CLINICAL PROTOCOL — A7471055

TREATMENT ACCESS PROTOCOL FOR PATIENTS PREVIOUSLY TREATED WITH DACOMITINIB ON A CLINICAL TRIAL IN JAPAN

Compound:	PF-00299804
Compound Name:	Dacomitinib
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
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[redacted]

Document History

Document	Version Date	Summary of Changes
Original Protocol	28 January 2015	Not Applicable (N/A)

Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
ATP	adenosine triphosphate
BUN	blood urea nitrogen
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAI	dosage and administration instructions
DMC	data monitoring committee
DVT	deep vein thrombosis
EC	ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Group
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EDTA	edetic acid (ethylenediaminetetraacetic acid)
GCP	Good Clinical Practice
HDPE	High Density PolyEthylene
HER	Human Epidermal Growth Factor receptor
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IEC	institutional ethics committee
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
KRAS	Kirsten Rat Sarcoma viral oncogene homolog
LFT	liver function test
LSLV	last subject last visit
N/A	not applicable
NCIC-CTG	National Cancer Institute of Canada-Clinical Trials Group
NSCLC	non-small cell lung cancer
OS	overall survival
PCD	primary completion date
PFS	progression-free survival
PS	performance status
PT	prothrombin time
RTK	receptor tyrosine kinase

SAE	serious adverse event
SOP	standard operating procedure
SRSD	single reference safety document
ULN	upper limit of normal
US	United States
WBC	white blood cell

PROTOCOL SUMMARY

Indication:

This treatment extension study will enroll patients with advanced cancer who are receiving single-agent dacomitinib in a prior study in Japan, and have the potential to derive clinical benefit without unacceptable toxicity from continued single-agent dacomitinib treatment.

Background and Rationale:

Dacomitinib is an orally available, selective adenosine triphosphate (ATP)-competitive irreversible small-molecule inhibitor of Human Epidermal Growth Factor receptor (HER, erbB) family receptor tyrosine kinases (RTKs) including the epidermal growth factor receptor (EGFR, HER-1), HER-2 receptor (erbB2), and HER-4 (erbB4) receptor and their oncogenic variants (ie, EGFR exon 19 deletion, EGFR L858R point mutation, and EGFR T790M mutation).

Dacomitinib is being developed globally in locally advanced or metastatic non-small cell lung cancer (NSCLC) after at least one prior chemotherapy regimen. In the course of development, Phase 2 and 3 studies are being conducted in several NSCLC treatment settings.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure (IB).

Indications of activity have been seen in a number of dacomitinib clinical trials. This protocol permits continued access to dacomitinib for patients who participated in other dacomitinib monotherapy treatment protocols and have the potential to derive clinical benefit without unacceptable toxicity from continued dacomitinib treatment. This treatment access protocol is only open to patients in Japan.

Patients will follow a schedule of visits and data collection that permits continued safety monitoring.

Objectives:

Primary Objective:

- To allow access to dacomitinib for patients who received dacomitinib on a prior study in Japan and who have the potential to derive continued clinical benefit from single-agent dacomitinib treatment without unacceptable toxicity based upon the investigator's judgment.

Secondary Objective:

- To monitor the specific long-term safety and tolerability of single-agent dacomitinib in patients who have already received dacomitinib on a prior study in Japan.

Endpoints:

Adverse events as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE.v4.0).

Study Design:

This is a multi-center, open-label, treatment extension study open in Japan only. Eligible patients include those with advanced cancer who received and tolerated single-agent dacomitinib in a prior clinical study and have the potential to derive continued clinical benefit based on investigator judgment. Patients enrolled in this extension study may continue to receive dacomitinib starting at the current dose level in the prior study. Dose reductions and re-escalations are allowed based on tolerability. Patients may continue to be treated with dacomitinib on this protocol as long as there is evidence of clinical benefit in the judgment of the investigator. Adverse events will be graded according to NCI CTCAE v4.0, and monitored according to the frequency outlined in the Safety Review Plan.

Study Treatment:

Patients will receive continuous daily dosing of dacomitinib at a dose of 45 mg, 30 mg, or 15 mg. The starting dose of dacomitinib on this treatment extension study will be the patient's ending dose from the prior study.

Patients may continue single-agent dacomitinib treatment on this treatment extension study as long as there is reasonable evidence of clinical benefit without unacceptable toxicity per investigator judgment and with agreement of the Sponsor (see Section 6.1 Patient Withdrawal).

Statistical Methods:

Due to the nature of this study, the number of patients to be enrolled is not predetermined.

No statistical methods will be employed to test a specific hypothesis in this study. Only descriptive summaries of safety will be provided, and no inferential analyses are planned.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides details of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for additional information on certain specific procedures and assessments required for compliance with the protocol.

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

Table 1. SCHEDULE OF ACTIVITIES

Protocol Activity	Screening (≤28 days prior to study entry)	Cycle 1 Day 1	Cycles 2 and beyond		End of Treatment	Follow-up Visit[9]
			Every 8 weeks	Every 6 months		
Informed Consent[1]	X					
Patient History	X					
Registration		X				
Laboratory						
Hematology[2]	X		X		X	
Blood Chemistry[3]	X		X		X	
Urinalysis[4]	X					
Pregnancy test[5]	X	X			X	
Safety/Disease Assessments						
Tumor Assessments[6]				X		
AdAdverse Event Assessments[7]		X	X	X	X	X
Concomitant Medication[8]		X	X	X	X	X
Study Treatment						
Dacomitinib		As per dosing regimen in original protocol				

