Janssen Research & Development *

Clinical Protocol

A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

42756493BLC2001; Phase 2
Amendment 9

JNJ-42756493

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	19 January 2015
Amendment 1	02 April 2015
Amendment 2	25 June 2015
Amendment 3	9 August 2016
Amendment 4	03 May 2017
Amendment 5	11 October 2017
Amendment 6	8 May 2019
Amendment 7	15 July 2020
Amendment 8	03 August 2021
Amendment 9	04 October 2022

Amendments below are listed beginning with the most recent amendment.

Amendment 9 (04 October 2022)

The overall reason for the amendment: To add a Long-term Extension (LTE) Phase with minimal assessments for subjects who have completed the Drug-drug Interaction (DDI) Substudy and who continue to derive benefit from treatment with erdafitinib.

Applicable Section(s)	Description of Change(s)
Rationale: The LTE Phase was added to reduce the burden of assessments for subjects who are continuing treatment with erdafitinib after completion of the DDI Substudy.	
Synopsis, 2.3. Overview of Study Design, Attachment 12: Drug-drug Interaction Substudy Drug-Drug Interaction (DDI) Substudy Summary DDI Table 29 (Added), 3. Study Design, 6.1. Administration of Study Drug, 9.1. Study Procedures, 9.1.5. Long-Term Extension Phase (Added) 9.3. Safety Evaluations, 9.5. Radiologic Assessment for Identification of Disease Progression, 10.1. Completion, 10.2. Discontinuation of Study Treatment, 11. Statistical Methods 12. Adverse Event Reporting	The LTE Phase was added to the main protocol sections and DDI Substudy in Attachment 12. The LTE Phase was the topic of Section 9.1.5, and the Time and Event Schedule was provided in DDI Table 29 (subsequent tables were renumbered). The end of study and study completion definitions were revised. The administration of study drug was updated. Aspects of the LTE phase including access to continue treatment with erdafitinib were mentioned as appropriate throughout the attachment. Added that radiological assessments and safety assessments including laboratory assessments were to be performed based on the investigator's discretion during the LTE phase, data for subjects in the LTE Phase were not to be added to the clinical database, and all SAEs and associated concomitant therapies were to be reported through the Company Safety Repository.
Rationale: To incorporate the Protocol Clarification from March 2022 regarding the Day −2, 0-hour pharmacokinetic (PK) sample during dosing with midazolam.	
Attachment 12: Drug-drug Interaction Substudy DDI Table 28	Added additional PK sampling time under DDI Assessments, the PK blood sampling for midazolam, at Day −2, 0 hr (taken prior to administration of midazolam).

Applicable Section(s)	Description of Change(s)
Rationale: To incorporate the Protocol Clarification from July 2022 regarding the timing of the radiological assessment in relation to Cycle 1 Day 1 (C1D1)**.**	
Attachment 12: Drug-drug Interaction Substudy DDI Table 28	Added notation under Screening, the inclusion/exclusion criteria row, that the radiological assessment will be done within 35 days of C1D1.
Rationale: To provide clarity on usage of LTE Phase Time and Events Schedule for the subjects in the LTE Phase.	
Attachment 12: Drug-drug Interaction Substudy DDI Table 28	Added a note explaining that LTE Phase Time and Events Schedule should be followed for the subjects who re-consent in the LTE Phase.
Rationale: To provide clarity on usage of LTE Phase Time and Events Schedule for the subjects in the LTE Phase and end of treatment (EoT) visit.	
Attachment 12: Drug-drug Interaction Substudy DDI Table 28	Added a note explaining that LTE Phase Time and Events Schedule should be followed for the subjects who re-consent in the LTE Phase. Added a footnote b explaining that EoT visit will not be required for subjects who re-consent to LTE phase.

Amendment 8 (03 August 2021)

The overall reason for the amendment: To facilitate enrollment by expanding the enrollment criteria for the Drug-Drug Interaction (DDI) Substudy to include patients with advanced solid tumors, in addition to urothelial carcinoma, that harbor target fibroblast growth factor receptor (FGFR) mutations or FGFR gene fusions who have progressed after prior systemic therapy and who do not have standard of care options.

Applicable Section(s)	Description of Change(s)

Rationale: To facilitate enrollment, the DDI substudy population was expanded to patients with advanced solid tumors, in addition to urothelial carcinoma, that harbor target FGFR mutations or FGFR gene fusions who have progressed after prior systemic therapy and who do not have standard of care options. Also, the absolute neutrophil count (ANC) was made less restrictive for this population.

Synopsis; 2.3 Overview of Study Design; Attachment 12 Drug-Drug Interaction Substudy, Title of Attachment 12; Substudy Summary; 1.2 Substudy Rationale; CCI ; 2 Objectives and Endpoints; 3 Study Design; 4 Subject Population; 4.1 Inclusion Criterion for the DDI Substudy; 4.2 Exclusion Criterion for the DDI Substudy; DDI Table 30; 9.1.1 Molecular and DDI Substudy Screening	The Synopsis and Attachment 12 (DDI Substudy Title, Substudy Summary, and Sections 2 and 3) were revised to reflect the modified population to be enrolled in the DDI Substudy, ie, subjects with advanced solid tumors that harbor target FGFR mutations or FGFR gene fusions. Sections 2 and 3 provide a more detailed description of these subjects as those with an unresectable, locally advanced, or metastatic solid tumor malignancy. In addition, in Attachment 12, Section 4.1, the population was expanded as noted (Criterion 2, and revision of wording in Criterion 3). In Section 2.3, the duration of the DDI substudy was provided and distinguished from the main study. The footnote in the introduction of Section 4 describing the population as similar to that of the main study was removed. In Attachment 12, Section 4.1 (Criterion 4), molecular eligibility was expanded to target FGFR mutations or FGFR gene fusions. In Attachment 12, Section 4.2 (new Criterion 17 and 18), exclusions for FGFR gatekeeper and resistance alterations, and exclusions for pathogenic somatic mutations for non-small cell lung cancer (NSCLC), respectively, were added.

	Due to the expansion of the population to all tumor types, the rationale (Attachment 12, Section 1.2) and the benefit-risk assessment (Attachment 12, Section 1.6) have been updated. The rationale also states the main purpose of the study (added as a short first paragraph) with reference to the detail in Section 1.3 of Attachment 12. CCI [redacted] In addition, the ANC inclusion requirement (Attachment 12, Section 4, Criterion 6) was changed to ≥1000/mm^3 (previously >1500/mm^3), based on the observed safety profile of erdafitinib without clinically significant hematological adverse events. In Attachment 12, Section 9.1.1, revised the molecular eligibility determination as follows: "Subjects must meet appropriate molecular eligibility criteria, as determined by available ["available" added and "local historical" removed for clarity] test results (from tissue or blood) using ["local" removed from this location] next-generation sequencing (NGS) ". Also, the last paragraph of this section was revised to clarify that archival tumor tissue will be sent to the central laboratory for concordance testing for alterations detected by the Qiagen Therascreen® FGFR RGQ RT-PCR kit if available.
Rationale: The adverse event reporting attribution definitions and severity criteria were updated for the DDI Substudy.	
12.1.2 Attribution Definitions; 12.1.3 Severity Criteria; Attachment 12, Section 12 Adverse Event Reporting	The attribution definitions (ie, assessment of causality) and severity criteria were updated for the DDI Substudy (Attachment 12, Section 12), while the applicable adverse reporting sections in the main study refer to these updates and reference the DDI Substudy Section 12.
Rationale: Text revised based on the reclassification of fluconazole as a moderate (not strong) CYP2C9 inhibitor. No drugs are currently classified as strong CYP2C9 inhibitors per the University of Washington's Drug Interaction Database. Also, instruction added for the use of organic cation transporter 2 (OCT2) and Cytochrome P (CYP) 3A4 substrates with erdafitinib.	
8.3 Precautions for Concomitant Medications	Updated precautions to specify that moderate CYP2C9 (previously strong) and strong CYP3A4 inhibitors should be used with caution. Paragraph added with instruction regarding OCT2 substrates. Also, added a statement that until further data become available, concomitant use of erdafitinib with CYP3A4 substrates with narrow therapeutic indices should be avoided.
Rationale: To provide guidance for patients with CYP2C9 *3/*3 genotype	
6.1 Administration of Study Drug; Attachment 12, 6.1 Administration of Study Drug	Guidance for patients with CYP2C9 *3/*3 genotype added.
Rationale: To align management of toxicities with erdafitinib across the program.	
6.3.3 Guidelines for the Management of Dry Mouth and Stomatitis;	Prophylaxis measures moved outside the dry mouth, stomatitis, dry skin and skin toxicity, and nail toxicity tables. Small edits made for

