is defined as an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The physician-in-charge will decide if a patient is capable of decision-making. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICD must be provided to the patient or the patient's LAR. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICDs must remain in each patient's study file and must be available for verification by study monitors at any time. The ICD should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICDs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICD for continued participation in the study.

10.3. Patient withdrawal

The enrolled patient or his/her LAR has the right to withdraw from this study at any point in time by informing their physician-in-charge. There will be no consequence on the existing and future medical care that they are entitled to.

Upon withdrawal of consent, the reason for withdrawal should be documented in the eCRF. All information already collected as part of the study will be retained for analysis provided the agreement of the patient is obtained. No further effort will be made for any subsequent data collection from the date of withdrawal.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with ethical principles in the Declaration of Helsinki, relevant legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices (GPP).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Human review of unstructured data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database.

The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug (including dacomitinib) that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to IQVIA/Pfizer Safety (Table 5) are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded and reported, within 24 hours of awareness using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported within 24 hours of awareness using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the

actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators").*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

Table 5. Pharmacovigilance Contacts of Pfizer for Each Country

Country	Fax	Email
China	10800714-1806 Non-English text 10800140-1838 Non-English text Alt. 1: +1 973-660-8920	CHN.AEReporting@pfizer.com
India	Toll-Free (local): 000800100-5961 Alt.1: +91 22 3919-7714 Alt. 2: +1 973-660-8935	IND.AEReporting@pfizer.com
Malaysia	Toll-free (local): 1800-81-6432 Alt.1: +603 2281-6384 Alt. 2: +1 973-660-8942	MYS.AEReporting@pfizer.com

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. WHO. *Cancer (factsheet)*. 2018; Available from: http://www. who.int/news-room/fact-sheets/detail/cancer.

2. Sher, T., G.K. Dy, and A.A. Adjei. *Small cell lung cancer*. in *Mayo Clinic Proceedings*. 2008. Elsevier.

3. Jorissen, R.N., et al., *Epidermal growth factor receptor: mechanisms of activation and signalling*, in *The EGF receptor family*. 2003, Elsevier. p. 33-55.

4. Zhang, Y.-L., et al., *The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis.* Oncotarget, 2016. **7**(48): p. 78985-78993.

5. Hanna, N.H., et al., *Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update*. Journal of Clinical Oncology, 2020.

6. NCCN. *NCCN Flash Updates: NCCN Guidelines®, NCCN Compendium®, and NCCN Imaging AUC™ for Non-Small Cell Lung Cancer*. 2019 [cited 2020 24 March 2020]; Available from: https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=1536.

7. Li, D., et al., *BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models.* Oncogene, 2008. **27**(34): p. 4702-4711.

8. Yap, T.A. and S. Popat, *Toward precision medicine with next-generation EGFR inhibitors in non-small-cell lung cancer.* Pharmacogenomics and personalized medicine, 2014. **7**: p. 285-295.

9. Gonzales, A.J., et al., *Antitumor activity and pharmacokinetic properties of PF-00299804, a second-generation irreversible pan-erbB receptor tyrosine kinase inhibitor.* Molecular cancer therapeutics, 2008. **7**(7): p. 1880-1889.

10. Mitsudomi, T., et al., *Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial.* The lancet oncology, 2010. **11**(2): p. 121-128.

11. Wu, Y.-L., et al., *Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial.* The Lancet Oncology, 2017. **18**(11): p. 1454-1466.

12. ASCO. *Dacomitinib vs Gefitinib in Advanced NSCLC With EGFR-Activating Mutations*. 2018 [cited 2020 24 March 2020]; Available from: https://www.ascopost.com/News/58920.

13. Mok, T.S., et al., *Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non–small-cell lung cancer and EGFR-activating mutations.* J Clin Oncol, 2018. **36**(22): p. 2244-2250.

14. Mok, T.S., et al. *Updated overall survival (OS) from extended follow up in ARCHER 1050: A randomized phase III study comparing dacomitinib with gefitinib as first-line therapy for patients with EGFR mutations*. 2019 May 6, 2020]; Available from: https://oncologypro.esmo.org/meeting-resources/esmo-asia-congress-2019/updated-overall-survival-os-from-extended-follow-up-in-archer-1050-a-randomized-phase-iii-study-comparing-dacomitinib-with-gefitinib-as-first-li.

15. Arcila, M.E., et al., *Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay.* Clinical cancer research, 2011. **17**(5): p. 1169-1180.

16. Pao, W., et al., *Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain.* PLoS medicine, 2005. **2**(3).

17. Sequist, L.V., et al., *Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors.* Science translational medicine, 2011. **3**(75): p. 75ra26-75ra26.

18. Yu, H.A., et al., *Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers.* Clin Cancer Res, 2013. **19**(8): p. 2240-7.

19. Ma, C., S. Wei, and Y. Song, *T790M and acquired resistance of EGFR TKI: a literature review of clinical reports.* Journal of thoracic disease, 2011. **3**(1): p. 10-18.

20. Westover, D., et al., *Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors.* Ann Oncol, 2018. **29**(suppl_1): p. i10-i19.

21. Jänne, P.A., et al., *Dacomitinib as first-line treatment in patients with clinically or molecularly selected advanced non-small-cell lung cancer: A multicentre, open-label, phase 2 trial.* Lancet Oncol, 2014. **15**(13): p. 1433-1441.

22. Pfizer, *Pfizer Unveils Positive Results from Asian Subgroup Analysis of ARCHER 1050. Significant Improvement in Progression-Free and Overall Survival In EGFR-Mutated Non-Small Cell Lung Cancer Patients Who Received First-Line Dacomitinib*. 2019, CISION PR Newswire: Singapore.

LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Annex 2A. Description of the Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
Grade 0	Fully active, able to carry on all pre-disease performance without restriction.
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
Grade 2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
Grade 3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
Grade 4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
Grade 5	Dead

Reference: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

Annex 2B. List of Conditions in the Charlson Comorbidity Index

[redacted]

Reference: Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40(5):373-383.
[a] With mutually exclusive categories.

Annex 2C. Definitions for Tumor, Node and Metastasis (TNM) Descriptors

Grade	T (primary tumor)
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)
T1	Tumor ≤3 cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways
T1a	Tumor ≤1cm
T1b	Tumor >1 but ≤2cm
T1c	Tumor >2 but ≤3cm
T2	Tumor >3 but ≤5cm or tumor involving: visceral pleura, main bronchus (not carina), atelectasis to hilum
T2a	Tumor >3 but ≤4cm
T2b	Tumor >4 but ≤5cm
T3	Tumor >5 but ≤7cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor >7cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus,

	spine; or tumor nodule(s) in a different ipsilateral lobe
	N (regional lymph nodes)
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
	M (distant metastasis)
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases (1 or >1 organ)

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.

Annex 2D. Lung Cancer Stage Grouping based on Tumor, Node and Metastasis (TNM) Grades

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.