SINGLE ARM STUDY TO EVALUATE THE SAFETY OF DACOMITINIB FOR THE FIRST-LINE TREATMENT OF PARTICIPANTS IN INDIA WITH METASTATIC NON-SMALL CELL LUNG CANCER WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)-ACTIVATING MUTATIONS

Protocol Number:	A7471064
Medicinal product:	Dacomitinib (PF-00299804)
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
European Clinical Trial Database (EudraCT) Number:	Not Applicable (N/A)
Universal Trial Number:	Not Applicable (N/A)
Phase:	Phase 4

Document History

Document	Version Date	Summary of Changes
Original protocol	01 April 2020	Not Applicable (N/A)

Abbreviations

This is a list of abbreviations used in the protocol template. All of these abbreviations may or may not be used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
CAP	Chest, Abdomen, Pelvis
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	clinical study agreement
CT	computerized tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCIS	ductal carcinoma in situ
DDR	discoidin domain receptor
DoR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EPHA6	ephrin type-A receptor 6
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
H2	histamine 2
HDPE	High Density PolyEthylene
HER	human epidermal growth factor receptor
HR	hazard ratio
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	Independent Radiologic Central
IUD	intrauterine device

Abbreviation	Term
IVRS	interactive voice response system
IWRS	interactive web response system
LCK	lymphocyte cell-specific protein tyrosine kinase
LFT	liver function test
LPD	Local Product Document
LPFV	last participant first visit
MedDRA	Medical Dictionary for Regulatory Activities
MNK	mitogen-activated protein kinase-interacting serine/threonine-protein kinase
MRI	magnetic resonance imaging
N/A	Not Applicable
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PASS	Post-Authorization Safety Study
PD	progressive disease
PET	positron emission tomography
PFS	Progression-Free Survival
PPI	proton pump inhibitor
PR	partial response
PS	performance status
PT	prothrombin time
QTc	QT interval corrected for heart rate
QTcF	QT interval calculated using Fridericia's correction factor
RECIST	Response Evaluation Criteria in Solid Tumor
RNA	ribonucleic acid
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SRSD	single reference safety document
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

PROTOCOL SUMMARY

Background

A subpopulation of patients with NSCLC harbors EGFR (also known as HER1/erbB1)-activating mutations in their tumors that are important oncogenic drivers for NSCLC. EGFR TKIs, including gefitinib, erlotinib, and afatinib, have been approved for use in this disease and are accepted standard first-line therapies, based on demonstrated improvement in tumor response and PFS compared with platinum-based doublet chemotherapy.[1,2,3,4]

Dacomitinib is a selective, ATP-competitive, irreversible, small-molecule inhibitor of HER of RTKs, including the EGFR (HER1), the HER2 receptor (erbB2), the HER4 receptor (erbB4), and their oncogenic variants (eg, EGFR with exon 19 deletion or exon 21 L858R substitution mutations).[5,6,7] Dacomitinib inhibited the activity of HER1, HER2, and HER4 in biochemical kinase assays, demonstrated dose-dependent inhibition of the HER1 and HER2 RTK phosphorylation in tumor xenografts expressing these RTK targets in vivo, and demonstrated inhibition of tumor growth or tumor regression in experimental models of cancer.[8] In in vitro studies, dacomitinib has shown greater potency when compared with gefitinib in NSCLC models characterized by EGFR-sensitive and -resistant mutations.[5] Dacomitinib potentially offers a therapeutic advantage over selective reversible EGFR TKIs (such as gefitinib or erlotinib) because the irreversible inhibition and highly selective properties of dacomitinib for the EGFR family of kinases result in sustained suppression of RTK activity. The long-lasting inhibition of receptor phosphorylation reduces concern over the potentially short plasma half-lives of the first-generation TKIs. Furthermore, the low nanomolar potency and irreversible binding of the intended targets reduce the need for high peak plasma levels, which in turn could minimize target-nonspecific toxicities. It has been shown that participants with NSCLC with EGFR-activating mutations may develop treatment resistance by the development of a gatekeeper mutation in exon 20 with a secondary point mutation T790M. Preclinical studies using dacomitinib inhibited the growth of cells harboring this secondary mutation, but this has not been demonstrated clinically.

Rationale

The pivotal study for regulatory approval of dacomitinib for first-line treatment of patients with NSCLC with EGFR activating mutations was Study A7471050. Study A7471050 was a multinational, randomized, open-label, Phase 3 efficacy and safety study comparing dacomitinib with gefitinib in patients with EGFR mutation positive locally advanced or metastatic newly diagnosed NSCLC or with recurrent NSCLC if the patient was treated with neoadjuvant or adjuvant therapy and had a 12-month disease-free interval.

