A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL-GROUP STUDY TO EVALUATE THE PLASMA PHARMACOKINETICS AND SAFETY OF DACOMITINIB IN PARTICIPANTS WITH SEVERELY IMPAIRED HEPATIC FUNCTION RELATIVE TO PARTICIPANTS WITH NORMAL HEPATIC FUNCTION

Investigational Product Number:	PF-00299804
Investigational Product Name:	Dacomitinib
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	A7471058
Phase:	1

Short Title: Hepatic Impairment Study

[redacted]

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original Protocol	14 November 2018	Not applicable (N/A)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Not applicable.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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 in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier[a]	**Screening**[b]	**Study Period**																	**Follow Up**[s] **or Early Termination**[t]
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**						**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 12**	
Hours After Dose			0	2	4	6	8	12	24	48	72	96	120	144	168	192	216	264	
Informed consent	X																		
CRU confinement[c]		X	→	→	→	→	→	→	→	→	→	→	→	X					
Review inclusion/exclusion criteria	X	X																	
Demography[d]	X																		
Medical/medication history (update)[e]	X	X																	
Physical examination, height, and body weight[f]	X	X												X					X[t]
Safety laboratory tests[g]	X	X							X					X					X[t]
Contraception check[h]		X												X					X[s,t]
Alcohol/tobacco use & Breath alcohol test[i]	X	X																	
FSH (only females amenorrheic for at least 12 months)	X																		
Urine drug testing	X	X																	
Supine 12-Lead ECG[j]	X		X			X								X					X[t]
Blood pressure and pulse rate[k]	X		X						X					X					X[t]
Child-Pugh assessment[l]	X																		

Visit Identifier[a]	Screening[b]	Study Period																Follow Up[s] or Early Termination[t]
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1						Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 12	
Hours After Dose			0	2	4	6	8	12	24	48	72	96	120	144	168	192	216	264	
Hepatitis B (HepBsAg, HepBcAb), Hepatitis C (HCVAb), and HIV tests	X																		
Study treatment administration[m]			X																
PK blood sampling[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Protein binding blood sampling[o]			X			X	X												
Pharmacogenomics blood sampling (CYP2D6)[p]		X																	
Pfizer Prep D1 banked sample(s)[q]		X																	
Prior/concomitant treatments	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[s,t]
CRU discharge[r]														X					
Serious and nonserious adverse event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[s,t]

Abbreviations: → = ongoing/continuous event; AE = adverse event; BMI = body mass index; CRU = clinical research unit; CYP = cytochrome P450; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HCVAb = hepatitis C antibody; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; PK = pharmacokinetic.

a. Day relative to start of study treatment (Day 1).
b. Screening will be performed within 28 days prior to the dosing of investigational product (dacomitinib) (Section 4.1).
c. All participants will be admitted to the CRU on Day -1. All participants will be required to stay in-house at least until the collection of the 144 hour PK sample following dacomitinib dosing.
d. Demographics will include participant height, weight, race, age and gender data collected during Screening.
e. Medical/medication history will include a history of illegal drug, alcohol, and tobacco use, as well as blood donation within 60 days prior to first dose. Medical/medication history will be recorded at Screening and updated when the participant is admitted to the CRU on Day -1.
f. A complete physical examination may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at the investigator site either during Screening or Day -1 only (height and body weight must be obtained at Screening to obtain BMI for eligibility criteria). If complete physical examination is performed during the screening visit, then only a brief physical examination is needed on Day -1. A brief physical examination may be conducted at the discretion of the investigator on Day 7 prior to discharge for new or ongoing AEs and during early termination.

[redacted]

g. Safety laboratory assessments including urinalysis, hematology (including prothrombin time/partial thromboplastin time), and chemistry will be performed at Screening, on Day -1, on Day 2, Day 7 prior to discharge and during early termination. All assessments must be collected following at least a 4-hour fast. For participants with severe hepatic impairment (Cohort 1), the Day -1 safety labs including liver function assessments and evaluation of renal function must be completed prior to dacomitinib dosing on Day 1, for review of inclusion/exclusion criteria. Additional assessments may be performed at the discretion of the investigator.
h. On Day -1, on Day 7 (or any subsequent day that coincides with discharge) and during follow-up or early termination, the investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to protocol contraception guidelines in Section 5.3.4.
i. Alcohol/tobacco use and alcohol breath test will be performed during Screening or on Day -1. These tests may also be performed at any other time at the discretion of the investigator.
j. A single 12-lead ECG will be obtained at Screening, 6 hours post-dose on Day 1, prior to discharge on Day 7 and during early termination. A triplicate ECG will be obtained approximately 2 to 4 minutes apart at pre-dose on Day 1. All ECG assessments will be made following at least a 10-minute rest in a supine position and should be collected before PK sample collection, if scheduled at the same time point.
k. Supine blood pressure will be determined following approximately 5-minute rest in a supine position.
l. The modified Child-Pugh assessment as outlined in Appendix 8 should be followed.
m. On Day 1, administration of dacomitinib will occur with approximately 8 oz (240 mL) of ambient temperature water after at least a 10 hour fast. Following dacomitinib administration, no food will be allowed for at least another 4 hours post dose except that a light snack or juice may be provided to a diabetic participant.
n. Blood samples (3 mL each) for PK will be taken upon completion of ECGs, blood pressure and pulse measurements. Serial blood samples for the measurements of dacomitinib and its metabolite, PF-05199265, will be collected prior to dosing and at 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 264 hours following dosing.
o. Blood samples (10 mL each) will be collected prior to dacomitinib dosing and at 6 and 8 hours following dosing.
p. One (1) blood sample (3 mL) only will be collected on Day -1 for CYP2D6 genotyping.
q. One (1) 4 mL blood sample should be drawn on Day -1. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
r. Participants will be eligible for discharge from the CRU following completion of the following: 144-hour PK sample collection, a single supine 12-lead ECG, supine blood pressure and pulse rate, discussion of the need for highly effective contraception, safety laboratory test, evaluation of participant-reported adverse events, review of prior and concomitant medications, brief physical examination, and body weight. Day 7 safety laboratory tests can be collected early (ie. On Day 6) so results are available in time for intended participant discharge on that day.
s. All participants will be followed up by phone call at least 28 days and up to 35 days after the administration of the dacomitinib dose for potential AEs, concomitant treatment use and to confirm appropriate contraception usage.
t. Participant withdrawal/early termination activities will include a brief physical examination (if there is a new or ongoing AE or a previous clinically significant abnormal physical finding), safety laboratory tests, a contraception check, a single supine 12-lead ECG, supine blood pressure and pulse rate, concomitant treatment and AE assessment.