6.3.4 Guidelines for the Management of Dry Skin and Skin Toxicity; 6.3.5 Guidelines for the Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia); 6.3.6 Guidelines for Eye Toxicity Associated With Vision Changes; 6.3.7 Guidelines for the Management of Dry Eye	consistency across the program. In Section 6.3.3, the prophylaxis measure for dry mouth related to mouthwash replaces "saline peroxide" with "salt and baking soda" (as in the stomatitis table). In Section 6.3.5, Grade 4 was removed from the paronychia table, as well as the definition of grades. In Section 6.3.7, artificial tear substitutes are recommended every 2 hours during awake time under the prophylactic (the change also applies to ocular demulcents under this subsection) and reactive management sections.
Rationale: The adverse event of special interest is termed "central serous retinopathy" (CSR, a grouped term).	
12.3 Procedures	Removed "adverse events of special interest" as a description of "corneal or retinal abnormalities".
Rationale: To update the guidance for study conduct during a national disaster based on the updated company template (non-live vaccines).	
8.1 Permitted Medications; Attachment 11 Guidance on Study Conduct During a National Disaster for Enrolled Subjects	Guidance relating to administration of non-live vaccines was added.
Rationale: Provide overview of efficacy and safety information now available for Study 42756493BLC2001 (Study BLC2001).	
1.2.1.1 Safety Experience; 3.1.1 Rational for the Study in the Target Indication;	Provided an overview of efficacy and safety information from the primary analysis (clinical cutoff of 15 March 2018) and updated analysis (clinical cutoff of 09 August 2019) of Study BLC2001. Also, in Section 1.2.1.1 referred the reader to the Erdafitinib Investigator's Brochure for recent safety information. Also, in Section 3.1.1, referred the reader to the rationale for the treatment of subjects with advanced solid tumors in DDI Substudy Section 1.2.
Rationale: Change for consistency with protocol template	
9.4.2 Clinical Laboratory Tests; 16.2.7 Protocol Clarification Communications (new); Attachment 12 Drug-Drug Interaction Substudy, Section 4.1 Inclusion Criteria	In Section 9.4.2, added a mention of Hy's Law and provided a reference to the reporting requirements. Added text regarding protocol clarification communications as new Section 16.2.7. In Attachment 12, Section 4.1 (Criterion 7), tubal closure was added as a contraceptives measure.
Rationale: Editorial changes were made.	
Throughout the document	Editorial changes were made, ie, "he or she" changed to "the subject". Tables and figures in the attachments were renumbered (were necessary) to flow with the main body of the protocol. The term FGFR-positive subject was revised to FGFR-eligible subject.

Amendment 7 (15 July 2020)

The overall reason for the amendment: The overall reason for this amendment is to add the drug-drug interaction (DDI) substudy, to fulfill the US Food and Drug Administration (FDA) post-marketing requirement to evaluate the interaction of repeated doses of erdafitinib with a sensitive cytochrome 450 (CYP) 3A substrate, as well as the post-marketing commitment to evaluate the interaction of repeated doses of erdafitinib with an organic cation transporter 2 (OCT2) probe substrate. In addition, instructions for study conduct during a national disaster was added along with other updates.

Applicable Section(s)	Description of Change(s)
Rationale: The DDI substudy was added to the protocol for the purpose of evaluating the potential inhibition or induction effects of erdafitinib on the CYP3A-mediated metabolism of the probe drug midazolam and the potential inhibition effect on the OCT2-mediated transport of the probe drug metformin. The study results are intended to provide guidance that will enable an update to the erdafitinib labeling and will help guide recommendations for administration of co-medications that are substrates for CYP3A4 or OCT2. NOTE: Subjects entering under the DDI substudy will follow procedures as advised in Attachment 12. For these subjects, DO NOT USE the Time and Events Schedule and the Eligibility Criteria in the body of the protocol (referred to in Attachment 12 as the "Main Protocol").	
Synopsis; Time and Events Schedules; 3, Study Design and Rationale; 4, Subject Population; Attachment 12	The DDI substudy has been added as Attachment 12. As this is an extensive attachment, a table of contents is provided. Subjects will be enrolled under the eligibility criteria provided in this attachment. Once subjects complete the DDI portion of the study, they will continue treatment with erdafitinib until disease progression, unacceptable toxicity, or until meeting another condition specified in the protocol. Safety assessments are continued, along with limited efficacy (for the purpose of signaling disease progression) CCI [redacted]. The assessments for the DDI substudy and thereafter during continued treatment with erdafitinib are provided in this attachment along with a Time and Events Schedule. Study participation ends with the End of Treatment Visit. The DDI substudy is mentioned in the synopsis. A reminder not to use the Time and Event Schedules and the eligibility criteria in the Main Protocol were added to these section headers, as well as mentioned at the beginning of Section 3.
Rationale: To add instructions to be followed during a national disaster.	
Time and Event Schedules (Table 2 and Table 3); Attachment 11, Guidance on Study Conduct for Enrolled Subjects During a National Disaster (new); 2.3, Overview of Study Design	Instructions to be followed during a national disaster are provided in Attachment 11. This attachment was referenced in Section 2.3 as well as the Time and Events Schedules (Footnote "a"). As no subjects were ongoing on Regimen 1, ie, 10 mg starting dose, changes were not applied to this table. (This guidance is found in similar sections of the DDI Substudy attachment noted earlier.)
Rationale: Updated the description of fluconazole to a moderate (previously strong) CYP2C9 inhibitor, per FDA classification. Provided updated information and guidance for use of strong CYP2C9 or CYP3A4 inhibitors, as well as moderate CYP2C9 inducers and strong CYP3A4 inducers, and erdafitinib.	

Applicable Section(s)	Description of Change(s)
8.3, Precautions for Concomitant Medications; Attachment 4, Drugs Classified as Strong or Moderate In Vivo Inhibitors and Inducers of CYP3A4/2C9 Enzymes	Updated fluconazole as a moderate CYP2C9 inhibitor (previously considered a strong inhibitor). Provided information regarding use of strong inhibitors of CYP2C9 or CYP3A4 with erdafitinib, including specific guidance to use these agents with caution during erdafitinib treatment. Provided information regarding moderate CYP2C9 inducers (no drugs are classified as strong CYP2C9 inducers) and strong CYP3A4 inducers and interaction with erdafitinib. Provided specific guidance to avoid the use of these agents (moderate CYP2C9 inducers and strong CYP3A4 inducers) with erdafitinib, as well as guidance for the use of moderate CYP3A inducers with erdafitinib. Attachment 4 was revised to provide drugs classified as strong or moderate in vivo inhibitors and inducers of CYP3A4/2C9. Previously moderate in vivo inhibitors of CYP3A4/2C9 were not included in the table.
Rationale: The management of elevated phosphate levels has been updated. To ensure consistency between the protocol and case report form (CRF) guidelines, harmonized rounding of phosphate values.	
6.3.2, Guidelines for the Management of Elevated Phosphate Levels; Table 14	Updated the management of elevated phosphate levels in Table 14. The values for grading of hyperphosphatemia have been revised throughout the protocol to include 2 decimals, for consistency with the CRF, and instructions for rounding the second decimal point were deleted. Also, small updates to the study and medical management were made and the toxicity grades (0 to 4) were added to the table. The update removed the information in the footnote regarding re-introduction of study drug in subjects deriving benefit from treatment; however, the primary location of this information in Section 10.2 remains.
Rationale: To update safety management guidelines for oral mucositis.	
6.3.3, Guidelines for the Management of Dry Mouth and Stomatitis; Table 15, Guidelines for the Management of Dry Mouth (Xerostomia); Table 16, General Prophylaxis and Guidelines for the Management of Oral Mucositis	Updated guidelines for general prophylaxis and management of oral mucositis were provided in Table 16. The general prophylaxis for dry mouth (which due to the above change now differs from oral mucositis) was removed from the text and was added to Table 15.
Rationale: To update safety management guidelines for nail toxicity.	
6.3.5, Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia); Table 18, General Prophylaxis and Guidelines for Management of Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy); Table 19, Guidelines for Management of Paronychia	Updated guidelines for the management of nail toxicity in Table 18 (the new table format adds general prophylaxis to the table). The general prophylaxis for the management of paronychia, previously in text was added to Table 19. Also, the descriptions of grades were removed from Table 19 for consistency across the program.