This study met its primary objective by demonstrating that dacomitinib was superior to gefitinib in prolonging PFS as determined by blinded IRC review in the first-line treatment of patients with locally advanced or metastatic EGFR-activating mutation-positive NSCLC (HR: 0.589; 95% CI: 0.469, 0.739; 1-sided p <0.0001). The estimated median PFS was

14.7 months (95% CI: 11.1, 16.6) for the dacomitinib arm versus 9.2 months (95% CI: 9.1, 11.0) for the gefitinib arm (data cutoff date: 29 July 2016).

However, since none of the participating study sites of Study A7471050 were located in India, the Central Drugs Standard Control Organization (India) requested the Sponsor to conduct a clinical study. The goal of Study A7471064, which is also a PASS, is to fulfill this regulatory request.

Study Objectives and Endpoints

Primary Objective

- To assess safety and tolerability of dacomitinib.

Secondary Objective

- To evaluate antitumor activity of dacomitinib by ORR and DoR.

Primary endpoint

- Incidence of AEs.

Secondary endpoint

- Confirmed ORR and DoR as assessed by the investigator using RECIST version 1.1.

Study Design

This is a Phase 4, open-label, single arm, multicenter, prospective clinical trial of dacomitinib for the first-line treatment of adult participants with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. This study will enroll a sufficient number of participants to ensure that 100 participants are treated with dacomitinib.

Study Treatments

Participants will take dacomitinib at the approved starting dose of 45 mg once a day. Participants will be treated until disease progression, participant refusal/lost to follow-up, or unacceptable toxicity.

Statistical Methods

The study's objectives are to assess the safety, tolerability and antitumor activity of dacomitinib. This study will enroll a sufficient number of participants to ensure that 100 participants are treated with dacomitinib. The number of participants is based on a request from the Central Drugs Standard Control Organization (India). With 100 participants, the rate of any AE can be estimated with the maximum standard error of

0.05. All participants who receive at least 1 dose of dacomitinib in this study will be included in the safety and antitumor activity analyses unless otherwise specified.

Analysis of Primary Endpoint:

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded by the Sponsor using MedDRA. The focus of AE summaries will be on treatment-emergent AEs, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, or treatment-related SAE will be summarized descriptively.

Additional Safety Analyses

Other safety parameters, including study treatment exposure, laboratory tests, ECG, vital signs measurements, dose reductions associated with AEs, and temporary and permanent discontinuations associated with AEs will be summarized descriptively.

Analysis of Secondary Endpoint:

Confirmed ORR and DoR as assessed by the investigator using RECIST version 1.1 will be summarized.

End of Study

The end of study is defined as 1 year after the LPFV date in the study. At the end of the study, participants who are on treatment and benefiting from dacomitinib treatment will be switched to commercially available dacomitinib if considered appropriate by the investigator, as soon as feasible.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the participant.

Visit Identifier	**Screening**	**Cycle 1 (28 days)**	**Day 1 of Every Cycle**	**End of Treatment**	**Follow up (up to 28 days)[1]**
Visit Window	**≤28 days**	**Day 1**	**±2 days**	**±7 days**	
Informed consent[2]	X				
Tumor history	X				
Medical history	X				
Physical examination and vital signs	X	X	X	X	
ECOG PS	X	X	X	X	
Contraception check[3] for women of childbearing potential		X	X	X	X
Laboratory					
Hematology	X	(X)*	X	X	
Blood chemistry	X	(X)*	X	X	
Pregnancy test[4]	X	(X)*	X	X	
Cardiac Monitoring					
12-Lead ECG[5]	X	(X)*			
Treatment					
Dacomitinib		Orally once a day, continuously			
Tumor Assessments					
CT or MRI Imaging[6]	X		(every 12 weeks ±1 week)	X[7]	
Other Clinical Assessments					
AEs[8]	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[9]	X	X	X	X	X

*(X) No need to repeat the assessment if it is performed within 7 days prior to Cycle 1 Day 1.

1. All participants will return to the study site up to 28 days after the last dose of study drug administration for assessment of potential AEs, recording of concomitant treatment use and to confirm appropriate contraception usage.
2. Informed consent: informed consent must be obtained prior to undergoing any study-specific procedures that are not considered standard of care.
3. Contraceptive check: female participants of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception from the time of the first negative pregnancy test at Screening, throughout the study and for at least 17 days after the last dose of dacomitinib.
4. For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed before investigational product administration at the screening visit, on Day 1 of every cycle* and at the end of treatment visit. A negative pregnancy result is required before the participant may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise

suspected) to confirm the participant has not become pregnant during the study. In the case of a confirmed pregnancy, the participant will be withdrawn from study medication and from the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

5. Triplicate 12-lead ECGs: 3 consecutive 12-lead ECGs pre-dose will be performed approximately 2 minutes apart to determine mean PR interval, QRS complex, and QTcF at baseline (Screening and Cycle 1 Day 1, if the ECG at Screening was performed more than 7 days before Cycle 1 Day 1). Additional ECGs may be collected as clinically indicated and as single ECGs.
6. Tumor assessment: tumor assessments will include all known or suspected disease sites. CT or MRI scans of the CAP and MRI of the brain will be performed at Screening and repeated every 12 weeks until the end of treatment. For all tumor assessments, the method of assessment that was used at Screening should be the same method used throughout the study. Responses will be confirmed ≥4 weeks after first occurrence of response, according to RECIST version 1.1 criteria.
7. Tumor assessment should be repeated at the end of treatment if more than 6 weeks have passed since the last evaluation.
8. AE assessments: AEs should be documented and recorded into the eCRF at each visit using NCI CTCAE version 4.03.