1. **Informed Consent:** All patients must sign an informed consent document prior to any study-related procedures that are not considered to be standard of care and prior to receiving study drug.
2. **Hematology:** Be performed according to local standard clinical practice. The interval for laboratory assessments should not be longer than every 8 weeks.
3. **Blood Chemistry:** Be performed according to local standard clinical practice. The interval for laboratory assessments should not be longer than every 8 weeks.
4. **Urinalysis:** Be performed according to local standard clinical practice.
5. **Pregnancy Test:** Pregnancy Test (serum or urine) for women of child-bearing potential shall be done at screening and before investigational product administration at the baseline visit. It should be repeated the end of study treatment, and additionally whenever one menstrual cycle is missed, or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs), or if required by local regulations.
6. **Tumor Assessments:** On-study tumor assessments should be performed according to site standard-of-care imaging modality. The interval for monitoring disease status and for progression of disease should not be longer than every 6 months.
7. **Adverse Event Assessment:** Following the first dose, adverse events (AEs) and serious adverse events (SAEs) should be assessed and documented during the study reporting period. All reported study drug-related adverse events must be followed until the event has resolved, returned to baseline, or has been deemed irreversible, or until death, whichever occurs first.
8. **Concomitant Medications:** Review medications taken by the patient since the last visit to determine whether or not treatment with dacomitinib is contraindicated.
9. **Follow-up Visit:** At least 28 days, and no more than 35 days, after discontinuation of treatment, patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

This treatment extension study will enroll patients with advanced cancer who are receiving single-agent dacomitinib in a prior study in Japan, and have the potential to derive continued clinical benefit without unacceptable toxicity from single-agent dacomitinib treatment.

Dacomitinib is a potent, orally available, selective adenosine triphosphate (ATP) competitive irreversible small molecule inhibitor of Human Epidermal Growth Factor receptor (HER, erbB) family receptor tyrosine kinases (RTKs) including the epidermal growth factor receptor (EGFR, HER 1), HER 2 receptor (erbB2), and HER 4 (erbB4) receptor and their oncogenic variants (ie, EGFR exon 19 deletion, EGFR L858R point mutation, and EGFR T790M mutation).

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. It represents a second generation, irreversible pan-HER inhibitor with superior biopharmaceutical and preclinical anti-tumor activity to the first generation, irreversible pan-HER inhibitor CI-1033. The development of dacomitinib has focused on addressing the potential liabilities of first generation pan-HER inhibitors, which includes limited clinical activity possibly due to insufficient drug exposure for adequate target suppression.

Dacomitinib has significantly improved pharmacokinetic properties (greater bioavailability, longer half-life, larger volume of distribution, and lower clearance) across all nonclinical species tested (rat, dog and monkey). In preclinical human tumor xenograft models, dacomitinib showed greater antitumor effects, better distribution of drug to the tumor, and greater and more sustained inhibition of HER activity in the tumor as compared with CI-1033. It exhibited anti-tumor effects in at least four different human xenograft models that express and/or overexpresss HER family members. The unique irreversible and highly selective properties of dacomitinib for the HER kinase family, results in sustained suppression of receptor tyrosine kinase activity. The long-lasting inhibition of receptor phosphorylation reduces concern over potentially short plasma half-lives. Furthermore, the low nanomolar potency and irreversible binding of the intended targets reduce the need for high peak plasma levels, which in turn could minimize target-nonspecific toxicities.

1.2. Clinical Experience with Dacomitinib in Humans

As of 16 May 2014, 2720 patients with advanced cancer have been enrolled and treated in 15 clinical trials evaluating the safety, efficacy, and pharmacokinetics of dacomitinib. Details regarding the dacomitinib clinical studies may be found in the dacomitinib Investigator Brochure (IB).

Ongoing safety monitoring at this stage in the development of dacomitinib included evaluation of adverse events in specific populations related to age, race, and hepatic and renal impairment. Although some of these populations were too small for statistical comparison, there was no evidence that any specific race group, elderly (65-75) or very elderly (>75) patients were at increased risk of more frequent or more severe adverse events. There has

not been evidence of hepatic or renal toxicity or an imbalance of other adverse events in patients enrolled with normal or abnormal (within protocol inclusion criteria) baseline renal or hepatic function. As with any ongoing study, the available data are preliminary in nature and are subject to change.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the IB.

1.2.1. Phase 3 Studies

Study BR.26 (A7471011) is a randomized, double-blind, placebo-controlled Phase 3 trial in refractory advanced non-small cell lung cancer (NSCLC) conducted as an Investigator-Initiated Research (IIR) study under the auspices of the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG). Enrollment began in December 2009. Efficacy and safety were monitored by an independent Data Monitoring Committee (DMC), and meeting outcomes shared with NCIC-CTG. Based on these DMC meetings to date, the study continued as planned without any recommended protocol changes. Enrollment was completed in this study with 720 patients randomized. There were 716 patients treated in this trial; 477 patients received dacomitinib and 239 patients received placebo. Three patients randomized to dacomitinib and 1 patient randomized to placebo were not treated. Currently, there are 2 patients still receiving active treatment (dacomitinib arm). Based on the clinical study report (CSR) data cutoff as of 11 October 2013, the study did not demonstrate improved overall survival (OS) versus placebo with statistical significance, and the primary objective of the study was not met.

Study A7471009 is a randomized double-blind Phase 3 trial of dacomitinib versus erlotinib in advanced NSCLC patients following progression after, or intolerance to, at least one (and no more than two) prior chemotherapies. Two co-primary populations were explored in this study: all patients with advanced NSCLC and NSCLC patients confirmed to be KRAS (Kirsten rat sarcoma viral oncogene homolog) wild-type. Patients were stratified by histology (adenocarcinoma versus non-adenocarcinoma), race (Asian versus non-Asian and Indian subcontinent race), ECOG (Eastern Cooperative Oncology Group) performance status (PS) (0-1 versus 2), and smoking status (never smoker, defined as ≤100 cigarettes, cigar or pipe lifetime versus ever smoker) at randomization. Enrollment was completed in this study with 878 patients randomized. There were 872 patients treated in this trial; 436 patients received dacomitinib, and 436 patients received erlotinib. Three patients randomized to dacomitinib and 3 patients randomized to erlotinib were not treated. Currently, there are 24 patients still receiving active treatment, and 93 patients are in long-term survival follow-up. Based on the CSR data cutoff as of 30 September 2013, the study did not demonstrate statistically improved progression-free survival (PFS) per independent review in the co-primary populations, and thus the primary objective was not met.