Applicable Section(s)	Description of Change(s)
Rationale: For the ophthalmic examination, tonometry was removed and slit lamp biomicroscopy was added. To clarify that all subjects must have an ophthalmologic examination performed at screening regardless of symptoms, and that a follow-up examination should be performed as clinically necessary based on clinical findings. To clarify that an Optical Coherence Tomography (OCT) will be performed.	
Time and Event Schedules (Table 2 and Table 3); 9.4.7, Ophthalmic Examination	On the Time and Events Schedules, the following notation has been added for the "Ophthalmologic Exam": A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment. (As no subjects were ongoing on Regimen 1, ie, 10 mg starting dose, changes were not applied to this table.) Changed "should" to "must" in the first sentence as follows: "All subjects must have an ophthalmological examination performed at Screening by an ophthalmologist . . .". Regarding the examination, "tonometry" was removed and "slit lamp biomicroscopy" was added. In addition, "where available, an Optical Coherence Tomography (OCT) should be performed [at Screening]" was replaced with simply "Optical Coherence Tomography (OCT)" at the end of the sentence that now clarifies that an OCT will also be performed at Screening. The Amsler grid test was removed from the list of assessments and this topic is addressed in a new sentence.
Rationale: The dose titration guidelines have been updated.	
6.2, Dose Up-titration Guidelines	The dose titration guidelines have been updated (will be used by subjects enrolled under the DDI Substudy). The Regimen 3 guidelines have been moved to Attachment 8 (with Regimens 1 and 2).

Rationale: Corneal or retinal abnormality of Grade 1 or 2 are reported as an adverse event. Updated information regarding Amsler grid testing.	
6.3.6, Guidelines for Eye Toxicity Associated With Vision Changes; Table 20; 12.3, Procedures	Clarified that a corneal or retinal abnormality of Grade 1 or 2 is reported as an adverse event; previously text stated reporting as an adverse event of special interest. (These abnormalities of Grade 3 or higher continue to be reported as serious adverse events.) This revision was also added to Section 12.3. The update to the Guidelines for Management of Eye Toxicity Table 20 removed information in the footnote regarding re-introduction of study drug in subjects deriving benefit from treatment; however, the primary location of this instruction in Section 10.2 remains. In Section 6.3.6, clarified text regarding instructions for an abnormal Amsler grid test as follows: However, if the subject has an abnormal Amsler grid test [added here "and otherwise normal ophthalmologic examination"] at baseline (during Screening), a repeat ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler grid test at Screening, or the subject has developed new clinical symptoms. Also, the description of a positive test was removed.
Rationale: Updated the management of dry eye.	
6.3.7, Guidelines for the Management of Dry Eye	Ocular demulcents were included as a recommendation for prophylactic management. Also, ocular demulcents were added to reactive management (and the more descriptive text "hydrating/lubricating eye gels and ointments" was removed).
Rationale: The end of study has been redefined due to the addition of the DDI substudy.	
Synopsis; 2.3, Overview of Study Design	Previous definition: The end of study is defined as the date when all subjects have completed the study treatment or 12 months after last subject is enrolled, whichever is later. New definition: The end of study is defined as the date when all subjects have completed the study treatment (Regimens 1 to 3) or until the last subject enrolled under the DDI substudy completes the end of treatment visit (whichever happens last).
Rationale: Updated text regarding disease-related events, per the protocol template.	
12.3.2, Serious Adverse Events; 12.3.4, Disease-related Events or Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	Text regarding disease-related events was removed from Section 12.3.2 and the new template text was added as Section 12.3.4.
Rationale: Updated safety reporting with the addition anticipated events.	
12.3.2, Serious Adverse Events	Updated safety reporting with the addition of a list of anticipated events and related protocol template text.

Rationale: The publication information was updated.	
17.11, Use of Information and Publication	The timeframe for submission of the completed study for publication was changed to within 18 months after the study end date (previously, "within 12 months of the availability of the final data (tables, listings, graphs)"). The amendment reflects the updated name for the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, ie, the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Also, the description of the requirement for authorship was provided in greater detail. The following sentence was added regarding disclosure of study results at the end of this section: "The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant." In third paragraph deleted "eCRF data" with "data".
Rationale: Clarified aspects of study oversight including the approval process for CCI [redacted] and the consent process for rescreening, the DNA component, CCI [redacted]. Additional clarification regarding screening, source documentation, and case report form (CRF) completion was added.	
16.2.2, Independent Ethics Committee or Institutional Review Board; 16.2.3, Informed Consent; 17.2.3, Financial Disclosure; 17.3, Subject Identification, Enrollment, and Screening Logs; 17.4, Source Documentation; 17.5, Case Report Form Completion	In Section 16.2.2, added that approval for the collection of optional samples for research and for the corresponding ICF text must be obtained from the Independent Ethics Committee/Institutional Review Board (IEC/IRB). In Section 16.2.3, added that a subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date. Also, added that subjects will be asked for consent to provide optional samples for research where local regulations permit. Clarified that where local regulations require, a separate ICF may be used for the required DNA component of the study. Removed unnecessary mention of "his/her" from this section. In new Section 17.2.3, detail regarding financial disclosure was added. In Section 17.3, clarified that subjects enrolled under the DDI substudy will not be randomized and that they may be rescreened. In Section 17.4, added the minimum source documentation requirements for eligibility and use of an eSource system. In Section 17.5, the statement regarding investigator verification of CRF data was moved from paragraph regarding subjective measures to paragraph regarding all CRF data.
Rationale: Radiographic scans will no longer be transferred to the central vendor, because at this stage of the study efficacy evaluations will be based on site-reported disease assessment, ie, independent evaluation will no longer be conducted.	
9.2, Efficacy	Removed the following sentence from the first paragraph: "The site will send all radiographic scans to a central vendor for possible future independent assessment to confirm the response, if needed."
Rationale: Submission of electrocardiograms (ECGs) to the central vendor was previously discontinued. Text regarding ECG submission was removed to reflect this earlier change in procedure.	
9.4.5, Electrocardiogram	Removed the last sentence of this section: "All ECGs will be submitted to a central vendor and may be reviewed by an independent cardiologist."
Rationale: Minor edits were made.	

Throughout the document	Minor editorial changes were made to improve clarity.
Attachment 5	Subtitle at bottom of graph was removed.

Amendment 6 (8 May 2019)

The overall reason for the amendment: To modify the end of study definition in order to continue to provide access to study treatment for subjects still taking erdafitinib after the planned final analysis while limiting the scope of longer-term data collection after the time of final analysis to safety data (eg, AEs, SAEs).

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Applicable Section(s)	Description of Change(s)
Rationale: The end of study definition was updated to extend access to erdafitinib for subjects still on study treatment at the time of final analysis.	
Synopsis Overview of Study Design, 3.1 Overview of Study Design	Text updated: The end of study is defined as the date when all subjects have completed the study treatment or 12 months after last subject is enrolled, whichever is later.
Rationale: The approximate duration of the study was updated due to the modification of the end of study definition.	
3.1 Overview of Study Design	Text updated: The entire duration of the study will be approximately ~~36~~60 months to completion (first subject's first visit to end of study).
Rationale: The definition of study completion was updated to reflect the updated end of study definition.	
17.9.1 Study Completion	Text updated: The study is considered completed ~~with the last follow-up survival assessment for the last subject participating in the study~~ when all subjects have completed the study treatment or 12 months after the last subject is enrolled, whichever is later.
Rationale: Provide extended access to study treatment for subjects still taking erdafitinib after the planned final analysis and limit the scope of data collection from the time of final analysis until the end of study.	
11.3.2 Final Analysis	Text added: For subjects still on study treatment after the final analysis the study Sponsor will continue to provide access to erdafitinib and collect safety data (eg, AEs, SAEs) until the end of study.
Rationale: Updated text on PK and biomarker sample collection to conclude at the implementation of Amendment 6 at the local site level.	
Time and Events Tables, Table 4, Table 5, 9.2.3 Pharmacokinetic Evaluations, 9.3.2 Predictive Biomarker Evaluations	Added table text in Time and Events Schedule and updated table footnotes and text in the PK and biomarker sections to clarify the termination of routine PK and biomarker sample collection while still allowing the collection of additional PK samples at any time for assessment of adverse events as clinically appropriate.
Rationale: Information on study drug management of elevated phosphate levels was updated according to the latest guidelines.	