   For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a participant after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. AEs (serious and nonserious) should be recorded on the CRF from the time the participant has taken at least 1 dose of study treatment through the last participant visit. If a participant begins a new anticancer therapy, the AE recording period for nonserious AEs ends at the time the new treatment is started. SAEs and deaths must be recorded and reported if they occur during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.
9. Concomitant medications and non-drug supportive interventions: all concomitant medications and non-drug supportive interventions should be recorded in the CRF from 28 days prior to start of study treatment and up to 28 days after the last dose of study treatment.

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Dacomitinib is an irreversible inhibitor of the kinase activity of the human EGFR family (EGFR/HER1, HER2, and HER4) and certain EGFR-activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation).[5,6,7] In vitro dacomitinib also inhibited the activity of DDR1, EPHA6, LCK, DDR2, and MNK1 at clinically relevant concentrations. Dacomitinib demonstrated dose-dependent inhibition of EGFR and HER2 autophosphorylation and tumor growth in mice bearing subcutaneously implanted human tumor xenografts driven by HER family targets including mutated EGFR. Dacomitinib also exhibited antitumor activity in orally-dosed mice bearing intracranial human tumor xenografts driven by EGFR amplifications.

Dacomitinib is a kinase inhibitor indicated for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations.

1.2. Background and Rationale

1.2.1. Background

A subpopulation of patients with NSCLC harbors EGFR (also known as HER1/erbB1)-activating mutations in their tumors that are important oncogenic drivers for NSCLC. EGFR TKIs, including gefitinib, erlotinib, and afatinib, have been approved for use in this disease and are accepted standard first-line therapies, based on demonstrated improvement in tumor response and PFS compared with platinum-based doublet chemotherapy.[1,2,3,4]

Dacomitinib is a selective, ATP-competitive, irreversible, small-molecule inhibitor of HER of RTKs, including the EGFR (HER1), the HER2 receptor (erbB2), the HER4 receptor (erbB4), and their oncogenic variants (eg, EGFR with exon 19 deletion or exon 21 L858R substitution mutations).[5,6,7]

In in vitro studies, dacomitinib has shown greater potency when compared with gefitinib in NSCLC models characterized by EGFR-sensitive and -resistant mutations.[5] Dacomitinib potentially offers a therapeutic advantage over selective reversible EGFR TKIs (such as gefitinib or erlotinib) because the irreversible inhibition and highly selective properties of dacomitinib for the EGFR family of kinases result in sustained suppression of RTK activity. The long-lasting inhibition of receptor phosphorylation reduces concern over the potentially short plasma half-lives of the first-generation TKIs. Furthermore, the low nanomolar potency and irreversible binding of the intended targets reduce the need for high peak plasma levels, which in turn could minimize target-nonspecific toxicities. It has been shown that participants with NSCLC with EGFR-activating mutations may develop treatment resistance by the development of a gatekeeper mutation in exon 20 with a secondary point mutation, T790M. Preclinical studies using dacomitinib inhibited the growth of cells harboring this secondary mutation, but this has not been demonstrated clinically.

1.2.2. Rationale

The pivotal study for regulatory approval of dacomitinib for first-line treatment of patients with NSCLC with EGFR activating mutations was Study A7471050. Study A7471050 was a multinational, randomized, open-label, Phase 3 efficacy and safety study comparing dacomitinib with gefitinib in patients with EGFR mutation positive locally advanced or metastatic newly diagnosed NSCLC or with recurrent NSCLC if the patient was treated with neoadjuvant or adjuvant therapy and had a 12-month disease-free interval.

This study met its primary objective by demonstrating that dacomitinib was superior to gefitinib in prolonging PFS as determined by blinded IRC review in the first-line treatment of patients with locally advanced or metastatic EGFR-activating mutation-positive NSCLC (HR: 0.589; 95% CI: 0.469, 0.739; 1-sided p <0.0001, representing a 41.1% reduction in risk of disease progression or death). The estimated median PFS was 14.7 months (95% CI: 11.1, 16.6) for the dacomitinib arm versus 9.2 months (95% CI: 9.1, 11.0) for the gefitinib arm (data cutoff date: 29 July 2016).