Study A7471050 is a randomized, open-label, Phase 3 study comparing the efficacy and safety of first-line treatment with dacomitinib to treatment with gefitinib in patients with Stage IIIB/IV NSCLC conducted in collaboration with SFJ Pharmaceuticals. All patients will have tumors that test positive for one EGFR activating mutation (deletion 19 or L858R), and all tumors will have histology consistent with adenocarcinoma or its pathologically

accepted variants. Approximately 440 patients will be randomized (1:1) to one of two treatment arms. This study is being conducted in China, Hong Kong, Italy, Japan, Poland, and Spain. At the time of the IB cutoff date, there were 130 patients randomized and treated in this study (66 patients randomized to dacomitinib and 64 patients randomized to gefitinib).

1.3. Background and Rationale

Dacomitinib is being developed globally in locally advanced or metastatic NSCLC after at least one prior chemotherapy regimen. In the course of development, Phase 2 and 3 studies are being conducted in several NSCLC treatment settings:

- After failure of prior chemotherapy and EGFR directed treatment [refractory setting];
- After one or two prior systemic therapies [2^{nd}/3^{rd} line]; and
- In selected patients who have had no prior therapy for advanced disease.

Indications of activity have been seen in a number of dacomitinib clinical trials. This protocol permits continued access to dacomitinib for patients who participated in other dacomitinib monotherapy treatment protocols and have the potential to derive clinical benefit without unacceptable toxicity from continued dacomitinib treatment. This treatment access protocol is only open to patients in Japan.

Patients will follow a schedule of visits and data collection that permits continued safety monitoring.

Complete information for this compound may be found in the SRSD.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To allow access to dacomitinib for patients who received dacomitinib on a prior study in Japan and who have the potential to derive continued clinical benefit from single-agent dacomitinib treatment without unacceptable toxicity based upon the investigator's judgment.

2.1.2. Secondary Objective

- To monitor the specific long-term safety and tolerability of single-agent dacomitinib in patients who have already received dacomitinib on a prior study in Japan.

2.2. Endpoints

- Adverse events as assessed by NCI Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE.v4.0).

3. STUDY DESIGN

This is a multi-center, open-label, treatment extension study open in Japan only. Eligible patients include those with advanced cancer who received and tolerated single-agent dacomitinib in a prior clinical study and have the potential to derive continued clinical benefit based on investigator judgment. Patients enrolled in this extension study may continue to receive dacomitinib starting at the current dose level in the prior study. Dose reductions and re-escalations are allowed based on tolerability. Patients may continue to be treated with dacomitinib on this protocol as long as there is evidence of clinical benefit in the judgment of the investigator. Adverse events will be graded according to NCI CTCAE v4.0, and monitored according to the frequency outlined in the Safety Review Plan.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Received dacomitinib on another clinical trial in Japan and judged by the investigator to be deriving ongoing clinical benefit.

2. No ongoing NCI CTCAE Grade 3 or intolerable Grade 2 adverse events related to dacomitinib treatment on the prior study.

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

4. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5. Male and female patients of childbearing potential and at risk for pregnancy must agree to continue to use a highly effective method of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.

4.2. Exclusion Criteria

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

1. Patients who meet one or more study withdrawal criteria on the prior study using dacomitinib in Japan.

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

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

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

5. Pregnant female patients; breastfeeding female patients; male and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 90 days after the last dose of investigational product.

4.3. Registration Criteria

The Sponsor must approve the enrollment of each patient. Patients will be registered into the study provided that they have satisfied all patient selection criteria and have withdrawn from their original dacomitinib clinical study prior to enrollment in this study.

4.4. Lifestyle Guidelines

All male and female patients who, in the opinion of the investigator, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 90 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected the most appropriate method of contraception for the individual patient from the permitted list of contraception methods (see below) and instruct the patient in its consistent and correct use. Patients need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

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

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

2. Correctly placed copper-containing intrauterine device (IUD).

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

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

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

Patients should avoid extended unprotected exposure to sunlight (eg, sunbathing) or tanning for the duration of the study period.

4.5. 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.

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

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This is an open-label trial. The starting dose of dacomitinib will be the same as the last dose the patient received in the original study.

Treatment will be administered orally in continuous fashion. For purposes of scheduling visits and assessments, cycles of 4 weeks (28 days) in length will be defined.

5.2. Patient Compliance

There are no compliance criteria that are pre-specified for inclusion in analyses of study endpoints. The patients will bring unused study drug and empty containers to each study visit. The number of tablets will be counted and if more or less than expected, patients will be asked to account for missed doses. The investigator and site study team will also evaluate patient compliance with the study regimen. Potential reasons for non-compliance dosing (ie, AEs, lost medication) will be followed up by the study site personnel and strategies to improve dosing compliance will be explored.

5.3. Drug Supplies

Pfizer Global Research and Development will supply dacomitinib (PF-00299804) tablets.

5.3.1. Dosage Form(s) and Packaging

Dacomitinib will be provided as tablets for oral administration. The 45 mg, 30 mg, or 15 mg tablets will be supplied in High Density PolyEthylene (HDPE) bottles for oral administration. The bottles will be properly labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

Dispensing will be in bottles provided in quantities appropriate for the study visit schedule. The patient should be instructed to maintain the product in the bottle provided throughout the course of dosing.