Applicable Section(s)	Description of Change(s)
Table 14; Table 21	Switched ordering of footnotes a and b according to updated table and updated the definition of persistent hyperphosphatemia in footnote a. Updated study drug management for serum phosphate levels of 7.0-9.0 mg/dL (2.3-2.9 mmol/L), >9.0-10 mg/dL (>2.9 mmol/L), >10.0 mg/dL (>3.2 mmol/L) and significant alteration in baseline renal function or Grade 3 hypocalcemia.
Rationale: Information on study drug management of eye toxicity was updated according to the latest guidelines.	
Table 20	Added monitoring information for retinal epithelial detachment under Grades 1, 2, and 3 study drug management. Updated study drug management information for Grade 3 toxicity from "permanently discontinue" to "withhold" erdafitinib.
Rationale: Information on prohibited and concomitant medications were updated according to latest guidelines and study information.	
8.2 Prohibited Medications; 8.3 Precautions for Concomitant Medications; ~~8.3.1 Concomitant Use of Strong CYP3A/2C9 Inhibitors/Inducers~~	Removed medications that increase serum calcium and phosphate levels from the prohibited medications list. Removed subsection "8.3.1 Concomitant Use of Strong CYP3A/2C9 Inhibitors/Inducers" and updated the text on potential strong inducers of CYP3A4 and CYP2C9 with the latest study information and source information. Removed subheading "Concomitant Use of P-gp Substrates" and updated P-gp substrate text and source information.
Rationale: Updated wording to align with relevant changes to the protocol template since the last amendment was issued.	
9.4 Safety Evaluations; 17.3 Subject Identification, Enrollment, and Screening Logs	Updated wording: clinically stable ~~endpoint~~ condition Updated wording: ~~date of birth~~ age at initial informed consent
Rationale: Minor errors were noted.	
Throughout the document	Minor editorial changes were made to improve clarity. JNJ-42756493 and JNJ42756493 were replaced with erdafitinib where applicable.

Amendment 5 (11 October 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Precautionary language regarding concomitant medications was added, based on in vitro data showing that erdafitinib is a P-gp inhibitor.

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Applicable Section(s)	Description of Change(s)
Rationale: Precautionary language was added regarding concomitant use of P-gp substrates.	
8.3.2, Concomitant Use of P-gp Substrates (new section)	Text added: Erdafitinib was shown to inhibit, in in vitro experiments, human P-glycoprotein (P-gp) at concentrations achieved at therapeutic doses in humans. If the compound is administered with drugs that are substrates of P-gp, there is the potential for observing increased concentrations of the substrate drug. Therefore caution should be exercised for co-administered drugs that are P-gp substrates, such as digoxin, dabigatran, apixaban, etc.
Rationale: New food effect data show that erdafitinib may be taken with or without food.	
6.1 Administration of Study Drug	Each dose should be taken ~~at least 1 hour before eating or at least 2 hours after a meal,~~ at approximately the same time each day, **with or without food**. ~~In this same time frame,~~ Subjects should avoid consuming grapefruit or Seville oranges due to CYP450 3A4/5 inhibition

Amendment 4 (3 May 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: To clarify the post treatment follow-up period and timing between enrollment and Cycle 1 Day 1 for Regimen 3 subjects.

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Applicable Section(s)	Description of Change(s)
Rationale: To clarify the post treatment follow-up period, as the 6-month timeframe was confusing and unnecessary, and the timing between enrollment and Cycle 1 Day 1 for Regimen 3 subjects.	
Time and Events Tables 3.1, Overview of Study Design 12.3.1, All Adverse Events 12.3.2, Serious Adverse Events	Clarified that follow-up for drug-related toxicity or serious adverse events was not restricted to a maximum of 6 months following the end of study visit
10.1, Completion	Clarified that a subject will be considered to have completed the study if they have died, and deleted previous condition of follow-up for 6 months after disease progression
Time and Events Table, Regimen 3	Added sentence: Cycle 1 Day 1 must occur no more than 3 days after the Randomization transaction in IWRS

Amendment 3 (9 August 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: As recommended by the Data Review Committee (DRC) following their review of Interim Analysis 1 (IA1) data for Study BLC2001, an analysis was conducted of safety and efficacy data in urothelial cancer of the 2 different dosing schedules (6 mg once daily continuous and 10 mg once daily intermittent [7-day-on/7-day-off] schedules; both with possible up-titration to 8 mg and 12 mg, respectively). From the BLC2001 data no new safety signals were identified. Also, it was observed that, for subjects attaining a phosphate level of at least 5.5 mg/dL, the ORR was higher (57%, 4/7 subjects) as compared to those who did not attain this same level (21%, 3/14 subjects). From Study EDI1001, it was known that 6 mg once daily continuous was a well-tolerated schedule without significant unplanned treatment interruptions, while 9 mg once daily continuous in non-selected patients frequently led to treatment interruptions or dose reductions. Based on observed data and PK/PD modeling, it seemed possible to increase the highest continuous dose to 9 mg once daily in subjects who did not attain the target phosphate level of 5.5 mg/dL or higher. Furthermore, approximately half of the subjects starting at 6 mg once daily were up-titrated to 8 mg once daily, and most tolerated this higher dose without the need for interruptions for hyperphosphatemia or other drug-related, mainly skin and nail, toxicity. Modeling was performed to assess different scenarios for dosing, including up-titration to 8 mg from a starting dose of 6 mg, or a starting dose of 8 mg with potential up-titration to 9 mg in selected patients. Based on this modeling, the starting dose of the study will be increased to 8 mg once daily, with a provision for up-titration to 9 mg once daily for subjects whose serum phosphate levels on Day 14 do not reach a target of at least 5.5 mg/dL, in the absence of drug related toxicity. Subjects will remain at 8 mg once daily if their serum phosphate levels on Cycle 1 Day 14 are within the target range of 5.5 to <7.0 mg/dL. Any further elevations of serum phosphate will be managed as per protocol guidelines.

Applicable Section(s)	Description of Change(s)
Rationale: To implement procedures for Regimen 3, added T&E table (Table 3), revised description of study design, provided rationale, new dose up-titration guidelines and dose modification guidelines,	
Time and Events Table 3	New table added
1, Introduction	Added update on Regimen 3
2, Objectives and Hypotheses	Revised to reflect selected dose regimen, added secondary objective for other dose regimens
3.1, Overview of Study Design 9.1.2, Screening Phase	Revised text to include Regimen 3 after IA1, updated Figure 3
3.2.2, Rationale for Phase 2 Dose Selection	Updated with rationale for dose in Regimen 3
5, Treatment Allocation and Blinding 6.1, Administration of Study Drug	Updated with dose in Regimen 3
6.2, Dose Up-titration Guidelines	Moved guidelines for Regimen 1 and Regimen 2 to Attachment 8, added guidelines for Regimen 3
6.3, Dose Modifications and Dose Delays	Updated with guidelines for Regimen 3
9.1.3, Treatment Phase	Added provision for subjects in Regimen 1 or Regimen 2 to move to Regimen 3
9.1.4, End-of-Treatment 9.1.5, Follow-up Phase 9.2, Efficacy	Added reference to Table 3
11.1, Sample Size Determination	Moved description for Regimen 1 and Regimen 2 to Attachment 9, added description for Regimen 3