However, since none of the participating study sites of Study A7471050 were located in India, the Central Drugs Standard Control Organization (India), requested the Sponsor to conduct a clinical study. The goal of Study A7471064, which is also a PASS, is to fulfill this regulatory request.

Complete information for this compound may be found in the SRSD, which for this study is the India LPD.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary		
• To assess safety and tolerability of dacomitinib.	• The primary estimand is the incidence of AEs from the time of first dose to 28 days post last dosing date or the date of initiation of a new anticancer therapy, whichever occurs first for all participants who receive at least one dose of dacomitinib, regardless of dosing interruptions or dosing compliance.	• Incidence of AEs.
Secondary		
• To evaluate antitumor activity of dacomitinib by ORR and DoR.	• The secondary estimand is the treatment effect of dacomitinib as assessed by the investigator from time of first dose (for ORR) or time of first tumor response (for DoR) until disease progression, death or initiation of a new anticancer therapy, whichever occurs first for all participants who receive at least one dose of dacomitinib without regard to tolerability or discontinuation from treatment.	• Confirmed ORR and DoR as assessed by the investigator using RECIST version 1.1.

3. STUDY DESIGN

This is a Phase 4, open-label, single arm, multicenter, prospective clinical trial of dacomitinib for the first-line treatment of newly diagnosed adult participants with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. This study will enroll a sufficient number of participants to ensure that 100 participants are treated with dacomitinib.

4. PARTICIPANT SELECTION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom the protocol intervention is considered appropriate by their health care provider.

4.1. Inclusion Criteria

Participant eligibility should be reviewed and documented by an appropriate member of the investigator's study team before participants are included in the study.

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC with EGFR-activating mutations (exon 19 deletion mutation or L858R substitution mutation in exon 21) as detected by an appropriate test.

    - It is acceptable for participants with the presence of the exon 20 T790M mutation together with either EGFR-activating mutation (exon 19 deletion mutation or the L858R substitution mutation in exon 21) to be included in this study.

2. No prior treatment with systemic therapy for metastatic NSCLC. Completed neoadjuvant/adjuvant chemotherapy and/or combined modality chemotherapy/radiation therapy permitted only in cases in which there is a minimum of 12 months disease-free interval between completion of systemic therapy and recurrence of NSCLC. Prior treatment with an EGFR-TKI or other TKIs is not allowed.

3. Participants with asymptomatic CNS metastases (including participants controlled with stable or decreasing steroid use within the last 2 weeks prior to study entry) will be eligible.

4. Age ≥18 years.

5. ECOG PS of 0-2.

6. Adequate hematologic, renal and liver function as defined as:

    a. ANC ≥1,000/mm^3;

b. Platelets ≥50,000/mm^3;

c. Hemoglobin ≥8 g/dL;

d. Estimated creatinine clearance ≥30 mL/min as calculated using the method standard for the institution;

e. Total serum bilirubin <1.5 × ULN;

f. AST and ALT ≤2.5 × ULN (≤5.0 × ULN in case of liver metastases).

7. Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade <1 except for AEs that in the investigator's judgment do not constitute a safety risk for the participant.

8. Serum or urine pregnancy test (for females of childbearing potential) negative at Screening. Female participants of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception from the time of the first negative pregnancy test at Screening, throughout the study and for at least 17 days after the last dose of assigned treatment.

9. Evidence of a personally signed and dated informed consent document indicating that the participant or a legally acceptable representative has been informed of all pertinent aspects of the study.

10. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria

Participants presenting with any of the following will not be included in the study:

1. Any evidence of mixed histology that includes elements of small cell or carcinoid lung cancer.

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

3. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (<10 fractions) must have been completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation must have completed at least 2 weeks prior to study entry. Whole brain radiation must have completed at least 4 weeks prior to study entry. Prior irradiation to >25% of the bone marrow.

4. Major surgery within 4 weeks prior to first dose of dacomitinib. Minor surgical procedures (eg, port insertion) are not excluded, but sufficient time should have passed for adequate wound healing.

5. Known prior or suspected severe hypersensitivity to dacomitinib or any component of its formulation.

6. History or known presence of interstitial fibrosis, interstitial lung disease, pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis.

7. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

8. Evidence of active malignancy (other than current NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, DCIS of the breast or localized and presumed cured prostate cancer) within the last 3 years prior to first dose of dacomitinib.

9. Breastfeeding female participants.

10. Participation in other studies involving investigational drug(s) (Phases 1-4) within 2 weeks before the current study begins and/or during study participation.

11. Participants who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees directly involved in the conduct of the study.

12. Pregnant female participants; female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol (Section 4.3.1) for the duration of the study and for up to 17 days after the last dose of investigational product.

4.3. Life Style Guidelines

4.3.1. Contraception

Female participants of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception from the time of the first negative pregnancy test at Screening, throughout the study and for at least 17 days after the last dose of dacomitinib.