2. INTRODUCTION

Dacomitinib (PF-00299804) is a selective, adenosine triphosphate (ATP) competitive, irreversible, small-molecule inhibitor of the HER (ERBB) family of receptor tyrosine kinases (RTKs), including the epidermal growth factor receptor (EGFR, HER1), the HER2 receptor (ERBB2), the HER4 receptor (ERBB4), and their oncogenic variants (eg, EGFR with del exon 19 or L858R mutations). It is currently approved for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR-activating mutations.

2.1. Study Rationale

The primary metabolic pathways for dacomitinib in human liver microsomes and human hepatocytes in vitro are comprised of oxidation and glutathione conjugation. In vitro studies with human liver microsomes and recombinant cytochrome P450 (CYP) (rCYP) enzymes indicated that the formation of PF-05199265 (O-desmethyl dacomitinib) was mediated primarily by CYP2D6, while CYP3A was involved in the formation of other minor oxidative metabolites observed in humans following oral administration of a single dose of [^{14}C]dacomitinib.

In the absorption, distribution, metabolism, and excretion (ADME) study in humans (Study A7471020), following oral administration of a single [^{14}C]dacomitinib dose (45 mg, 100 μCi) to 6 male healthy participants, approximately 79% of the administered radioactive dose was recovered in feces (approximately 20% unchanged dacomitinib) and 3% in urine (<1% unchanged dacomitinib). Dacomitinib is orally bioavailable with mean absolute bioavailability of 80%. These data indicated significant hepatic component in the elimination of dacomitinib and minimal renal excretion of dacomintib.

A dedicated hepatic impairment clinical study of dacomitinib (Study A7471018) in participants with mild or moderate hepatic impairment has been completed.
Study A7471018 was a multi-center, Phase 1, open-label, non-randomized, single-dose, parallel group study conducted to evaluate the impact of mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) on the pharmacokinetics (PK) of dacomitinib. In that study, a total of 25 men who had normal hepatic function (n = 8), mild hepatic impairment (n = 8), or moderate hepatic impairment (n = 9) but were otherwise healthy were enrolled and received a single 30 mg dose of dacomitinib following an overnight fasting for at least 8 hours. Results demonstrated that plasma dacomitinib area under the concentration time curve from time 0 to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}) were similar in participants with mild hepatic impairment and were reduced marginally (by 15% and 20% for AUC_{inf} and C_{max}, respectively) for participants with moderate hepatic impairment relative to participants with normal hepatic function.

The effect of hepatic impairment on dacomitinib was further evaluated using the National Cancer Institute (NCI) hepatic impairment classification in a pooled population PK analysis of 1381 participants, which included 158 participants with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate transaminase [AST] > ULN, or total bilirubin >1 to 1.5 × ULN with any AST), 5 participants with moderate hepatic impairment (total bilirubin >1.5 to 3 × ULN and any AST) and 1 participant with severe hepatic impairment (total bilirubin > 3 × ULN and any AST). Limited data (n=1) were available for severe hepatic impairment. Participants with mild hepatic impairment had similar dacomitinib clearance (CL) compared to participants with normal hepatic function. Dacomitinib CL was higher in participants with moderate hepatic impairment with mean CL of 31.4 L/h (n=5) compared to 20.5 L/h (n=1202) in participants with normal hepatic function. Hepatic function was not a significant covariate on dacomitinib CL.

Based on the results from both the formal hepatic impairment Study A7471018 and the pooled population PK analysis, mild or moderate hepatic impairment is considered to not have a clinically relevant effect on dacomitinib PK. Therefore, no dose adjustment of dacomitinib is recommended in patients with mild or moderate hepatic impairment. Insufficient data are however available regarding the use of dacomitinib in patients with severe hepatic impairment to provide dosing recommendations in this patient population.

The purpose of this study is to evaluate the effect of severe hepatic impairment on the single dose PK of dacominitinib.

2.2. Background

2.2.1. Nonclinical Pharmacology

Dacomitinib is a highly selective irreversible small molecule inhibitor of the HER (human epidermal growth factor receptor) family of tyrosine kinases. The IC_{50} values against the human catalytic domains of HER-1, HER-2, and HER-4 (HER-3 does not possess tyrosine kinase activity) are 2.8 ng/mL (6.0 nM), 21.5 ng/mL (45.7 nM) and 34.7 ng/mL (74 nM), respectively. Dacomitinib is >500 × selective relative to the concentrations required to inhibit the janus kinase 3 (JAK3), protein kinase b (Akt), insulin-like growth factor 1 receptor (IGF1R), and the platelet-derived growth factor receptor (PDGFR) in kinase assays. The IC_{50} values are 1676, >18,800, >18,800, and 6298 ng/mL (3566, >40,000, >40,000, and 13,400 nM), respectively. Dacomitinib inhibits the tyrosine kinase activity of the HER family through binding at the ATP binding site, which results in covalent modification of a cysteine in the ATP binding pocket. Dacomitinib exhibited anti-tumor effects in 4 different human xenograft models that express and/or overexpress HER family members. In these xenograft models, the therapeutic activity ranged from complete regression to delayed progression. The inhibitory effects on tumor growth generally lasted throughout compound administration. An active metabolite, PF-05199265, has been identified which has similar inhibitory and selectivity profiles compared to dacomitinib.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In nonclinical species (rats, dogs, and monkeys), dacomitinib exhibited moderate to high total plasma clearance in relation to hepatic blood flow, high volume of distribution, and moderate to high oral bioavailability ranging from 56% to 109%. Ratios of the AUC from time 0 to 24 hours postdose (AUC_{24}) for PF-05199265, a circulating active metabolite in humans, to parent were 0.18 in rats and 1.9 in dogs after oral administration of dacomitinib for 3 days. In toxicokinetic studies with rats, rabbits, and dogs, systemic exposure of dacomitinib generally increased with increasing of dose within the dose ranges examined.