Applicable Section(s)	Description of Change(s)
11.2, Analysis Populations	Specified that the Primary Efficacy (PE) analysis population will consist of all subjects who are treated by at least 1 dose of study drug in Regimen 3
11.3.1, Primary Analysis	Adjusted to Regimen 3
11.7, Interim Analysis 11.8, Dose Selection Criteria	Moved these former sections to Attachment 9 since Amendment 3 rendered them obsolete
16.1, Study Specific Design Considerations	Added additional considerations for new dose regimen
Attachment 8	New attachment for dose up-titration guidelines for Regimen 1 and Regimen 2, since Amendment 3 rendered them obsolete
Attachment 9	New attachment for statistical methods (sample size determination, former sections 11.7 and 11.8) rendered obsolete by Amendment 3
Rationale: Based on recent preclinical data, added warnings about CYP2C9 interactions.	
8.3.1, Concomitant Use of Strong CYP3A4/2C9 Inhibitors/Inducers Attachment 4, Drugs Classified as Strong in vivo Inhibitors…	Revised guidance to includeCYP2C9
Rationale: Biomarker section updated. Pre-treatment, on-treatment, and end of treatment biopsy collection added to support investigation of the impact of JNJ-42756493 on: tumor immune cell infiltrate, bladder cancer molecular profile; and to assess markers of response and acquired resistance to study drug. PD-L1 status and bladder cancer subtyping (molecular profile) will be assessed in archival tissue to better understand the immune marker status and molecular profile of FGFR alteration positive and negative samples. A statement is added to indicate that additional tissue may be requested, or retrieved from existing samples, at any point in the study to support protocol-specified analyses, or retrospective analyses. In particular, additional samples may be needed to support the development of the FGFR molecular screening assay as a companion diagnostic test (CDx).	
Time and Events Table 3	Added pre-treatment, on-treatment, and end of treatment biopsy collection
Table 5, Biomarker Blood Sample Collection	Added blood sample on Cycle 2 Day 1 for subjects providing post treatment biopsy
2, Objectives and Hypotheses 9.2.2, Endpoint	Added exploratory objectives, endpoints for PD-L1 status, molecular profile, impact on tumor immune cell infiltrate, changes to tumor molecular profile
9.3.2, Predictive Biomarker Evaluations	Added section on tissue biomarkers, request for additional tissue if needed
11.5, Biomarker Analysis	Updated to include analyses of tissue samples
Rationale: Symptom Management Questionnaire added to help evaluate and explore the subject experience as part of the clinical study.	
Time and Events Table 3	Added Symptom Management Questionnaire
2, Objectives and Hypotheses 9.2.2 Endpoints	Added exploratory objective, endpoint, text for Symptom Management Questionnaire
9.4.11, Symptom Measurement Questionnaire	Added new section to describe questionnaire
Rationale: Clarifications to existing study procedures were made.	
Table 2	Adjusted visit windows to match Table 3

Applicable Section(s)	Description of Change(s)
Table 1, Table 2	Revised footnote “n” to match Table 3
6.3.2, Guidelines for the Management of Elevated Phosphate Levels	Added conversion to mmol/L and definitions of length of drug interruption and persistent hyperphosphatemia to Table 14
12.1.3, Severity Criteria	Added conversion to mmol/L to Table 22
6.3.6, Guidelines for Eye Toxicity Associated with Vision Changes	Clarified that Amsler grid test will be performed at the start of every cycle from Cycle 2 onwards
9.2.1.1, Radiographic Images Assessment	Clarified confirmatory scans are required for all unconfirmed PR/CR results
9.4.2, Clinical Laboratory Tests	Clarified alpha-1-glycoprotein performed by central lab using 2-hour post-dose sample from Cycle 1 Day 1
12.3.1, All Adverse Events	Clarified that AEs are collected until 30 days after last dose of study drug
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical and formatting changes were made.

Amendment 2 (25 June 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

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[redacted]

Applicable Section(s)	Description of Change(s)
Rationale: The T&E tables (Tables 1 & 2) were updated with additional visit windows to permit flexibility in scheduling radiology assessments and Cycle 1 Day 1 chemistry and hematology laboratory assessments. Table 4 updated as a result of overall rationale (bridging to blood-based assay and assessment of molecular signature of response and resistance/progression). Bicarbonate and chloride removed from Section 9.4.2 due to absence of acid/base disturbances associated with JNJ-42756493 (data from ongoing phase 1 study).	
Time and Events Table1 and Table 2	Updated footnotes to include window for Cycle 1 Day 1 chemistry and hematology labs. Updated footnotes to include visit window for radiology assessments. Updated footnotes to exclude requirement of PTH value availability prior to dosing, as this value is not essential for screening safety of the subject but provides assessment of an additional potential biomarker linked to Ca-P homeostasis.

Applicable Section(s)	Description of Change(s)
Time and Events Table 4, Section 11.5 Biomarker Analyses	Updated to include additional blood samples for biomarker research.
Synopsis, Section 9.3 Predictive and Pharmacodynamic Biomarker Evaluations	Added information on additional blood samples and intended analyses
Section 9.4.2 Clinical Laboratory Tests	Deleted bicarbonate and chloride from clinical chemistry table.
Rationale: Minor errors were noted	
Minor grammatical, formatting, or spelling changes Minor grammatical and formatting changes were made.	

Amendment 1 (2 April 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment enables inclusion of up-titration of dose in both treatment Regimens, and changes Regimen 2 from an interrupted schedule to a continuous dosing schedule.

Pharmacokinetic/pharmacodynamic modeling based on emerging data from Study42756493EDI1001 indicates that, at the 6 mg dose a 3-weeks on/1-week off dose regimen may be appropriate as it would avoid unscheduled interruptions due to hyperphosphatemia in approximately 25% of subjects. However, with dose reduction to 5 mg and 4 mg the number of subjects needing dose interruptions due to hyperphosphatemia is likely to be very small and therefore a 3-weeks-on/1-week-off dose regimen may not be necessary. Changing the schedule from the 3-weeks-on/1-week-off dose regimen to continuous daily dosing will mitigate this effect, but may result in unscheduled interruptions in approximately 25% of subjects at the 6 mg starting dose level; this is considered manageable.

Moreover, further modeling also indicated that in both selected dose regimens (ie, 6 mg once daily continuous and 10 mg once daily in a 7 days-on/7 days-off schedule) the dose can be further personalized based on the observed pharmacodynamic effect (phosphate level). Those subjects with suboptimal pharmacodynamic effect can be brought to target pharmacodynamic range (phosphate rage 5.5 to 7 mg/dL) by selective dose up-titration. Instituting these changes only in subjects with suboptimal pharmacodynamic effect who do not have significant toxicity will result in further dose optimization without significant increase in toxicity.

Applicable Section(s)	Description of Change(s)
Rationale: The T&E, Section 3.2.2 and Section 6 were adapted to reflect these changes.	
Synopsis and throughout protocol: Changes pertaining to Regimen 2	

Applicable Section(s)	Description of Change(s)
T&E Tables	Split in two tables (one per regimen) and includes changes in assessments as necessitated by the dose and schedule change. Added increased frequency of pregnancy testing.
Abbreviations	Several new abbreviations were added
Section 3.2.2 Rationale for Phase 2 Dose Selection	Rationale for dose regimen selection and up-titration added
Section 4.1 & 4.2: Inclusion/Exclusion criteria	Updated inclusion 4 to clarify eligibility for subjects treated with anti-PDL1/PD1 antibodies. Updated exclusion 1 to include specific parameters for immunotherapy
Section 6.2 Dose Up-titration Guidelines (new section)	Includes guidelines for up-titration. Subsequent sections in Section 6 are renumbered
Section 6.3 Dose Modifications and Dose Delays	Tables specifying dose reduction levels for both regimens are provided.
Rationale: The double barrier method is not considered to be an acceptable method by a Health Authority. Increased frequency of pregnancy testing recommended by Health Authority.	
Section 4.1 Inclusion Criteria Criterion 8	The double barrier method was removed
Rationale: Minor errors were noted	
Th oughout the prot col	Minor grammatical and formatting changes were made.

SYNOPSIS

A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

JNJ-42756493 (erdafitinib) is a selective and potent pan fibroblast growth factor receptor (FGFR) inhibitor with demonstrated clinical activity in patients with solid tumors with alterations in the FGFR pathway including urothelial carcinoma,[1] indicating the potential to be a new therapeutic option for these patients. In the proposed Phase 2 study, the efficacy and safety of erdafitinib in urothelial carcinomas harboring select FGFR aberrations will be evaluated at 3 dose regimens. The selected dose regimen upon implementation of Amendment 3 is 8 mg continuous daily dosing (Regimen 3).

OBJECTIVES AND HYPOTHESES

Primary Objective

- To evaluate the objective response rate (complete response [CR]+ partial response [PR]) of the selected dose regimen in subjects with metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations.