All female participants who, in the opinion of the investigator, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 17 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the participant, will select the most appropriate method of

contraception for the individual participant from the permitted list of contraception methods (see below) and instruct the participant in its consistent and correct use. Participants need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee, at each study visit, will discuss with the participant the need to use highly effective contraception consistently and correctly and document such conversation in the participant's chart. In addition, the investigator or his/her designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected. Male participants should use a condom, if their partners are pregnant or if they plan to father a child.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception is allowed provided the participant plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing IUD.

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.3.2. Sunlight Exposure

Participants should avoid extended unprotected exposure to sunlight (eg, sunbathing) or tanning for the duration of the study period and for approximately 4 weeks after last dose of study drug. At the time of initiation of dacomitinib, use of moisturizers and appropriate measures to limit sun exposure should be initiated.

5. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

ARM name	Dacomitinib 45 mg
Intervention name	Dacomitinib
Type	Small molecule
Dosage form	Tablet
Dose strength	15 mg
Dosage	Starting dose of 45 mg once a day
Route of administration	Oral
Sourcing	Provided centrally by the Sponsor
Packaging and labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement
Current/former name(s) or alias(es)	PF-00299804/dacomitinib

5.1. Allocation to Intervention/Treatment

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable CRF, if required.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

5.2. Drug Supplies

5.2.1. Dosage Form(s) and Packaging

Dacomitinib will be supplied by Pfizer Global Clinical Supply for oral administration as 15 mg tablets in HDPE bottles with desiccant and labeled according to local regulatory requirements.

Packaging and labeling for all study drugs will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. The information on the study drug will be in accordance with approved submission documents.

Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed and filed, as directed on the bottom of the Drug Shipment and Proof of Receipt form. The investigator must take responsibility for and must take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Refer to the Investigational Product Manual for further details.

5.3. Administration

The product will be administered in accordance with the India LPD.

The recommended dosage of dacomitinib is 45 mg taken orally once a day at approximately the same time each day, until disease progression, participant refusal/lost to follow-up, or unacceptable toxicity occurs. Dacomitinib can be taken with or without food.

The participant should take dacomitinib the same time each day. If the participant vomits or misses a dose, he/she should not take an additional dose or make up a missed dose but continue with the next scheduled dose.

The dose of dacomitinib should be reduced for adverse reactions as described in Table 1. Dose modifications for specific adverse reactions are provided in Table 2.

Table 1. Dacomitinib Recommended Dose Reductions for Adverse Reactions

Dose level	Dose (Once a Day)
First dose reduction	30 mg
Second dose reduction	15 mg

Table 2. Dacomitinib Dose Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Interstitial lung disease	Any Grade	• Permanently discontinue dacomitinib.
Diarrhea	Grade 2	• Withhold dacomitinib until recovery to less than or equal to Grade 1; then resume dacomitinib at the same dose level. • For recurrent Grade 2 diarrhea, withhold until recovery to less than or equal to Grade 1; then resume dacomitinib at a reduced dose.
	Grade 3 or 4	• Withhold dacomitinib until recovery to less than or equal to Grade 1; then resume dacomitinib at a reduced dose.
Dermatologic Adverse Reactions	Grade 2	• Withhold dacomitinib for persistent dermatologic adverse reactions; upon recovery to less than or equal to Grade 1, resume dacomitinib at the same dose level. • For recurrent persistent Grade 2 dermatologic adverse reactions, withhold until recovery to less than or equal to Grade 1; then resume dacomitinib at a reduced dose.
	Grade 3 or 4	• Withhold dacomitinib until recovery to less than or equal to Grade 1; then resume dacomitinib at a reduced dose.
Other	Grade 3 or 4	• Withhold dacomitinib until recovery to less than or equal to Grade 2; then resume dacomitinib at a reduced dose.

[a] NCI CTCAE Version 4.03.

If a participant cannot tolerate treatment after a dose reduction to 15 mg, treatment will be permanently discontinued.

If a participant fails to recover within 2 weeks of interruption for a drug-related AE, treatment will be discontinued unless there is discussion of the clinical circumstance with the Sponsor and agreement that the participant may resume treatment after an interruption of greater than 2 weeks.

If a participant subsequently tolerates treatment well at the reduced level in the judgment of the investigator, the dose may be increased to the next dose level.

5.4. Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the India LPD. See the Investigational Product Manual for storage conditions of the product.

Storage conditions stated in the SRSD will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study, on all business days. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the India LPD storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions.

Site staff will instruct participants on the storage requirements for take home medications including how to report temperature excursions.