After oral administration, [^{14}C]dacomitinib undergoes oxidation and glutathione conjugation as the primary metabolic pathways in rats, dogs, and humans. Formation of PF-05199265 is mediated primarily by CYP2D6 and to a lesser extent, by CYP2C9. CYP3A4 contributes to the metabolism of dacomitinib in the formation of other minor oxidative metabolites. The route of excretion of radioactivity in rats, dogs, and humans was primarily via feces.

Dacomitinib and PF-05199265 demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A activities in human liver microsomes. However, dacomitinib and PF-05199265 inhibited CYP2D6 activity, and may have the potential for clinically relevant drug-drug interaction (DDI) with concomitantly administered CYP2D6 substrates. No significant induction of CYP3A, CYP1A2 or CYP2B6 in cryopreserved human hepatocytes was observed. Based on in vitro data, dacomitinib may have the potential to inhibit uridine-diphosphate glucuronosyltransferase (UGT)1A1 activity.

Dacomitinib has a low potential to cause DDI by inhibiting the efflux transporters P-glycoprotein (P-gp) systemically, organic anion transporting polypeptides (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and human bile salt export pump (BSEP). However, dacomitinib may have the potential to inhibit breast cancer resistance protein (BCRP), P-gp in the gastrointestinal (GI) tract, and OCT1.

2.2.3. Nonclinical Safety

Dacomitinib was assessed in a series of nonclinical studies that included repeated-dose toxicity studies in rats and dogs up to 6 or 9 months in duration, respectively, and safety pharmacology, genotoxicity, and reproductive embryo-fetal development studies. Based on the nonclinical studies conducted, the kidney, digestive system, epithelial cells, and liver have been identified as the primary target tissues/organs of toxicity. Based on the results of the genotoxicity assays conducted, dacomitinib would not be expected to pose a genetic risk for acute or chronic dosing in humans. Embryo-fetal development studies were performed in rats and rabbits where the effects were limited to reductions in maternal and fetal body weight, and lower maternal food consumption. There was no teratogenicity, mortality, or moribundity detected at any dose level tested.

2.2.4. Clinical Overview

As of 29 July 2016, 3182 patients have been treated in 17 clinical studies and 143 healthy participants and 15 patients with solid tumors have been treated in 9 clinical pharmacology studies. Dacomitinib was administered to 2148 of the patients in these trials, in 1975 patients as a single agent or in combination with figitumumab (CP-751,871, a monoclonal antibody targeting the IGF1R), crizotinib (an anaplastic lymphoma kinase [ALK], mesenchymal-epithelial transition [MET] and c-ROS oncogene 1 [ROS1] tyrosine kinase inhibitor), or gedatolisib (PF-05212384, a phosphoinositide 3-kinase [PI3K]/mTOR inhibitor), and in 173 patients in Phase 1 combination therapy studies. Most patients treated in clinical studies had locally advanced or metastatic NSCLC. There were 1473 patients with NSCLC who received single-agent dacomitinib 45 mg once daily (QD), the maximum tolerated dose as determined by Studies A7471001, A7471003, and A7471005. Of these patients, 394 patients had NSCLC with EGFR-activating mutations; 255 of these patients received dacomitinib as first-line treatment.

The most frequently reported adverse events (AEs) in ≥10% of patients included GI-related, skin-and-nail-related, respiratory, and constitutional events.

Results from Study A7471015 indicated that dacomitinib can be administered with or without food. Following a single oral administration of dacomitinib at 45 mg in patients with advanced malignant solid tumors, the median time to reach the maximum observed plasma concentration (T_{max}) of dacomitinib occurred approximately at 5 to 6 hours after dosing. Dacomitinib underwent extensive extravascular distribution with a geometric mean apparent volume of distribution (V_z/F) ranging from 2424 to 2537 L/h and had a mean apparent terminal plasma half-life ($t_{½}$) ranging from 54 to 80 hours. Following administration of multiple daily doses of dacomitinib at 45 mg to patients with advanced malignant solid tumors, steady-state was reached within 14 days, accumulation of dacomitinib in patients ranged from 5.0 to 6.4-fold for AUC, reflecting the observed long $t_{½}$. The geometric AUC over dosing interval (AUC_{tau}) and C_{max} of dacomitinib at steady-state ranged from 1621 to 2213 ng•h/mL and 79.5 to 108.0 ng/mL, respectively. Plasma exposure of dacomitinib increased proportionally with dose in the dose range of 2 mg to 60 mg, indicating linear PK.

Dacomitinib undergoes oxidative metabolism and glutathione conjugation. Oxidative metabolism of dacomitinib involves CYP2D6 for the formation of O-desmethyl dacomitinib (PF-05199265) and CYP3A for the formation of other minor oxidative metabolites. The O-desmethyl metabolite, PF-05199265, is also a potent inhibitor of the HER kinase family in vitro. However, the steady-state exposure of PF-05199265 in human plasma is <20% when compared with the exposure observed for dacomitinib. Furthermore, PF-05199265 is also highly bound to plasma proteins (>99%), which indicates that the unbound fraction for PF-05199265 in plasma is <1% of the reported total plasma exposure.