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

5.4. Administration

Patients will self-administer dacomitinib at their ending dose schedule from the prior study until they experience unacceptable toxicity, tumor progression, or death. Patients will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing. The tablets will be taken with at least 6 oz. (180 mL) of water on an empty stomach (defined as less than 500 calories within 2 hours before or after intake of study medication).

Patients must be instructed that if they miss a day's dose, they must not make up missed doses on following days, but simply resume the dosing schedule. Likewise, patients must be instructed that if they vomit at any time after taking a dose, they must not "make it up" with an extra dose the same day, but resume subsequent dose the next day as prescribed. Any missed or vomited doses must be indicated in the source documents and Case Report Form (CRF), just as all administered doses are documented.

5.5. Dose Modification

Dacomitinib will be available at 3 dose strengths, 45 mg, 30 mg, and 15 mg once daily.

Table 2 outlines dose modifications that will apply to patients order to manage treatment-related toxicity that is not controlled by optimal supportive care, or not tolerated due to symptomatology or interference with normal daily activities regardless of severity.

Table 2. Doses of Study Drug Administered

Dose level	Dacomitinib
Level 0	45 mg
Level -1	30 mg
Level -2	15 mg

Dose reductions may take place whenever toxicity that is not controlled with optimal supportive care is noted during the trial. If a patient subsequently tolerates therapy well in the judgment of the investigator, resumption of the next higher dose level may be undertaken. If a patient still cannot tolerate treatment after a dose reduction to the lowest dose of 15 mg, treatment will be discontinued. If a patient is responding to dacomitinib but is requiring a dose modification below 15 mg, the investigator must discuss the situation with the Sponsor's Medical Monitor.

For Grade 3, Grade 4, or intolerable Grade 2 toxicity, treatment will be interrupted. Upon recovery to Grade ≤2 or baseline, and per the clinical judgment of the investigator and agreement of the patient, the treatment will be resumed:

- For treatment interruption due to Grade 3 or intolerable Grade 2 toxicity, treatment may be resumed at the same or a lower dose level;
- For episodes of Grade 4 toxicity, reduction to the next lowest dose level is mandated.

If the patient fails to recover within 2 weeks of discontinuation, treatment will be discontinued unless there is discussion of the clinical circumstance with the Sponsor and agreement that the patient may resume treatment after a lapse of greater than 2 weeks. The patient will undergo end of treatment evaluations and follow-up visit as per Schedule of Activities.

5.6. Adverse Event Management

Specific guidance which has been developed for the management of common EGFR tyrosine kinase inhibitor toxicity at various grades is provided in Appendix 1. In general (and not as substitute for consideration of the more specific guidance in Appendix 1):

For diarrhea, patients should begin therapy with loperamide at first evidence of increased frequency of bowel movement with adjustment in dose or prescription of alternative medication when necessary. The potential need for increased oral hydration (including electrolyte-containing fluids) should also be evaluated. There is a risk of pre-renal azotemia noted from poor fluid intake in the face of diarrhea and/or stomatitis. Monitor renal function tests and consider supplemental IV hydration if necessary.

For prevention of dry skin, patients should begin a regimen of moisturizers prior (ideal) or with start of dosing, and use appropriate measures to prevent excessive sun exposure.

Treatment of acneiform rash may include topical steroids, topical antibiotics, and oral antibiotics.

Mucositis can be treated with antibiotic-free oral rinse; chlorhexidine should be avoided.

Other measures may be utilized per the investigator judgment or emerging data-driven guidelines where these are available

5.7. Drug Storage

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

Investigational product should be stored in its original container and in accordance with the drug label. See the Dosage and Administration Instructions (DAI) for storage conditions of the product.

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

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

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

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

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

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

5.8. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

5.9. Concomitant Treatment(s)

Anticancer therapy with agents other than dacomitinib is not allowed.

5.9.1. CYP2D6 Substrates

The use of drugs that are highly dependent on CYP2D6 for metabolism requires consideration of both the therapeutic index and the degree of CYP2D6 metabolism. Substitution within the therapeutic class is recommended if possible, otherwise the directions below should be followed.

- Drugs dependent on CYP2D6 metabolism with narrow therapeutic index are prohibited: eg, procainamide, pimozide and thioridazine.

- Administration of drugs which are highly dependent on CYP2D6 metabolism: dose reduction should be based on substrate sensitivity to CYP2D6 metabolism. As a guidance, a starting dose reduction of 75% (25% of the dose given without co-administration with dacomitinib) and close clinical monitoring is required.

- For drugs that are partly dependent on CYP2D6-mediated metabolism, there is a high likelihood of supra-therapeutic exposure in combination with dacomitinib. No dose reduction is required when starting dacomitinib but clinical monitoring is required and, based on patient response, dose-reduction may be necessary.

- Pro-drugs, or drugs with highly active metabolites such as codeine and tramadol should be replaced by an alternative within the therapeutic class as conversion to the pharmacologically active moiety is CYP2D6 metabolism-dependent and their exposure with the co-administration of dacomitinib may be sub-therapeutic. Opiates such as morphine, hydromorphone, oxymorphone and oxycodone can be used as substitutes to replace codeine or tramadol for analgesia.

Appendix 2 provides a comprehensive list of CYP2D6 substrates coded according to the therapeutic index and the degree of CYP2D6 metabolism. This is not an all-inclusive list. If there is uncertainty whether a concomitant medication is contraindicated, the Investigator should contact the Sponsor study team.

5.9.2. P-glycoprotein

Concurrent administration of drugs which are P-glycoprotein (P-gp) substrates and have a narrow therapeutic index should be monitored for exaggerated effect and/or toxicities.