The Investigational Product Manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

5.5. Drug Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product Manual.

Participants will be required to return all unused dacomitinib tablets at every cycle. The number of tablets returned by the participant should be counted, documented, and recorded by site personnel to support the accountability process. Study site personnel must make reasonable efforts to obtain study drug packaging and any unused tablets from participants who do not routinely return them at study site visits. Unreturned tablets will be considered to have been taken unless reported otherwise by the participant. For additional information regarding accountability, please refer to the Investigational Product Manual.

The Sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.6. Concomitant Treatment(s)

The use of permitted concomitant medication must be in accordance with the India LPD.

All concomitant medications and non-drug supportive interventions should be recorded in the CRF from 28 days prior to start of study treatment and up to 28 days after the last dose of study treatment.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with reason for use and dates of administration including start and end dates.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.6.1. Prohibited Concomitant Treatments

Concomitant use with a PPI decreases dacomitinib concentrations, which may reduce dacomitinib efficacy. The concomitant use of PPIs with dacomitinib should be avoided. As an alternative to PPIs, use locally-acting antacids or an H2-receptor antagonist. Dacomitinib should be administered at least 6 hours before or 10 hours after taking an H2-receptor antagonist.

Concomitant use of dacomitinib increases the concentration of drugs that are CYP2D6 substrates which may increase the risk of toxicities of these drugs. The concomitant use of dacomitinib with CYP2D6 substrates should be avoided as minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities.

Other Antitumor or Experimental Drugs

No additional systemic antitumor therapy will be permitted while participants are receiving a study therapy.

6. STUDY PROCEDURES

6.1. Screening

All participants being considered for the study and eligible for Screening must sign an informed consent for the study before completing any study-specific procedures. Participants will be screened within 28 days prior to first dosing of dacomitinib to confirm that they meet the eligibility criteria for the study. The required Screening assessments are summarized in the Schedule of Activities and Section 7 Assessments.

6.2. Study Period

For study treatment period procedures, see Schedule of Activities and Section 7 Assessments.

6.3. Follow-up Visit

All participants will return to the study site up to 28 days after the last dose of study drug administration for assessment of potential AEs, recording of concomitant treatment use and to confirm appropriate contraception usage.

6.4. Participant Withdrawal

Withdrawal of Consent: Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

Lost to Follow-Up: All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's medical record. In any circumstance, every effort should be made to document participant outcome, if possible. The investigator should inquire about the reason for withdrawal, request the participant to return for a final visit, if applicable, and follow up with the participant regarding any unresolved AEs.

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

7.1. Antitumor Activity Assessments

7.1.1. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. CT or MRI scans of CAP and MRI of the brain will be performed at Screening and repeated every 12 weeks ±1 week until the end of treatment. For all tumor assessments, the method of assessment that was used at Screening should be the same method used throughout the study. Tumor assessment should be repeated at the end of treatment if more than 6 weeks have passed since the last evaluation.

Assessment of response will be made using RECIST version 1.1 (Appendix 1).[9] Confirmation of response will be required ≥4 weeks after initial response is observed.

7.2. Safety Assessments

The following parameters will be assessed at time points detailed in Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

- Physical examinations and vital signs;
- ECOG PS;
- Safety laboratory data;
- 12-lead ECG.

7.2.1. Physical Examinations and Vital Signs

Participants will have a physical examination to include major body systems, body weight, blood pressure and pulse rate at the time points described in the Schedule of Activities. Blood pressure and pulse rate should be taken pre-dose with the participant in the seated position after the participant has been sitting quietly for at least 5 minutes. Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.2.2. Electrocardiograms

ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS complex, QT interval, and QTcF.

Three (3) consecutive 12-lead ECGs pre-dose will be performed approximately 2 minutes apart to determine mean PR interval, QRS complex, and QTcF at baseline (Screening and Cycle 1 Day 1, if the ECG at Screening was performed more than 7 days before Cycle 1 Day 1). Additional ECGs may be collected as clinically indicated and as single ECGs.

If the participant experiences signs or symptoms of a cardiac or neurologic disorder (specifically syncope, dizziness, seizures, or stroke), ECG should be obtained at the time of the event.

If there is finding of QTcF >500 msec, the ECG must be repeated. If there is finding of QTcF >500 msec again (ie, ≥ CTCAE Grade 3), the ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia's correction formula is applied.

An electronic reading of prolonged QTc must be confirmed by a manual reading. Before concluding that an episode of QTc prolongation is due to study drug, thorough consideration should be given to potential precipitating factors (eg, a change in the participant's clinical condition, the effect of concurrent medication, electrolyte disturbance) and a possible evaluation by a specialist. If the QTcF reverts to ≤500 msec, and it is the opinion of the

investigator and the Sponsor that the prolongation was not due to the study drug, treatment may be continued with regular ECG monitoring.

7.2.3. ECOG PS

Refer to Appendix 2 for ECOG PS criteria.