A dedicated hepatic impairment study (Study A7471018) was conducted to evaluate the effect of hepatic impairment on dacomitinib exposure after a single 30 mg dose. This was a Phase 1 open-label, non-randomized, single-dose, parallel-group study in 25 participants with mild hepatic impairment (Child-Pugh Class A, score 5-6, n = 8), moderate hepatic

impairment (Child-Pugh Class B, score 7-9, n = 9), and a control group of healthy participants with normal hepatic function (n = 8). The results showed that the mean fraction of dacomitinib unbound in plasma (f_u) was identical across the 3 groups (f_u = 0.02). The mean (percent coefficient of variation [%CV]) f_u of PF-05199265 was 0.00011 (28%), 0.00016 (69%), and 0.00025 (62%) for participants with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment, respectively. Results also showed that mild hepatic impairment status did not alter dacomitinib plasma exposures and that moderate hepatic impairment status reduced dacomitinib plasma exposures (AUC_{inf} and C_{max} by 15% and 20%, respectively) as compared to normal hepatic function. These changes are not considered clinically significant and no starting-dose adjustment is currently recommended for patients with mild or moderate hepatic impairment. In addition, a single oral 30 mg dose of dacomitinib was well tolerated in participants with mild or moderate impaired hepatic function. No participants in the normal hepatic function group or the mild hepatic impairment group experienced an AE. One (1) participant in the moderate hepatic impairment group died due to a road traffic accident. This death was classified as a serious adverse event (SAE) and was considered to be severe but was not treatment-related. There were no laboratory safety tests, vital signs results, or electrocardiogram (ECG) results of clinical concern.

2.3. Benefit/Risk Assessment

Dacomitinib is not expected to provide any clinical benefit to the participants of this study. This study is designed to evaluate safety, tolerability, and PK in participants with severe hepatic impairment and matched controls to assist the further clinical development of dacomitinib.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of dacomitinib may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	Primary:
• To evaluate the effect of severe hepatic impairment on the single dose plasma PK of dacomitinib.	• Plasma C_{max} and AUC_{inf} of dacomitinib. If AUC_{inf} cannot be reliably estimated, then AUC from time 0 to the time of last quantifiable concentration (AUC_{last}) will be used as the primary endpoint.
Secondary:	Secondary:
• To assess the safety and tolerability of a single oral dose of dacomitinib in participants with normal hepatic function and participants with severe hepatic impairment.	• Overall safety profile as characterized by laboratory test abnormalities, physical examination, vital signs, ECGs, and AE monitoring.
Tertiary/Exploratory:	Tertiary/Exploratory:
• To characterize the effect of severe hepatic impairment on other plasma PK parameters of dacomitinib and its metabolite PF-05199265.	• Plasma AUC_{last}, apparent oral clearance (CL/F), V_z/F, $t_{½}$, T_{max}, f_u, unbound AUC_{inf} ($AUC_{inf,u}$), unbound AUC_{last} ($AUC_{last,u}$), unbound C_{max} ($C_{max,u}$), unbound CL/F (CL_u/F) and unbound V_z/F ($V_{z,u}/F$) for dacomitinib; C_{max}, AUC_{inf}, AUC_{last}, $t_{½}$, T_{max}, f_u, $AUC_{inf,u}$, $AUC_{last,u}$, $C_{max,u}$ for PF-05199265, as data permit.
• To analyze CYP2D6 genotype in pharmacogenetic samples.	• CYP2D6 phenotype.
• To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).

4. STUDY DESIGN

4.1. Overall Design

This will be a Phase 1, open-label, parallel-group study to investigate the effect of severe hepatic impairment on the plasma PK, safety and tolerability after a single oral 30 mg dose of dacomitinib under fasted conditions.

At Screening, the modified Child-Pugh classification score as outlined in Appendix 8 will be utilized to assess entry criteria and to assign participants into the appropriate hepatic impairment group (Table 1). The modified Child-Pugh classification criteria will permit enrollment of participants with a history of Stage 3 or Stage 4 encephalopathy who are receiving medication(s) to prevent recurrent encephalopathy; participants with clinically active Stage 3 or 4 encephalopathy will be excluded from participation in the study. The criteria will also allow enrollment of participants with history of severe ascites who are on medication(s) to control their ascites. Details of the modified Child-Pugh assessment can be found in Appendix 8.

Table 1. Hepatic Function Categories Based on Child-Pugh Classification

Cohort	Description	Child-Pugh Score	Number of Participants
1	Severe hepatic impairment	Class C (10 to 15 points)	8
2	Normal hepatic function	Not applicable	8[a]

a. Participants in Cohort 2 may be dosed to a maximum of 10 participants to ensure that the age of each participant in Cohort 2 is within ±10 years and the body weight is within ±15 kg to the median age and median body weight of participants in Cohort 1, respectively.

Approximately 18 participants will be enrolled into the study to ensure at least 6 PK evaluable (having data for estimating primary PK parameters for dacomitinib) participants in each cohort. Participants who withdraw may be replaced upon agreement with the Sponsor.

The participants from the severely impaired hepatic function cohort will be recruited first, and a median value for age and weight will be determined for all evaluable participants across study sites in this cohort. Then the control participants from the normal hepatic function cohort will be recruited later such that the age of each participant in Cohort 2 is within ±10 years and the body weight is within ±15 kg of the median of the participants in the severe hepatic impairment cohort (Cohort 1). An attempt will be made to maintain a similar male/female ratio and racial make-up between Cohorts 1 and 2. Approval from the Sponsor must be obtained ***before*** proceeding with dosing participants in Cohort 2.