Secondary Objectives

- To evaluate the objective response rate of the selected dose regimen in chemo-refractory subjects
- To evaluate progression-free survival (PFS), duration of response, and overall survival of the selected dose regimen in all and chemo-refractory subjects
- To evaluate the response rate in biomarker-specific subgroups (translocations versus mutations) with the selected dose regimen
- To evaluate the objective response rate, PFS, duration of response, and overall survival of the other dose regimens tested
- To evaluate the safety and pharmacokinetics of erdafitinib of all dose regimens

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OVERVIEW OF STUDY DESIGN

This is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of 2 different dose regimens (Regimen 1: 10 mg oral study drug once daily on an intermittent schedule [Days 1 through 7 and Days 15 through 21 of a 28-day cycle]; Regimen 2: 6 mg oral study drug once daily on a continuous schedule [Days 1 through 28 of a 28-day cycle]), and selection of a more favorable dose regimen for erdafitinib in subjects with metastatic or surgically unresectable urothelial cancer with select FGFR genetic alterations. Based on analysis of data up to Interim Analysis 1 (IA1), the Data Review Committee (DRC) decided to terminate further enrollment to the intermittent schedule and select the continuous schedule with a starting dose of 8 mg and possible up-titration to 9 mg (Regimen 3) for further enrollment. It is expected that approximately 180 subjects with specified FGFR genetic alterations will be enrolled in the study, of which about 30 subjects will be treated with Regimen 1, about 50 subjects will be treated with Regimen 2, and approximately 100 subjects will be treated with Regimen 3. When approximately 88 subjects have been treated in Regimen 3, if less than 80 subjects are chemo-refractory, then enrollment of chemo-naïve subjects in Regimen 3 will be stopped but enrollment of chemo-refractory subjects will continue until at least 80 chemo-refractory subjects are treated in Regimen 3 or a total of approximately 100 subjects are treated with Regimen 3.

The study comprises a Screening Phase (molecular screening and full study screening), a Treatment Phase, and a post-treatment Follow-up Phase. Prior to IA1, subjects were randomized to 1 of 2 treatment regimens and stratified according to Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin level, FGFR alteration type, pretreatment status, and disease distribution. After IA1, subjects will be assigned to Regimen 2. Following implementation of Amendment 3, all new subjects will be assigned to Regimen 3.

Subjects will be assessed for disease response according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) guidelines. The end of study is defined as the date when all subjects have completed the study treatment (Regimens 1 to 3) and all subjects enrolled under the drug-drug interaction (DDI) substudy are no longer receiving treatment with erdafitinib.

SUBJECT POPULATION

Key inclusion criteria include the following: ≥18 years of age with histologic demonstration of metastatic or surgically unresectable transitional cell carcinoma of the urothelium CCI ECOG performance status score 0, 1, or 2; measurable disease according to the RECIST guidelines, version 1.1 at baseline; progressive disease after receiving at least 1 prior systemic chemotherapy; or ineligible for cisplatin per full inclusion criteria.

DOSAGE AND ADMINISTRATION

The erdafitinib study drug is formulated as 3-, 4-, and 5-mg tablets for oral use. Prior to IA1, subjects were randomized to receive 10 mg of oral study drug once daily on Days 1 through 7 and Days 15 through 21 of a 28-day cycle (Regimen 1) or 6 mg of oral study drug once daily on Days 1 through 28 of a 28-day cycle (Regimen 2). After IA1, subjects will receive 6 mg of oral study drug once daily on Days 1 through 28 of a 28-day cycle (Regimen 2). Following implementation of Amendment 3, subjects will receive 8 mg oral study drug once daily on Days 1 through 28 of a 28 day cycle (Regimen 3).

EFFICACY EVALUATIONS

Subjects will have response evaluations performed by radiographic image assessments according to RECIST version 1.1 guidelines until disease progression, initiation of subsequent anticancer therapy, or withdrawal of consent, whichever occurs first.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Subjects' tumors will be analyzed for the presence of select FGFR translocations and mutations to assess for molecular eligibility criteria. Phosphate levels will be evaluated throughout the study as a pharmacodynamic marker for safety. Pre-dose, on-treatment and end-of-treatment blood samples will be collected for the exploration of use of a blood-based assay for molecular eligibility and for assessment of the molecular signature of response and resistance/progression. Collected tumor tissue will be used to assess immune marker status and to identify the molecular subtype of urothelial cancer. Tumor biopsies, if feasible, will be collected to assess changes in immune cell markers, and other biomarkers, in response to treatment. CCI [redacted]

SAFETY EVALUATIONS

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, clinical laboratory tests and ECOG performance status at specified time points as described in the protocol.

STATISTICAL METHODS

Before IA1, the plan was to evaluate 2 dose regimens, with subjects being randomized in a 1:1 ratio to receive either Regimen 1 (10 mg) or Regimen 2 (6 mg). Once a favorable dose regimen was selected, enrollment in the other dose regimen was to be discontinued. The study was to enroll approximately 165 subjects with approximately 110 subjects at the selected dose. There were 2 planned interim analyses for safety, futility, and dose selection.

After IA1, a starting dose of 8 mg once daily was selected by the DRC. As a result, the primary analysis for the primary endpoint will be conducted 6 months after enrollment of the last subject in Regimen 3. Response will be assessed by investigators and may be assessed by an Independent Radiologic Review Committee (IRRC). The IRRC assessment of response will be used for the primary analysis if the primary objective is achieved by the investigators' assessments. The null hypothesis will be rejected at overall α level of 0.025 (1-sided).

DDI Substudy with Continued Erdafitinib Treatment Until Disease Progression

The DDI substudy, which addresses a post-marketing requirement and commitment, was added with Amendment 7. This is a multicenter, open-label, single sequence substudy to evaluate the effects of erdafitinib daily dosing on the pharmacokinetics of the probe drugs midazolam and metformin, which are metabolized by CYP3A and transported by OCT2, respectively, in subjects with advanced solid tumors, including those with metastatic or surgically unresectable urothelial cancer, that harbor target FGFR mutations or FGFR gene fusions. Approximately 22 subjects will be enrolled in this DDI substudy at select study sites to obtain 15 pharmacokinetic-evaluable subjects. After completion of the DDI substudy, subjects will continue treatment with 8 mg erdafitinib once daily (with titration to 9 mg once daily based on phosphate levels) until disease progression. Safety assessments will be conducted, along with limited efficacy for the purpose of identifying disease progression) CCI [redacted]. A Long-Term Extension (LTE) Phase was added. During the LTE, subjects who completed the DDI portion of the study and continue to benefit from erdafitinib treatment, will continue to receive erdafitinib. During the LTE, data will not be captured in the clinical database; only serious adverse events will be reported through the company safety repository.

TIME AND EVENTS SCHEDULES (For DDI Substudy – see Attachment 12)

Table 1: REGIMEN 1 Time and Events Schedule (10 mg starting dose, 7 days on/7 days off)

Parameter	Molecular Eligibility Assessment	Full Study Screening		Treatment C1 – ALL subjects Treatment C2 & C3 – ONLY up-titrated (12 mg 7 days on/7 days off) subjects			Subsequent Cycles Day 1 (starting C2 for subjects non up-titrated; starting C4 for subjects up-titrated to 12 mg)	End-of-Treatment[t]	Follow-Up Phase[u]
				Day 1	Day 7(-1)	Day 21(-2)			
Visit Window	N/A	Within 30 days	Within 14 days	C1: N/A C2&3: -2 to +3 days	-1 day	-2 days	-2 to +3 days	Within 30 days after last dose	±7 days
Screening/Administrative									
Informed Consent[a] (molecular and full study)	X	X							
Medical History[b]		X							
Tumor Tissue[c]	X								
Randomization to treatment[d]			X						
Study Drug Administration									
erdafitinib				On Days 1 through 7; off Days 8 through 14; On Days 15 through 21, off Days 22 through 28					
Safety Assessments									
Physical Examination[e]		X		X	X (C1 only)		X	X	
Vital signs[f,g]		X		X	X (C1 only)		X	X	
ECOG performance status[h]			X	○ X			X		
Urine or serum pregnancy test[i]			X	X (C2 &C3 only)			X	X	
Triplicate 12-lead ECG[g,j]		X		X[v] (C1 only)	X[w] (C1 only)				
Echocardiography (MUGA)[k]		X							

Table 1: REGIMEN 1 Time and Events Schedule (10 mg starting dose, 7 days on/7 days off)