7.2.4. Clinical Safety Laboratory Assessments

The required laboratory tests are listed in Appendix 3. Hematology and blood chemistry will be collected at the time points described in the Schedule of Activities table and analyzed at local laboratories. Laboratory tests may also be performed when clinically indicated. Local laboratory certification(s) and reference ranges should be provided to the Sponsor prior to study participant screening activity.

7.2.5. Pregnancy Testing

For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed before investigational product administration at the screening visit, on Day 1 of every cycle and at the end of treatment visit. A negative pregnancy result is required before the participant may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) to confirm the participant has not become pregnant during the study. In the case of a confirmed pregnancy, the participant will be withdrawn from study medication and from the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any nonserious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a participant after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

AEs (serious and nonserious) should be recorded on the CRF from the time the participant has taken at least 1 dose of study treatment through the last participant visit.

If a participant begins a new anticancer therapy, the AE recording period for nonserious AEs ends at the time the new treatment is started. SAEs and deaths must be recorded and reported if they occur during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;

- Drug interactions;
- Extravasation;
- EDP;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong participant, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the AE page of the CRFs and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated AE(s) are captured on an AE CRF page (refer to Section 8 Adverse Event Reporting section for further details).

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death.

- Is life-threatening (immediate risk of death).

- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).

- Results in congenital anomaly/birth defect.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTC Grade 5 (see Section 8.8 Severity Assessment).

- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. The important medical event should be reported as serious, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other AE outcomes.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 × ULN concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For participants with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For participants with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

    Concurrent with

    - For participants with preexisting values of total bilirubin above the normal range: Total bilirubin level increased by 1 × ULN **or** ≥3 × ULN (whichever is smaller).

The participant should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or

C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, participant has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual participant;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the participant's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 8.13 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male participant has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study participant or study participant's partner becomes or is found to be pregnant during the study participant's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE Report Form and EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Withdrawal Due to Adverse Events (See Also Section on Participant Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a participant withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study participant/legally acceptable representative. In addition, each study participant/ legally acceptable representative will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study participant initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.13.3. Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in an SAP, which will be maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

This is a single arm study with no statistical hypothesis testing. The primary objective of the trial is to evaluate the safety and tolerability of single-agent dacomitinib for the first-line treatment of participants in India with metastatic NSCLC with EGFR activating mutations.

9.1.1. Estimands

The primary estimand is the incidence of AEs from the time of first dose to 28 days post last dosing date or the date of initiation of a new anticancer therapy, whichever occurs first for all participants who receive at least one dose of dacomitinib, regardless of dosing interruptions or dosing compliance.

The secondary estimand is the treatment effect of dacomitinib as assessed by the investigator from time of first dose (for ORR) or time of first tumor response (for DoR) until disease progression, death or initiation of a new anticancer therapy, whichever occurs first for all participants who receive at least one dose of dacomitinib without regard to tolerability or discontinuation from treatment.

9.2. Sample Size Determination

The study's objectives are to assess the safety, tolerability and antitumor activity of dacomitinib. This study will enroll enough participants to ensure that 100 participants are treated with dacomitinib. The number of participants is based on a request from the Central Drugs Standard Control Organization (India). With 100 participants, the rate of any AE can be estimated with the maximum standard error of 0.05. All participants who receive at least 1 dose of dacomitinib in this study will be included in the safety set which will be used in the safety and antitumor activity analyses unless otherwise specified.

9.3. Data Sources

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are to be filed at the investigator site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

9.4. Antitumor Activity Analysis

All antitumor activity analyses will be performed on the safety set. Treated participants who do not have adequate baseline or post-baseline tumor assessment will be considered as non-responders.

9.4.1. Analysis of Primary Endpoint

Not Applicable.

9.4.2. Analysis of Secondary Endpoints

Secondary endpoints are confirmed ORR and DoR as assessed by the investigator using RECIST version 1.1.

ORR: ORR is defined as the percent of participants with best overall response as confirmed CR or confirmed PR according to RECIST version 1.1. ORR will be provided along with the corresponding 95% CI based on Wilson's Score Method.

DoR: DoR is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or death due to any cause, whichever occurs first. For participants whose responses proceed from PR to CR, the onset of PR is taken as the onset of response. DoR will be summarized in the population of participants with a confirmed CR or confirmed PR using the Kaplan Meier method and will be displayed graphically where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median will be provided. Censoring for DoR will be described in the SAP. In case the number of participants with Progressive Disease after a confirmed CR or confirmed PR is small, the use of Kaplan Meier method may be limited, and descriptive statistics may be provided.

9.5. Analysis of Other Endpoints

Not Applicable.

9.6. Safety Analysis

All safety analysis will be conducted on the safety set and will include all data collected from the time of first dose to 28 days post last dosing date or the date of initiation of a new anti-cancer therapy, regardless of dosing interruptions or dosing compliance.