In this study, participants will be screened for participation within 28 days prior to the dosing of dacomitinib. Each participant will be admitted to the clinical research unit (CRU) on Day -1. Results from the Day -1 safety assessments will be reviewed along with the screening assessments and the participant's recent medical history to ensure that each participant meets the inclusion and exclusion criteria for this study as defined in Sections 5.1 and 5.2 of this protocol, respectively. Additional assessment may be done at the discretion of the investigator. Participants who meet the inclusion and exclusion criteria for the study on Day -1 will be assigned a randomization number on Day 1 (see Section 6.3 for details), and will be enrolled into the study.

Following an overnight fast of at least 10 hours, participants will be administered a single oral 30 mg dose of dacomitinib with approximately 240 mL (8 ounces) of ambient temperature water on the morning of Day 1. No food will be allowed for at least 4 hours post-dose except that a light snack or juice may be provided to diabetic participants. Each participant will undergo serial blood sampling to determine plasma concentrations of dacomitinib and PF-05199265 until 264 hours (Day 12) post-dose. At pre-dose and at 6 and 8 hours post-dose, separate aliquots of blood (10 mL) will be collected for measurement of protein binding. Participants will be confined to the unit until Day 7.

After the PK data from all participants with severe hepatic impairment (Cohort 1) have been reviewed, the Sponsor will notify the site if additional participants for Cohort 1 are required. If no additional participants are required, recruitment for participants with normal hepatic function (Cohort 2) will begin. If the PK variability is greater than expected, additional participants may be enrolled in Cohort 1 and the sample size for Cohort 2 will also be increased accordingly.

Physical examinations, single or triplicate supine 12-lead ECG, vital sign measurements, and clinical laboratory tests will be conducted and AEs will be monitored throughout the study to assess safety. All participants will be followed up by a phone call at least 28 days and up to 35 days after dacomitinib dosing.

4.2. Scientific Rationale for Study Design

A parallel group design will be utilized to compare the dacomitinib PK between participants with normal hepatic function and participants with severely impaired hepatic function but are otherwise healthy. The participants from the severely impaired hepatic function cohort will be recruited first, then the participants from the normal hepatic function cohort will be recruited later to match the median demographics from severe hepatic impairment group. The modified Child-Pugh classification system will be the method used in this study to identify participants with severe hepatic impairment. Additionally, total bilirubin and AST will be assessed in this study as per the recommendations of the National Cancer Institute Organ Dysfunction Working Group Criteria for assessment of hepatic impairment.[2]

This study is designed using a single dose of dacomitinib considering that single dose plasma PK of dacomitinib has been documented to be generally predictive of exposure at steady state. All participants enrolled in this study will receive 1 single oral 30 mg dose of dacomitinib administered as tablet(s). The PK samples will be collected serially up to 264 hours postdose, which has been shown to be adequate for participants with normal, mild or moderate hepatic function. This sampling duration is also expected to be adequate for characterizing the elimination phase of the plasma dacomitinib concentration-time profile for participants with severe hepatic impairment, for whom the elimination half-life of dacomitinib may be prolonged.

Dacomitinib undergoes both oxidative metabolism and glutathione conjugation. Oxidative metabolism of dacomitinib involves CYP2D6 for the formation of major circulating metabolite, PF-05199265, which has similar in vitro pharmacological activities as dacomitinib. Therefore the plasma PK for both dacomitinib and PF-05199265 will be evaluated in this study.

Since CYP2D6 metabolism is a component of dacomitinib elimination, genetic polymorphisms of CYP2D6 may have the potential to alter dacomitinib PK. A 3-mL blood sample will be collected on Day -1 from each participant for genotyping CYP2D6 polymorphism. Only participants identified as an CYP2D6 extensive metabolizer (EM) or CYP2D6 intermediate metabolizer (IM) will be included in the primary statistical analysis to evaluate the impact of severe hepatic impairment on dacomitinib plasma PK.

Banked biospecimens will be collected for exploratory pharmacogenomics (PGx)/genomic analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's (IP's) mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

In the current study, a single 30 mg oral dose of dacomitinib will be administered to participants with normal hepatic function or participants with severe hepatic impairment. The single oral dose of dacomitinib 30 mg is the same dose that was tested in the previously conducted hepatic impairment study of dacomitinib (Study A7471018), where this dose was well-tolerated in participants with mild or moderate hepatic impairment. There were no clinically significant findings in vital signs, clinical laboratory test parameters, or ECGs.

Hence previous investigations have indicated that mild and moderate hepatic impairment had no clinically relevant effects on dacomitinib PK, and no adjustment of starting dose is currently recommended for patients with mild or moderate hepatic impairment. In addition, there were 1473 patients with advanced NSCLC who received dacomitinib 45 mg QD, the recommended starting dose. Following multiple oral administration of 45 mg QD doses, accumulation of dacomitinib in patients ranged from 5.0- to 6.4-fold for AUC_{tau}. The AUC in participants receiving a single 30 mg dose is expected to be 7.5 to 9.6 fold lower than the exposure in patients receiving 45 mg QD at steady state.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1. All Participants

Age and Sex:

1. Male and/or female participants of non-childbearing potential must be 18 to 75 years of age, inclusive, at the time of signing the informed consent document (ICD).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Weight:

3. Body mass index (BMI) of 17.5 to 40 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.1.2. Additional Inclusion Criteria for Participants with Normal Hepatic Function (Cohort 2)

1. No known or suspected hepatic impairment based on liver function tests (eg, alanine aminotransferase [ALT], AST, alkaline phosphatase [ALP], and bilirubin), albumin and prothrombin time defined as the following, with a single repeat permitted to assess eligibility, if needed:

    a. ALT and AST ≤upper limit of normal (ULN);

b. Total bilirubin ≤ULN. Note that participants with a history of Gilbert syndrome (and hence elevated total bilirubin) are eligible provided direct bilirubin level is ≤ULN **plus** ALT and AST are ≤ULN **plus** alkaline phosphatase, hemoglobin, and reticulocyte count are all ≤ULN;

c. ALP ≤ULN;

d. Albumin within the normal range (local laboratory ranges);

e. Prothrombin time ≤ULN.

2. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, complete physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead ECG or clinical laboratory tests.

3. Participants must fit the demographic-matching criteria, including:

- Body weight ±15 kg of the median of the severe hepatic impairment cohort (Cohort 1), as provided by the Sponsor.

- Age ±10 years of the median of the severe hepatic impairment cohort (Cohort 1), as provided by the Sponsor.

5.1.3. Additional Inclusion Criteria for Participants with Severely Impaired Hepatic Function (Cohort 1)

1. Satisfy the criteria for Class C (severe hepatic impairment) of the modified Child-Pugh classification.

2. A diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computerized tomography scan, or magnetic resonance imaging (MRI).

3. Stable hepatic impairment, defined as no clinically significant known change in disease status within the last 30 days, as documented by the participant's recent medical history (eg, no worsening clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time by more than 50%).

4. Stable drug regimen is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to the dosing of dacomitinib.

5. History of alcohol abuse is permissible providing that the results of alcohol test are negative at Screening or on Day -1, and the participant is willing and able to abide by the lifestyle guidelines described in Section 5.3.2 of this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. All Participants

Medical Conditions:

1. Any condition possibly affecting drug absorption (eg, gastrectomy).
2. Other 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 IP 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.
3. History of or current positive results for human immunodeficiency virus (HIV).

Prior/Concomitant Therapy:

Not applicable.

Prior/Concurrent Clinical Study Experience:

4. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP used in this study (whichever is longer).
5. Hypersensitivity to dacomitinib or its excipients.

Diagnostic Assessments:

6. A positive urine drug test. Participants with severe hepatic impairment (Cohort 1) will be eligible to participate if their urine drug test is positive with a drug for a prescribed condition that is not expected to interfere with the PK of dacomitinib.

Other Exclusions:

7. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
8. History of sensitivity to heparin or heparin-induced thrombocytopenia.
9. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
10. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.2.2. Additional Exclusion Criteria for Participants with Normal Hepatic Function (Cohort 2)

In addition, participants in the normal hepatic function cohort (Cohort 2) presenting with any of the following will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies deemed relevant for participation in this study, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.

3. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If initial supine BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

4. Screening 12-lead ECG demonstrating corrected QT (Fridericia method) (QTcF) >450 msec and/or a QRS complex >120 msec. If initial QTcF exceeds 450 msec, or QRS complex exceeds 120 msec, the ECG should be repeated 2 more times and the average of the three QTcF and/or QRS complex values should be used to determine the participant's eligibility.

5. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case by case basis following approval by the Sponsor. Herbal supplements and hormone replacement therapy must have been discontinued at least 28 days prior to the dose of dacomitinib.

6. Participants with a history of or current positive results for hepatitis B or hepatitis C, including hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb).

5.2.3. Additional Exclusion Criteria for Participants with Severely Impaired Hepatic Function (Cohort 1)

1. Other clinically significant disease that contraindicates study drug or that may affect the PK of dacomitinib (stable, chronic, controlled disorders such as hypertension and diabetes may be acceptable upon Sponsor agreement).

2. Hepatic carcinoma and hepatorenal syndrome.

3. Undergone porta-caval shunt surgery.

   NOTE: Participants with a transjugular intrahepatic portosystemic shunt (TIPS) are permitted provided that they meet the Child-Pugh classification criteria.

4. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than 1 month prior to study entry.

5. Any clinically significant laboratory abnormality except for those parameters influenced by hepatic impairment.

6. Participants with an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation, with a single repeat permitted to assess eligibility, if needed;

7. Presence of clinically active Stage 3 or 4 encephalopathy.

8. Severe uncontrolled ascites and/or pleural effusion.

9. Screening supine blood pressure ≥160 mm Hg (systolic) or ≥90 mm Hg (diastolic), on a single measurement following at least 5 minutes of rest. If initial supine BP is ≥160 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the participant's eligibility.

10. Screening supine 12-lead ECG demonstrating QTcF >470 msec. If initial QTcF exceeds 470 msec, the ECG should be repeated two more times and the average of the three QTcF values should be used to determine the participant's eligibility.

11. Use of food, drugs, or dietary supplements that may affect the PK of dacomitinib within 7 days or 5 half-lives (whichever is longer) prior to the dose of dacomitinib. Use of medications that are not believed to affect participants' safety and are medically necessary for the treatment and maintenance of hepatic disease and other pre-existing and/or concurrent stable comorbid conditions are permitted with approval by the Sponsor. Limited use of nonprescription medications that are not believed to affect participants' safety or the overall results of the study may be permitted on a case by case basis with approval by the Sponsor. Herbal supplements and hormone replacement therapy must have been discontinued at least 28 days prior to the dose of dacomitinib.

12. Use of CYP2D6 substrates with a narrow therapeutic index.

13. Use of food or drugs that are CYP2D6 inhibitors within 7 days or 5 half-lives (whichever is longer) prior to the first dose of dacomitinib until the completion of the last PK sample collection. All concomitant medication must be approved by the Sponsor.

[redacted]

14. Use of proton-pump inhibitors (PPIs) within 7 days prior to the first dose of dacomitinib until the completion of the last PK sample collection.

15. Participants will abstain from taking lactulose or other medications which could result in diarrhea or have excessive (>2) bowel movements per day within 24 hours prior to dacomitinib dosing and 24 hours post dosing.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample on Day 1.

- Water is permitted until 1 hour prior to dacomitinib administration on Day 1. Water may be consumed without restriction beginning 1 hour after dosing. No food will be allowed for at least 4 hours postdose except that a light snack or juice may be provide to a diabetic particpant.

- Lunch will be provided approximately 4 hours after dacomitinib dosing on Day 1.

- Dinner will be provided approximately 9 to 10 hours after dacomitinib dosing on Day 1.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of IP until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Participants will undergo an alcohol breath test as indicated in SoA.