Parameter	Molecular Eligibility Assessment	Full Study Screening		Treatment C1 – ALL subjects Treatment C2 & C3 – ONLY up-titrated (12 mg 7 days on/7 days off) subjects Day 1	Day 7(-1)	Day 21(-2)	Subsequent Cycles Day 1 (starting C2 for subjects non up-titrated; starting C4 for subjects up-titrated to 12 mg)	End-of-Treatment[t]		Follow-Up Phase[u]
Visit Window	N/A	Within 30 days	Within 14 days	C1: N/A C2&3: -2 to +3 days	-1 day	-2 days	-2 to +3 days	Within 30 days after last dose		±7 days
Ophthalmologic Exam[l]		X								
Amsler Grid Test[m]		X		X (C2 & C3 only)				X	X	
Clinical Laboratory Assessments										
Hematology[g,j]			X	X[aa]				X[x]	X	
Chemistry[g,j]			X	X[y,aa]		X (Phos only)	X[y, z]	X[y]	X	
Efficacy Assessments										
Radiological assessment[n]		X		Once every 6 weeks during the first 3 months, then once every 12 weeks for the next 9 months, and once every 4 to 6 months until disease progression						
Pharmacokinetic and Biomarker Assessments										
PK blood sampling[g]				X[o] Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations. Additional samples may be collected at any time for assessment of adverse events as clinically appropriate.						
Biomarker blood sampling[g]		X		X[p] Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations.					X[p]	
Ongoing Subject Review										
Concomitant Medications		X		X---------- ----------X						
Adverse Events[q]		X		X---------- ----------X						X[r]
Survival status and subsequent anticancer therapies										X[s]

Abbreviations: C= cycle; CDRH=Center for Devices and Radiological Health; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FGFR=fibroblast growth factor receptor; ICF=informed consent form; MUGA=multi-gated acquisition scan; PD=pharmacodynamics; Phos=phosphate; PK=pharmacokinetic

[a] Subjects may be presented with a molecular eligibility ICF to allow for the assessment of archived tumor tissue. Subjects who meet the tumor molecular eligibility criteria will be further screened for full study eligibility, for which subjects may be presented a separate Full-Study ICF within 30 days prior to Cycle 1 Day 1.

[b] Histological documentation of specific tumor type and prior anticancer therapy. Record demographic information.

[c] Only available tumor tissue (quantity as noted in the Laboratory Manual) should be sent for analysis. No biopsies will be performed for purposes of molecular eligibility until approval is given by local regulatory agencies where applicable (e.g. approval of an Investigational Device Exemption (IDE) by the FDA/Center for Devices and Radiological Health (CDRH).

[d] Randomization will occur within 3 days prior to Cycle 1 Day 1. All information required for randomization purposes must be available at the time of randomization including: ECOG performance status score, hemoglobin value, FGFR alteration type (communicated by sponsor by time of randomization), disease distribution (presence or absence of visceral metastases: lung, liver, and bone) based upon baseline radiographic imaging performed during screening window, and pretreatment status (chemo-refractory versus chemo-naive) obtained by subject history/medical records.

[e] At Screening, a complete physical examination will be performed including height, weight, and oral/tympanic temperature. During the treatment period, limited physical examination of affected organs will be done, including weight and oral/tympanic temperature.

[f] Including heart rate, systolic and diastolic blood pressure.

[g] On the day of visits with multiple measurements (clinical laboratory testing, ECG, PK/PD, and vital signs), the order of assessments will be per local site standards.

[h] ECOG performance status score of 0, 1, or 2 required within the 14 days prior to Cycle 1 Day 1, up until pre-dose of Cycle 1.

[i] Urine or serum β-hCG test, for women of childbearing potential and when sexually active at screening, at Day 1 of each subsequent cycle (following C1D1) and the end of treatment. Enrolled subjects should be counselled regarding appropriate contraception as required on Day 1 of every cycle.

[j] Clinical laboratory test results (except PTH) and ECG results must be available in real time prior to dosing with study drug as required in the schedule. Values/results of previous testing should be available for comparison as clinically necessary.

[k] If echocardiogram is not available, MUGA can be used.

[l] Ophthalmological examinations should be performed by an ophthalmologist and should include assessment of visual acuity, tonometry, fundoscopy (examination of both central and peripheral zones should be performed), and where available Optical Coherence Tomography (OCT).

[m] Amsler grid testing should be performed by study physician or nurse (as directed by specific site instructions); please see Attachment 5 for Amsler grid pictorial

[n] Radiological assessment of response using imaging technology. Identical methodology should be used for disease assessment at baseline and throughout the study whenever possible. Baseline radiological assessment (refer to Section 9.2) will be obtained within 30 days before administration of the first dose of study drug. Radiological assessment will be performed once every 6 weeks (+/-3 days, -14 to +3 days for scans confirming initial response) during the first 3 months, then once every 12 weeks (+/-1week) for the next 9 months, and once every 4 to 6 months until disease progression. All unconfirmed PR/CR require confirmation of response within 4 to 6 weeks of first assessment, as per RECIST 1.1.

[o] Pharmacokinetic sampling schedule is provided in Table 4.

[p] Biomarker sampling schedule is provided in Table 5.

[q] Adverse events will be collected from the day of the full study ICF signing until 30 days after the subject's last dose of study drug. Adverse events may be collected by telephone call, and clinic visits.

[r] Subjects who discontinue study drug due to drug-related toxicity will continue to be monitored for this toxicity until the toxicity resolves to baseline, stabilizes, or is deemed irreversible, the subject dies, or subsequent therapy is started, whichever occurs first.

[s] May be assessed via telephone call.

[t] The End-of-Treatment Visit must occur within 30 days after subject discontinues treatment last dose of study drug.

[u] All subjects are to have a Follow-up Visit every 12 weeks (±7 days) in the Follow-Up Phase. For subjects who discontinue study drug before disease progression, tumor assessment should be continued as if the subject is still on treatment.

[v] Pre-dose

[w] To be performed 2 hours post-dose, at approximately the same time of day as the Day 1 ECG was performed

[x] Every third cycle starting on Cycle 3 Day 1: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count

[y] Parathyroid hormone (PTH) will only be assessed pre-dose on Cycle 1 Day 1, Cycle 1 Day 21, Cycle 2 Day 1, and Cycle 3 Day 1.

[z] Decision to up-titrate to 12 mg 7 days on/7 days off should be determined based on C1D21 phosphate value, and as per dose up-titration guidelines in Section 6.2.

[aa] Cycle 1 Day 1 chemistry and hematology may be performed the day prior to Cycle 1 Day 1.

Table 2: REGIMEN 2 Time and Events Schedule (6 mg starting dose, 28 days continuous)

Parameter	Molecular Eligibility Assessment	Full Study Screening		Treatment C1 – ALL subjects Treatment C2 & 3 – ONLY up-titrated (8mg/day) subjects[a]			Subsequent Cycles: Day 1 (starting at C2 for subjects non up-titrated; starting at C4 for subjects up-titrated to 8 mg daily)[a]	Subsequent cycles (C2 and C3): Day 14 (ONLY non up-titrated subjects that continue at 6mg/day)[a]	End-of-Treatment[a,t]	Follow-Up Phase[a,u]
				Day 1	Day 7(-1)	Day 21(-2)				
Visit Window	N/A	Within 30 days	Within 14 days	C1: N/A C2&3: -2 to +2 days	-1 day	-2 days	-2 to +2 days	-2 to +2 days	Within 30 days after last dose	±7 days
Screening/Administrative										
Informed Consent[b] (molecular and full study)	X	X								
Medical History[bb]		X								
Tumor Tissue[c]	X									
Randomization to treatment[d]			X							
Study Drug Administration										
erdafitinib				Daily on Days 1 through 28						
Safety Assessments										
Physical Examination[e]		X		X	X (C1 only)		X		X	
Vital signs[f,g]		X		X	X (C1 only)		X		X	
ECOG performance status[h]			X	X			X			
Urine or serum pregnancy test[i]			X	X (C2 & C3 only)			X		X	
Triplicate 12-lead ECG[g,j]		X		X[v] (C1 only)	X[w] (C1 only)					
Echocardiography		X								

Table 2: REGIMEN 2 Time and Events Schedule (6 mg starting dose, 28 days continuous)