5.9.3. Strong Amines

Lidocaine exposures may significantly increase in the presence of strong amines, such as dacomitinib. Lidocaine may be used systemically but clinical monitoring (including telemetry) is recommended.

5.10. Supportive Care

Patients may receive ongoing supportive and palliative care (eg, pain control) as clinically indicated throughout the study.

Patients who are receiving bisphosphonates at study entry may continue bisphosphonates while on study. However, the initiation of bisphosphonate therapy after enrollment will be considered progression of disease unless otherwise agreed by the investigator in consultation with the Sponsor.

6. STUDY PROCEDURES

Informed Consent: All patients being considered for this study must sign an informed consent document prior to any study-related procedures that are not considered to be standard of care and prior to receiving study drug.

Registration: The site staff will fax/e-mail a complete Registration Form to the designated Sponsor study team member. The Sponsor will assign a patient identification number, which will be used on all CRF pages and other study-related documentation or correspondence referencing that patient and fax/e-mail to the site.

Assessments for screening and all other study time points are detailed in the Table 1 (Schedule of Activities).

6.1. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site. Reasons for withdrawal include, but are not limited to the following:

- Progressive disease;
- Unacceptable toxicity;
- Global deterioration of health-related symptoms;
- Study non-compliance;
- Pregnancy;
- Patient request;
- Lost to Follow-Up;
- Study termination by Sponsor.

If a patient requires more than 2 consecutive weeks of dosing interruption, a discussion should be held with the Sponsor to determine whether or not to withdraw the patient from the study.

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

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

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the

investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pregnancy Testing

For female patient of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit, and at the end of treatment visit. A negative pregnancy result is required before the patient may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and at the end of the study to confirm the patient has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication and from the study.

7.2. Baseline Demographics

Demographic data will include date of birth and gender. The patient's prior dacomitinib study number and prior patient ID number will be noted on the CRF.

7.3. Patient History

The patients' prior history will include their cancer history, medical history and dates of the first and most recent dacomitinib administration.

7.4. Laboratories

Laboratory assessments (eg, hematology, blood chemistry, and urinalysis) are to be performed according to local standard clinical practice and results should be documented in the patient's clinic chart, but will not need to be reported on the CRF. The interval for laboratory assessments should not be longer than 8 weeks.

7.5. Tumor Assessments

Tumor assessments while the patient is receiving study treatment will be performed according to each site's standard-of-care imaging modality and clinical practice. The results should be documented in the patient's clinic chart but will not need to be reported on the CRF. The interval for monitoring disease status and for progression of disease should not be longer than 6 months.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

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

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

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

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

- Abnormal test findings;

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

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

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

- Medication errors involving patient exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

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

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

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

SAE with Common Terminology Criteria (CTC) Grade 5 (see section on Severity Assessment).

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

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

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between study drug and an event specified below, these events should not be reported by the investigator as SAEs as described in the Serious Adverse Event Reporting Requirements section on this protocol. These events are anticipated to occur commonly in a population with advanced NSCLC. However, these events should still be captured as AEs in the CRF.

Protocol-specified events that will not normally be reported in an expedited manner:

- Pulmonary embolism;
- Deep vein thrombosis (DVT);
- Pneumonia;
- Dyspnea;
- Respiratory distress or failure.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epidemiology data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a regular basis per internal standard operating procedures.

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

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

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

    Concurrent with

    - For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric

wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

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

that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.0 CTC document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

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

8.9. Causality Assessment

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

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

8.10. Exposure During Pregnancy

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.11. 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 adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the study master file.

8.12. Withdrawal Due to Adverse Events (Also See Section 6.1)

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

As noted in the Protocol-Specified Serious Adverse Events section, should an investigator judge one of the identified protocol-specified SAE to have a causal relationship with the investigational product the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

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

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

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

Due to the nature of this study, the number of patients to be enrolled is not predetermined.

9.2. Efficacy Analysis

Efficacy will not be analyzed in this protocol.

9.3. Analysis of Other Endpoints

Only descriptive summaries of safety will be provided, and no inferential analysis is planned.

Demographic characteristics such as age, gender, and race will be tabulated. The number of patients treated and the number of patients who withdrew from the study, as well as reasons for discontinuation, will be summarized.

Study drug administration will be summarized for all patients who received at least one dose of study medication.

9.4. Safety Analysis

The as-treated population will be the primary population for evaluating safety.

The as-treated population will include all patients who receive any study medication and will be included in the summaries and listings of safety data. Overall safety profile and toleration of dacomitinib will be characterized by type, frequency, severity (as graded by version 4.0 of the NCI CTCAE), timing and relationship of study therapy of adverse events.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to

third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

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

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

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

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

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

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

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

12.4. Patient Recruitment

Patient recruitment efforts are not required for this study because this study is open to patients previously treated on other dacomitinib trials.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial

End of Trial is defined as Last Subject Last Visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of dacomitinib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a time period set by Pfizer. As directed by

Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

www.clinicaltrials.gov

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

The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, Food and Drug Administration (FDA)-approved products, Pfizer posts results within 1 year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results 1 year from LSLV;

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or 1 year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within 1 year of discontinuation of the program (if there are no plans for out licensing, or within 2 years if out licensing plans have not completed).

Primary completion date is defined as the date that the final patient 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.

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

15.2. Publications by Investigators

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

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

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

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

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

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

16. REFERENCES

NA

17. APPENDICES

Appendix 1. Adverse Event Management Guidelines

In all instances, it is recommended that patients be instructed at time of starting drug therapy to call the Investigator/Site if no improvement in symptoms has been observed after 24 hours of patient taking the recommended/optimal pharmacologic treatment.

Abbreviations:

BSA: Body Surface Area

ADL: Activities of Daily Living

Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden (definitions per NCI CTCAE v4.0).