- Consumption of caffeinated drinks and nicotine containing products (≤5 cigarettes per day or equivalent) is permitted during participation in the study; however, participants will abstain from nicotine or caffeine containing products for at least 2 hours prior to any scheduled ECG or BP determinations.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dacomitinib dosing.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IP/entered in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Additionally during Screening:

- For inclusion and Child-Pugh classification, clinical laboratories that are deemed inconsistent, by the investigator, with the usual stage of hepatic impairment may be repeated;

- For eligibility purposes, vital signs, laboratory tests, or ECG results may be repeated if an abnormal result is observed at the initial reading;

- In the event that the participation of a participant in the study is delayed and any required screening procedures will be outside of the allowed screening window (28 days), these screening procedures can be repeated;

- Participants who are not qualified based on a reversible medical condition or mild/acute/intercurrent illness may be re-evaluated after further testing/examination or re-screened after the condition has resolved.

6. 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.

For the purposes of this protocol, the term IP may be used synonymously with study intervention.

6.1. Study Intervention Administered

For this study, the IP is dacomitinib.

Tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive a single 30 mg dacomitinib tablet at approximately 0800 hours (±2 hours). Investigator site personnel will administer dacomitinib tablet with approximately 240 mL of ambient temperature water. Participants will swallow the tablet whole, and should not manipulate or chew the tablet prior to swallowing.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. 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 IP accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

8. 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.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the IP ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of IP, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Tablets will be dispensed at the CRU in the individual dosing containers by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

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.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Study Intervention Compliance

IP will be administered under the supervision of investigator site personnel. The oral cavity of each participant will be examined following dosing to ensure the IP was taken.

6.5. Concomitant Therapy

For participants with normal hepatic function (Cohort 2), use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of IP. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the Sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

For participants with severe hepatic impairment (Cohort 1), stable concomitant medications may be given if they are considered necessary for the welfare of the participants(eg, standard therapy for the underlying diseases), considering these medications are not contraindicated with dacomitinib and are unlikely to interfere with the PK of dacomitinib.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of IP will be documented as a prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatments.

6.6. Dose Modification

Participants in this study will receive a single oral dose of 30 mg dacomitinib. No dose modification is allowed.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Not applicable since this is a single dose study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of 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 or her or persons previously authorized by the participant to provide this

information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of IP or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the IP to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an intravenous (IV) catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 140 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Efficacy assessments are not applicable in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and body weight will also be measured and recorded as per the SoA. For measuring body weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of body weight.

8.2.2. Vital Signs

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.3. Electrocardiograms

Single or triplicate 12-Lead ECG should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and corrected QT (QTc) intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected on Day 1 at predose will serve as each participant's time-controlled baseline QTc value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after dacomitinib dosing should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory test assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory test values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive IP.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving IP), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the IP.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety 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 IP must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the IP under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until 3 weeks after the last dose.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the IP by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the IP under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

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

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the Sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form only when associated with an SAE.

8.4. Treatment of Overdose

For this study, any dose of dacomitinib greater than 30 mg will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor immediately.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until dacomitinib can no longer be detected systemically (at least 17 days, 5 × dacomitinib half-life).

3. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety only when associated with an SAE.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Pharmacokinetic Assessment of Dacomitinib and PF-05199265

Blood samples of approximately 3 mL, to provide a minimum of 1 mL of plasma, will be collected into appropriately labeled tubes containing dipotassium ethylenediamine tetraacetic acid (K_2EDTA) at each specified time point for measurement of plasma concentrations of dacomitinib and its metabolite PF-05199265 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF). Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Samples will be used to evaluate the PK of dacomitinib and PF-05199265. Samples collected for analyses of dacomitinib and PF-05199265 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of dacomitinib and PF-05199265 will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised.

8.5.2. Protein Binding Assessment

Blood samples (10 mL of blood to obtain 4 ml of plasma) for protein binding analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the SoA. The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the protein binding samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs.

The blood samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

8.7. Genetics

8.7.1. CYP2D6 Genotyping Analysis

A 3-mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected. DNA samples will be analyzed for the purpose of determining the genotype of CYP2D6.

Genes for other drug-metabolizing enzymes or transporters suspected to be involved in the metabolism and/or excretion of dacomitinib may also be evaluated. No other genes will be analyzed.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual or by the Sponsor.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response. Genes and other analytes (eg, proteins, ribonucleic acid (RNA), nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in laboratory manual or by the Sponsor.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

Approximately 18 participants will be enrolled into the study to ensure 6 PK evaluable participants in each of the 2 cohorts. This sample size is consistent with recommendations from the Food and Drug Administration (FDA) Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling[3] (issued by Center for Drug Evaluation and Research [CDER]/ Center for Biologics Evaluation and Research [CBER], May 2003).

9.3. Populations for Analysis

Population	Description
Safety	All participants assigned to dacomitinib and who take 1 dose of dacomitinib.
PK Concentration	All participants who take 1 dose of dacomitinib and have at least 1 dacomitinib plasma concentration.
PK parameter	All participants who take 1 dose of dacomitinib and have at least 1 dacomitinib plasma PK parameters of primary interest.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

AEs, ECGs, BP, pulse rate, and safety laboratory test data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory test, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively by cohort, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by cohort and time.

The number (%) of participants with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated by cohort:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

9.4.3. Other Analyses

PGx data will be collected and retained for future analyses, but will not be analyzed, specifically, for this study.

9.4.3.1. Pharmacokinetic Analyses

The effect of hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals (CIs) around the estimated difference between the Test (severe hepatic impairment cohort; Cohort 1) and the Reference (normal hepatic function; Cohort 2) using a one-way analysis of variance (ANOVA) model based on natural log transformed data. Only participants with CYP2D6 EM and IM in each cohort will be included in this analysis.