9.6.1. Analysis of Primary Endpoint

The primary endpoint is the incidence of AEs. AEs will be summarized by type, frequency, severity (as graded by the investigator according to NCI CTCAE version 4.03 and coded by the Sponsor using MedDRA), timing, seriousness and relationship to dacomitinib. The focus of AE summaries will be on treatment-emergent AEs, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, or treatment-related SAE will be summarized descriptively. AEs leading to death or discontinuation of study treatment, events classified as Grade ≥3, treatment-related events, and SAEs will also be summarized. Detailed information collected for each AE will be listed with a description of the event, duration, whether the AE was serious, intensity, relationship to study treatment, action taken, and clinical outcome.

Study Treatment Exposure

Drug exposure will be summarized using descriptive statistics. The number and percentage of participants with dose reduction, temporary/permanent discontinuations and the corresponding reasons will also be summarized. The number and percentage of participants with dose reductions/modifications and the corresponding reasons will also be summarized.

Laboratory Tests

Laboratory test results will be graded according to NCI CTCAE version 4.03. Data will be summarized by the type of laboratory test. Summary of laboratory abnormalities will be presented by maximum CTCAE Grade. For laboratory tests without an NCI CTCAE grade definition, results will be categorized as normal (within normal ranges), abnormal, or not done. Shift tables will be provided to examine the distribution of laboratory abnormalities.

Vital Signs

Vital signs data will be summarized using descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (ie, unscheduled assessments will be excluded).

Electrocardiograms

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged, and all summary statistics and data presentations will use the triplicate averaged data.

QTc using standard correction factors (ie, Fridericia's [default correction], Bazett's [if necessary], and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT interval, HR, RR interval, PR interval, QRS complex, QTcF.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) of QTcF and other ECG parameters will be used to summarize baseline values.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/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 participant. 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 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 is 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.

In most cases, the source documents are the participant's chart in the hospital or the physician's office. In these cases data collected on the CRFs must match the data in those charts.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, according to local regulations, or as specified in the 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 (eg, 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. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer 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.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008) and Schedule Y, Drugs and Cosmetics Act 1940 and Rules 1945.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local India regulatory requirements and laws.

12.3. Participant Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include OMITTING participant 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 form and will be password protected 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 is compiled for transfer to Pfizer and other authorized parties, participant names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study participants. The study site will maintain a confidential list of participants who participated in the study linking their numerical code to the participant's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participant personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local India regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the Sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study participant, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a participant's legally acceptable representative, the participant's assent (affirmative agreement) must subsequently be obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his/her own consent, the source documents must record why the participant did not provide consent (eg, decisionally impaired adult), how the investigator determined that the person signing the consent was the participant's legally acceptable representative, the consent signer's relationship to the study participant (eg, parent, spouse) and that the participant's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant or the participant's legally acceptable representative, when applicable, before any study-specific activity is performed. The investigator will retain the original of each participant's signed consent/assent document.

12.4. Participant Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, 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 the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF STUDY

13.1. End of Study

The end of study is defined as 1 year after the LPFV date in the study. At the end of study, participants who are on treatment and benefiting from dacomitinib treatment will be switched to commercially available dacomitinib if considered appropriate by the investigator, as soon as feasible.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the EudraCT, www.ctri.nic.in (Clinical Trials Registry-India) and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

15.2. Publications by Investigators

Pfizer has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the Study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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Appendix 1. RECIST version 1.1 Tumor Assessment Criteria

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

1. Measurable Lesions.

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

2. Non-measurable Lesions.

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥10 but <15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical examination and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

3. Special Considerations Regarding Specific Lesions.

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

- If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as target lesions and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One (1) exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- Complete Response (CR): disappearance of all target lesions.
- Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For participants having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by the RECIST 1.1 Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 3.

Table 3. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; SD = stable disease; PD = progressive disease; PR = partial response.

Best overall response

The best overall response is determined once all the data for the participant is known. Best response in trials in which confirmation of complete or partial response is not required (ie, randomized trails) is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered not evaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later).

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

Appendix 2. ECOG Classification of Performance Status

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

Appendix 3. Clinical Laboratory Tests

The tests detailed in Table 4 will be performed by the local laboratory. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 4 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 4. Protocol Required Safety Laboratory Assessments

Hematology	Clinical Chemistry[1]	Other
Hemoglobin Platelet count WBC count Absolute neutrophil count Absolute lymphocyte count Absolute monocyte count	Creatinine Alkaline phosphatase AST, ALT Total bilirubin Calcium (total or ionized) Lactate dehydrogenase Magnesium Potassium Glucose, random Sodium BUN or urea Albumin	Pregnancy test (urine or serum) will be performed at the screening visit, on Day 1 of every cycle, at the end of treatment visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected.

1. In case of potential cases of Drug-Induced Liver Injury, please also refer to protocol Section 8.6.2 Potential Cases of Drug-Induced Liver Injury.