GABA: Gamma-Aminobutyric Acid

DIARRHEA

- Patients should be encouraged to drink 8 to 10 large glasses of clear liquids per day while on study in order to maintain adequate hydration;
- General dietary measures to limit impact of diarrhea could include:
    - Stop all lactose-containing products in patients with evidence of lactose intolerance;
    - Eat frequent small meals if experiencing increased frequency of stools;
    - Consider low-fat regimen enriched with bananas, rice, applesauce, and toast.

	Diarrhea Management Guideline
Grade of Event	Management/Next Dose
Grade 1: increase of <4 stools per day over baseline;	Loperamide 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. (During the night the patient may take 4mg of loperamide every 4 hours). Fluid intake of at least 2 liter (L) should be maintained to avoid dehydration: patients are to drink 8-10 large glasses of clear liquids. Consideration for maintenance of electrolyte balance would include electrolyte-containing drinks, broth, clear juices. ***Study Treatment:*** should be continued at same dose.
Grade 2: increase of 4-6 stools per day over baseline;	Loperamide as above, or consider use of diphenoxylate hydrochloride and atropine sulfate formula (eg Lomotil®, Diarced®, Co-Phenotroope®) at standard doses. Fluid intake of at least 2 L should be maintained to avoid dehydration. Monitor patient closely and consider intravenous hydration. ***Study Treatment:*** If not improved to Grade <1 within 24 hrs despite use of loperamide, hold treatment until Grade 1. If diarrhea of Grade >1 recurs after initial improvement, consider reduction of 1 dose level.
Grade 3: increase of ≥7 stools per day over baseline; or incontinence; or limiting self care ADL: or hospitalization indicated	Oral therapy with diphenoxylate hydrochloride and atropine sulfate formula, or tincture of opium. Fluid intake of at least 2 L should be maintained, intravenously if necessary. Consider use of octreotide (Sandostatin®) 100-150 microgram (μg) subcutaneously twice daily with escalation to 500 μg three times daily. Consider hospitalization if does not improve to Grade 2 within 24 hours, or in presence of fever, abdominal pain,etc. ***Study Treatment:*** Hold therapy. Upon resolution to Grade ≤1, resume therapy with consideration of reduction of one dose level
Grade 4: life-threatening	Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leucocytosis, marked dehydration, etc. ***Study Treatment:*** Hold until ≤ Grade 1. Mandatory dose reduction of one dose level

DERMATOLOGIC TOXICITY

Acneiform/ Papulopustular Rash:

	Acneiform/ Papulopustular Rash Management Guideline
Grade 1: <10% body surface area (BSA) papules and/or pustules (with or without symptoms of pruritis or tenderness)	**Topical steroids *** **And** **Topical antibiotic bid** (clindamycin 1 - 2%, erythromycin 1% - 2%, metronidazole 1%)
Grade 2: 10 to 30% BSA papules and/or pustules (with or without symptoms of pruritis or tenderness), or psychosocial impact, or limited instrumental ADL	**Oral antibiotic for at least 4 weeks** (doxycycline 100 mg bd, minocycline 100 mg bd or oxytetracycline 500 mg bd); Stop topical antibiotic if being used **And** **Topical steroids ***
Grade 3: >30% BSA papules and / or pustules (with or without symptoms of pruritis or tenderness); *or* • limiting self-care ADL: or • associated with local superinfection with oral antibiotics indicated	**Oral antibiotic for 4 weeks** (doxycycline 100 mg bd, minocycline 100 mg bd or oxytetracycline 500 mg bd) **If infection suspected** (yellow crusts, purulent discharge, painful skin/nares): switch oral antibiotic to broad spectrum/gram negative cover for at least 10 days consider skin swab for bacterial culture, **And** **Topical steroids (continue)*** Consider dermatology consultation
*** Moderate/Low strength steroids include:**	*Triamcinolone acetonide 0.025%* Desonide 0.05% Alclometasone 0.05% cream

	Fluticasone propionate 0.05% For patients intolerant or allergic to tetracycline antibiotics, use an antibiotic with Staphloccoccus coverage (eg, cephalexin, sulfamethoxazole/ trimethoprim)

Dry Skin/Xerosis:

Prophylaxis against dry skin would include:

- Initiation of skin moisturizing cream or ointment regimen upon establishment of eligibility (ie, prior to first dose) (avoid skin lotions, as they may contain alcohol);
- Avoidance of excessive exposure to hot water during showering/bathing;
- Avoidance of household tasks involving immersion in hot water/ detergent/solvents;
- Avoidance of excessive sun exposure/tanning. Use sunscreen containing zinc oxide or titanium dioxide with SPF at least 30: apply every two hours when exposed to sun.

	Xerosis/ Dry Skin Management Guideline
Grade 1: <10% BSA and no associated erythema or pruritis	Over-the-counter Moisturizing cream or ointment to face bid **AND** Ammonium lactate 12% (or equivalent) cream to body bid
Grade 2: 10 to 30% BSA and associated with erythema or pruritis; or limited instrumental ADL	OTC Moisturizing cream or ointment to face bid; **AND** Ammonium lactate 12% cream OR salicylic acid 6% cream to body bid
Grade 3 >30% BSA and associated with pruritis; or limiting self-care ADL	OTC Moisturizing cream or ointment to face bid; **AND** Ammonium lactate 12% cream OR salicylic acid 6% cream to body bid **AND** Topical steroid* to eczematous areas bid
*Moderate/Low strength steroid include:	*Triamcinolone acetonide 0.025% (Aristocort A cream)* Desonide 0.05% (DesOwen cream, lotion) Alclometasone 0.05% cream (Allocate cream) Fluticasone propionate 0.05%

Paronychia:

Miminization of periungal trauma and superinfection is advised:

- Wearing comfortable shoes,
- trimming nails but avoiding aggressive manicuring,
- wearing gloves while cleaning (eg, household, dishes).