One-way ANOVA will be used to compare the natural log transformed AUC_{inf}, AUC_{last} and C_{max}, and $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$ of dacomitinib and PF-05199265, as data permit, for severe hepatic impairment cohort (Test) to the normal hepatic function cohort (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios as a percentage.

The dacomitinib PK parameters (AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, $C_{max,u}$, T_{max}, $t_{½}$, CL/F, CL_u/F, V_z/F, and $V_{z,u}/F$) and PF-05199265 PK parameters (AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, $C_{max,u}$, T_{max}, $t_{½}$) will be summarized descriptively by cohort. Boxplots of mean, median and individual participant parameters will be made by cohort for AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, and $C_{max,u}$. Similar presentations will also be made for other PK parameters, if considered relevant. Dacomitinib and PF-05199265 total and unbound concentrations will be listed and summarized descriptively by PK sampling time and cohort. Summary profiles (means and medians) of the dacomitinib and PF-05199265 concentration-time data will be plotted by cohort on linear and semi-log scale. Individual participant concentration time profiles will be also presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

9.4.3.2. Pharmacodynamic Analyses

Not applicable.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the Sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose selection decisions, and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the Sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IP, 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.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the Sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the Sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-Sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-Sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-Sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the

centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan/contracts.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the Sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the Sponsor or its agents to prepare the investigator site for the inspection and will allow the Sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the Sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

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

Data reported on the CRF or entered in the electronic CRF (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.

10.1.8. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the Sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the Sponsor 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The Sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/team SharePoint site/study portal/clinical trial management system (CTMS)/study team on demand (StoD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 2) will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count PT/INR WBC count Total neutrophils (abs) Eosinophils (abs) Monocytes (abs) Basophils (abs) Lymphocytes (abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	At screening only: • FSH[b] • Urine drug screening[c] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus

Abbreviations: abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; qual = qualitative; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

Investigators must document their review of each laboratory safety report.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the clinical study report (CSR). Samples to be used for this purpose will be shipped to either a Pfizer-approved Biospecimen Banking System (BBS) facility or other designated laboratory and retained for up to 1 year following the completion of the study.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the IP under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	None	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the Sponsor. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 3 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s) (eg, 5 terminal half-lives) plus an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent;

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Use of an additional highly effective contraceptive method with a failure rate of <1% per year as described below in Section 10.4.4 for a female partner of childbearing potential.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant, not a WOCBP (see definitions below in Section 10.4.3), is eligible to participate.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female.

    - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;
    - Injectable.

3. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- 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 IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP;

- 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).

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

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the IP, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an 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) to Pfizer Safety 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 Safety 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 baby, 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 to Pfizer Safety 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 the IP.

Additional information regarding the EDP may be requested by the Sponsor. 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 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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to dacomitinib or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 1 years or other period as per local requirements or will not be stored beyond the completion of this study (eg, CSR finalization)].
    - Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (Tbili) elevations (>2 × ULN) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and Tbili values will be elevated within the same laboratory sample). In rare instances, by the time Tbili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to Tbili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and Tbili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a Tbili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR Tbili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - 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).

    - Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and Tbili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the Sponsor.

The participant should return to the investigator 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 and Tbili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and Tbili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS complex >120 msec).
• New-onset right bundle branch block (QRS complex >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Modified Child-Pugh Classification (CPC) of Liver Dysfunction

CPC score is calculated from the sum of the points for each CPC criteria:

CPC Classification	Level of dysfunction	Score
C	Severe	≥10

Assessment Parameters	Assigned Score for Observed Findings		
	1 point	2 point	3 point
Encephalopathy grade (refer to table below)	0	1 or 2	3 or 4[a]
Ascites	Absent	Slight	Moderate[b]
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, seconds prolonged	<4	4 to 6	>6

a. Including participants with a history of stage 3 or stage 4 encephalopathy receiving medication(s) to prevent recurrent encephalopathy; participants with clinically active stage 3 or 4 encephalopathy are excluded from participation in the study.
b. Including participants with history of severe ascites on medication(s) to control their ascites.

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4	Unrousable coma, no personality/behavior, decerebrate

10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
%CV	percent coefficient of variation
abs	absolute
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
Akt	protein kinase b
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{24}	area under the concentration time curve from time 0 to 24 hours post-dose
AUC_{inf}	area under the concentration time curve from time 0 to infinity
$AUC_{inf, u}$	unbound AUC_{inf}
AUC_{last}	area under the concentration time curve from time 0 to the time of last quantifiable concentration
$AUC_{last, u}$	unbound AUC_{last}
AUC_{tau}	area under the concentration time curve over doing interval tau
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSEP	bile salt export pump
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CK	creatine kinase
C_{max}	maximum observed plasma concentration
$C_{max, u}$	unbound C_{max}
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CL/F	apparent oral clearance
CL_u/F	unbound CL/F
CPC	Child-Pugh Classification
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CTMS	clinical trial management system
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury

Abbreviation	Term
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EM	extensive metabolizer
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
f_u	fraction of unbound drug in plasma
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IGF1R	insulin-like growth factor 1 receptor
IM	intermediate metabolizer
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JAK3	janus kinase 3
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test
MDRD	Modification of Diet in Renal Disease
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
N/A	not applicable
NCI	National Cancer Institute

Abbreviation	Term
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PCD	primary completion date
PD	pharmacodynamic(s)
PDGFR	platelet-derived growth factor receptor
PGx	pharmacogenomic(s)
P-gp	P-glycoprotein
PI	principal investigator
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
PR	pulse rate
PT	prothrombin time
QD	once daily
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
ROS1	ROS oncogene 1
RTK	receptor tyrosine kinase
rCYP	recombinant cytochrome P450
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal phase half-life
Tbili	total bilirubin
TIPS	transjugular intrahepatic portosystemic shunt
T_{max}	time to reach the maximum observed plasma concentration
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution
$V_{z,u}/F$	Unbound V_z/F
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

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