	Paronychia Management Guideline
Grade 1 Nail fold edema or erythema; or disruption of the cuticle	Topical Antibiotics and vinegar soaks *
Grade 2 Localized intervention indicated; or oral intervention indicated (eg, antibiotic, antifungal, antiviral); or nail fold edema or erythema with pain; or associated with discharge or nail plate separation; or limiting instrumental ADL	Topical antibiotics and vinegar soaks* Apply silver nitrate weekly
Grade 3 Surgical intervention, or IV antibiotics indicated; or limiting self-care ADL	Topical antibiotics and vinegar soaks* Apply silver nitrate weekly Surgical consultation as needed
*Topical antibiotics/ vinegar soaks	*Topical antibiotics: Clindamycin 1%, erythromycin 1%* *Vinegar soaks consist of soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day* ± For a video on how to apply silver nitrate, visit: http://www.youtube.com/watch?v=HF5oopqheJY

Pruritis/Itching guidelines:

Prophylaxis against dry skin would include:

- Initiation of skin moisturizing regimen prior to first dose. Non-scented emollient skin cream should be used;
- Avoidance of excessive exposure to hot water during showering/ bathing;
- Avoidance of household tasks involving immersion in hot water/ detergent/ solvents;

- Avoidance of excessive sun exposure/ tanning. Use sunscreen containing zinc oxide or titanium dioxide with SPF at least 30: apply every two hours when sun exposure is anticipated.

	Pruritis Management Guideline
Grade 1: Mild or localized; or topical intervention indicated	Topical steroid moderate/low strength (as listed above for acneiform rash) or Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
Grade 2 Intense or widespread, intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); or oral intervention indicated; or limiting instrumental ADL	Topical steroid moderate strength or Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily **AND** Oral antihistamines
Grade 3: Intense or widespread, constant; or limiting self care ADL or sleep; or oral corticosteroid or immunosuppressive therapy indicated	Oral antihistamines **AND** GABA agonists (gabapentin or pregabalin) or Doxepin
	Antihistamines: diphenhydramine 25-50 mg tid; hydroxizine 25 mg tid; fexofenadine 60 mg tid GABA agonists (adjust if renal impairment) : Gabapentin 300 mg every 8 hours or Pregabalin 50-75 mg every 8 hours Tricyclics: Doxepin 25-50 mg every 8 hours

MUCOSITIS

Patients who have not had dental checkup within 6 months prior to start of dosing are encouraged to do so, especially to identify any persistent issue related to recent chemotherapy. Once on treatment, patients are to consult the site health care team prior to undertaking any dental or oral surgery procedure to determine if it would be appropriate to proceed depending on presence of any ongoing mucosal inflammation/ stomatitis.

Between scheduled visits, patient self-report of oral mucosal discomfort or of visible changes in appearance to oral mucosa is encouraged. Periodic systemic examination of the oral cavity is required at scheduled visits and as otherwise indicated by patient self-report between visits.

Patients should practice good oral care including a soft-bristle toothbrush replaced frequently and use of bland rinses or moisturizers.

Regular use of warm water non-medicated saline rinse is recommended if stomatitis develops. Frequent sips of water during meals may assist swallowing and therefore maintain caloric intake and hydration in patients experiencing oral pain

Use of chlorhexidine is to be avoided.

Topical anesthetics or systemic analgesics may be used as indicated in judgment of the investigator and according to local clinical practices. Topical steroid rinses have been reported to be helpful in severe cases (eg, dexamethasone 0.5 mg/5 ml swish and expectorate four times daily).

Consultation with nutritionist is to be considered if toxicity may compromise maintenance of adequate caloric intake.

Keratoconjunctivitis

	Keratoconjunctivtis Guideline
Grade 1 Asymptomatic or mild symptoms; intervention not indicated	No intervention or dose modification is mandated
Grade 2: Symptomatic; topical intervention indicated; or limiting instrumental ADL	Preservative free artificial tears, ointments, and /or other therapies as clinically indicated, with a follow-up examination within 2 weeks to include slit-lamp and fundoscopic exam as per the investigator judgment. ***Study Treatment***: If symptom lasts ≥2 weeks, withhold treatment until≤ Grade 1 and then reduce one dose level.
Grade 3: Limiting self-care ADL	Preservative free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks to include slit-lamp and fundoscopic exam as per the investigator judgment. ***Study Treatment:*** Drug should be withheld until recovers to≤ Grade 1 and then reduce one dose level.

Appendix 2. Guidance on Concomitant Medications involved in CYP2D6 Pathway

For CYP2D6 substrates, drugs for which substitution, dose modification and/or monitoring is advised are listed below along with the narrow therapeutic index drugs that are substrate of CYP2D6 and its administration is prohibited. This listing **is not an all-inclusive list, and** will be monitored by Sponsor study team for required updates (addition, deletion) but in all instances investigators should review potential for drug-drug interaction for concomitant medications and take appropriate measures of substitution or dose modification.

- For administration of drugs which are highly dependent on CYP2D6 metabolism:
    - Dose reduction should be based on substrate sensitivity to CYP2D6 metabolism. As a guidance a starting dose reduction of 75% (25% of the dose given without coadministration with dacomitinib) and close clinical monitoring is required.
- For the drugs that are partly dependent on CYP2D6-mediated metabolism, there is a high likelihood of supra-therapeutic exposure in combination with dacomitinib; **clinical** monitoring is required and dose-reduction may be necessary.
- Pro-drugs, or drugs with highly active metabolites such as codeine and tramadol should be replaced by an alternative within the therapeutic class as conversion to the pharmacologically active moiety is CYP2D6 metabolism-dependent and their exposure with the co-administration of dacomitinib may be subtherapeutic. Opiates such as morphine, hydromorphone, oxymorphone and oxycodone can be used as substitutes to replace codeine or tramadol for analgesia.

CODE	DRUG	THERAPEUTIC CLASS	CODE	DRUG	THERAPEUTIC CLASS
S	**amiflamine**	Monoamine Oxidase Inhibitors (MAOIs)	HS	**metoprolol**	Alpha/Beta Adrenergic Antagonists
HS	**amitriptyline**	Tricyclics and Tetracyclics	S	**mexiletine**	Antiarrhythmics
S	**aripiprazole**	Antipsychotics	S	**mianserin**	Tricyclics and Tetracyclics
HS	**atomoxetine**	Psychostimulants	S	**mirtazapine**	Tricyclics and Tetracyclics
S	**brofaromine**	Monoamine Oxidase Inhibitors (MAOIs)	HS	**nebivolol**	Alpha/Beta Adrenergic Antagonists
S	**bufuralol**	Alpha/Beta Adrenergic Antagonists	S	**nefazodone**	Serotonin Modulators
S	**carvedilol**	Alpha/Beta Adrenergic Antagonists	S	**nicergoline**	Vasodilators
S	**chlorpheniramine**	H-1 Receptor Antagonists	S	**nortriptyline**	Tricyclics and Tetracyclics
S	**chlorpromazine**	Antipsychotics	S	**(S)-ondansetron**	Serotonin HT3 Receptor Antagonists
S	**citalopram**	Serotonin Reuptake Inhibitors (SSRIs)	S	**oxycodone**	Opioids
S	**clomipramine**	Tricyclics and Tetracyclics	S	**pactimibe**	Other Antilipemics
S	**clozapine**	Antipsychotics	S	**paroxetine**	Serotonin Reuptake Inhibitors (SSRIs)
PD	**codeine**	Opioids	S	**perhexiline**	Vasodilators
S	**debrisoquine**	Other Antihypertensives	HS	**perphenazine**	Antipsychotics
HS	**desipramine**	Tricyclics and Tetracyclics	S	**phenformin**	Biguanides
S	**dexfenfluramine**	Anorexics	P	**pimozide**	Antipsychotics
HS	**dextromethorphan**	Antitussives	HS	**prajmaline**	Antiarrhythmics
S	**dihydrocodeine**	Opioids	P	**procainamide**	Antiarrhythmics
S	**donepezil**	Anticholinesterase Inhibitors	S	**propafenone**	Antiarrhythmics
HS	**doxepin**	Tricyclics and Tetracyclics	S	**propranolol**	Alpha/Beta Adrenergic Antagonists
S	**duloxetine**	Ser-Nor Reuptake Inhibitors (SNRIs)	S	**ranolazine**	Cardiovascular Drugs
S	**encainide**	Antiarrhythmics	S	**repinotan**	Serotonin Receptor Agonist
S	**fesoterodine**	Muscarinic Antagonists	S	**risperidone**	Antipsychotics
S	**flecainide**	Antiarrhythmics	S	**ritonavir**	Protease Inhibitors
S	**fluoxetine**	Serotonin Reuptake Inhibitors (SSRIs)	S	**sabeluzole**	CNS Agents
S	**fluphenazine**	Antipsychotics	S	**sparteine**	Antiarrhythmics
HS	**fluvoxamine**	Serotonin Reuptake Inhibitors (SSRIs)	PD	**tamoxifen**	Antineoplastic Hormonal
S	**gefitinib**	Kinase Inhibitors	S	**tamsulosin**	Alpha/Beta Adrenergic Antagonists
S	**haloperidol**	Antipsychotics	HS	**tetrabenazine**	CNS Agents
PD	**hydrocodone**	Opioids	P	**thioridazine**	Antipsychotics
S	**iloperidone**	Antipsychotics	S	**timolol**	Alpha/Beta Adrenergic Antagonists
S	**imipramine**	Tricyclics and Tetracyclics	HS	**tolterodine**	Muscarinic Antagonists
S	**lasofoxifene**	Estrogen Receptor Modulators	PD	**tramadol**	Other Analgesics
PD	**loratadine**	H-1 Receptor Antagonists	HS	**traxoprodil**	Neuroprotectors
S	**maprotiline**	Tricyclics and Tetracyclics	S	**trazodone**	Serotonin Modulators
S	**methadone**	Opioids	S	**trimipramine**	Tricyclics and Tetracyclics
S	**methamphetamine (MA)**	Recreational Drugs	HS	**tropisetron**	Serotonin HT3 Receptor Antagonists
S	**3,4-methylenedioxy-MA**	Recreational Drugs	S	**venlafaxine**	Ser-Nor Reuptake Inhibitors (SNRIs)
HS	**methoxyphenamine**	Beta Adrenoreceptor Agonist	HS	**vernakalant**	Antiarrhythmics
S	**Methylphenidate**	Psychostimulants	S	**zuclopenthixol**	Antipsychotics
S	**Metoclopramide**	Other Antiemetics			
HS	High likelihood of supratherapeutic exposure in combination with dacomitinib; dose-reduction and clinical monitoring IS required, if co-administration cannot be avoided: starting dose when coadministration with dacomitinib: 25% of original dose		P	Narrow therapeutic Index : Prohibited in combination with dacomitinib	
PD	pro-drug: active ingredient ONLY or partially upon CYP2D6 metabolism. High likelihood of subtherapeutic exposure in combination with dacomitinib		S	High likelihood of supratherapeutic exposure in combination with dacomitinib; clinical monitoring is required and dose-reduction may be necessary	
9/5/2012 v1.0 . Pfizer Inc.					