Parameter	Molecular Eligibility Assessment	Full Study Screening		Treatment C1 – ALL subjects Treatment C2 & 3 – ONLY up-titrated (8mg/day) subjects[a]			Subsequent Cycles: Day 1 (starting at C2 for subjects non up-titrated; starting at C4 for subjects up-titrated to 8 mg daily)[a]	Subsequent cycles (C2 and C3): Day 14 (ONLY non up-titrated subjects that continue at 6mg/day)[a]	End-of-Treatment[a,t]	Follow-Up Phase[a,u]
				Day 1	Day 7(-1)	Day 21(-2)				
(MUGA)[k]										
Ophthalmologic Exam[l]		X	A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment (Section 9.4.7)							
Amsler Grid Test[m]		X		X (C2&C3 only)			X		X	
Clinical Laboratory Assessments										
Hematology[g,j]			X	X[aa]			X[x]		X	
Chemistry[g,j]			X	X[y, z,aa]	X (Phos only)	X[y]	X[y]	X (Phos only)	X	
Efficacy Assessments										
Radiological assessment[n]		X		Once every 6 weeks during the first 3 months, then once every 12 weeks for the next 9 months, and once every 4 to 6 months until disease progression						
Pharmacokinetic and Biomarker Assessments										
PK blood sampling[g]				X[o] Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations. Additional samples may be collected at any time for assessment of adverse events as clinically appropriate.						
Biomarker blood sampling[g]		X		X[p] Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations.					X[p]	
Ongoing Subject Review										
Concomitant Medications		X		X---------- X						
Adverse Events[q]		X		X---------- X						X[r]
Survival status and subsequent anticancer therapies										X[s]

Table 2: REGIMEN 2 Time and Events Schedule (6 mg starting dose, 28 days continuous)

Parameter	Molecular Eligibility Assessment	Full Study Screening	Treatment C1 – ALL subjects Treatment C2 & 3 – ONLY up-titrated (8mg/day) subjects[a] Day 1	Day 7(-1)	Day 21(-2)	Subsequent Cycles: Day 1 (starting at C2 for subjects non up-titrated; starting at C4 for subjects up-titrated to 8 mg daily)[a]	Subsequent cycles (C2 and C3): Day 14 (ONLY non up-titrated subjects that continue at 6mg/day)[a]	End-of-Treatment[a,t]	Follow-Up Phase[a,u]

Abbreviations: C=Cycle; CDRH=Center for Devices and Radiological Health; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FGFR=fibroblast growth factor receptor; ICF=informed consent form; MUGA=multi-gated acquisition scan; PD=pharmacodynamics; Phos=phosphate; PK=pharmacokinetic

[a] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 11.

[b] Subjects may be presented with a molecular eligibility ICF to allow for the assessment of archived tumor tissue. Subjects who meet the tumor molecular eligibility criteria will be further screened for full study eligibility, for which subjects may be presented a separate Full-Study ICF within 30 days prior to Cycle 1 Day 1.

[c] Only available tumor tissue (quantity as noted in the Laboratory Manual) should be sent for analysis. No biopsies will be performed for purposes of molecular eligibility until approval is given by local regulatory agencies where applicable (e.g. approval of an Investigational Device Exemption (IDE) by the FDA/Center for Devices and Radiological Health (CDRH).

[d] Randomization will occur within 3 days prior to Cycle 1 Day 1. All information required for randomization purposes must be available at the time of randomization including: ECOG performance status score, hemoglobin value, FGFR alteration type (communicated by sponsor by time of randomization), disease distribution (presence or absence of visceral metastases: lung, liver, and bone) based upon baseline radiographic imaging performed during screening window, and pretreatment status (chemo-refractory versus chemo-naive) obtained by subject history/medical records.

[e] At Screening, a complete physical examination will be performed including height, weight, and oral/tympanic temperature. During the treatment period, limited physical examination of affected organs will be done, including weight and oral/tympanic temperature.

[f] Including heart rate, systolic and diastolic blood pressure.

[g] On the day of visits with multiple measurements (clinical laboratory testing, ECG, PK/PD, and vital signs), the order of assessments will be per local site standards.

[h] ECOG performance status score of 0, 1, or 2 required within the 14 days prior to Cycle 1 Day 1, up until pre-dose of Cycle 1.

[i] Urine or serum β-hCG test, for women of childbearing potential and when sexually active: at screening, at Day 1 of each subsequent cycle (following C1D1) and end of treatment. Enrolled subjects should be counselled regarding appropriate contraception as required on Day 1 of every cycle.

[j] Clinical laboratory test results (except PTH) and ECG results must be available in real time prior to dosing with study drug as required in the schedule. Values/results of previous testing should be available for comparison as clinically necessary.

[k] If echocardiogram is not available, MUGA can be used.

[l] Ophthalmological examinations must be performed at Screening by an ophthalmologist and should include assessment of visual acuity, fundoscopy (examination of both central and peripheral zones should be performed), and slit lamp biomicroscopy and Optical Coherence Tomography (OCT).

[m] Amsler grid testing should be performed by study physician or nurse (as directed by specific site instructions); please see Attachment 5 for Amsler grid pictorial

[n] Radiological assessment of response using imaging technology. Identical methodology should be used for disease assessment at baseline and throughout the study whenever possible. Baseline radiological assessment (refer to Section 9.2) will be obtained within 30 days before administration of the first dose of study drug. Radiological assessment will be performed once every 6 weeks (+/-3 days, -14 to +3 days for scans confirming initial response) during the first 3 months, then once every 12 weeks (+/-1week) for the next 9 months, and once every 4 to 6 months until disease progression. All unconfirmed PR/CR require confirmation of response within 4 to 6 weeks of first assessment, as per RECIST 1.1.

[o] Pharmacokinetic sampling schedule is provided in Table 4.

[p] Biomarker sampling schedule is provided in Table 5.

[q] Adverse events will be collected from the day of the full study ICF signing until 30 days after the subject's last dose of study drug. Adverse events may be collected by telephone call, and clinic visits.

Table 2: REGIMEN 2 Time and Events Schedule (6 mg starting dose, 28 days continuous)

Parameter	Molecular Eligibility Assessment	Full Study Screening	Treatment C1 – ALL subjects Treatment C2 & 3 – ONLY up-titrated (8mg/day) subjects[a]			Subsequent Cycles: Day 1 (starting at C2 for subjects non up-titrated; starting at C4 for subjects up-titrated to 8 mg daily)[a]	Subsequent cycles (C2 and C3): Day 14 (ONLY non up-titrated subjects that continue at 6mg/day)[a]	End-of-Treatment[a,t]	Follow-Up Phase[a,u]
			Day 1	Day 7(-1)	Day 21(-2)				

[r] Subjects who discontinue study drug due to drug-related toxicity will continue to be monitored for this toxicity until the toxicity resolves to baseline, stabilizes, or is deemed irreversible, the subject dies, or subsequent therapy is started, whichever occurs first.
[s] May be assessed via telephone call.
[t] The End-of-Treatment Visit must occur within 30 days after the subject discontinues treatment.
[u] All subjects are to have a Follow-up Visit every 12 weeks (±7 days) in the Follow-Up Phase. For subjects who discontinue study drug before disease progression, tumor assessment should be continued as if the subject is still on treatment.
[v] Pre-dose
[w] To be performed 2 hours post-dose, at approximately the same time of day as the Day 1 ECG was performed
[x] Every third cycle starting on Cycle 3 Day 1: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count
[y] Parathyroid hormone (PTH) will only be assessed pre-dose on Cycle 1 Day 1, Cycle 1 Day 21, Cycle 2 Day 1, and Cycle 3 Day 1.
[z] Decision to up-titrate to 8 mg daily should be determined based on the C2D1 pre-dose phosphate value, and as per dose up-titration guidelines in Section 6.2
[aa] Cycle 1 Day 1 chemistry and hematology may be performed the day prior to Cycle 1 Day 1.
[bb] Histological documentation of specific tumor type and prior anticancer therapy. Record demographic information.

Table 3: REGIMEN 3 Time and Events Schedule (8 mg starting dose, 28 days continuous)

Parameter	Molecular Eligibility Assessment	Full Study Screening		Cycles 1, 2, 3[a]			Cycle 4[a]		Cycle 5+[a]	End of Treatment[a]	Follow-Up[a]
				Day 1	Day 14	Day 21	Day 1	Day 14	Day 1		
Visit Window	N/A	-30 days	-14 days	C2, C3: -2 to +2 days	-1 day	-2 days	-2 to +2 days	-2 to +2 days	-2 to +2 days	+30 days after last dose	every 12 weeks ±7 days
Screening/Administrative											
Informed Consent (molecular and full study)[b]	X	X									
Medical history[w]		X									
Tumor tissue for molecular screening, biomarker testing [c]	X										
Study Drug Administration: Cycle 1 Day 1 must occur no more than 3 days after the Randomization transaction in IWRS											
erdafitinib				Daily on Days 1 through 28							
Safety Assessments											
Physical examination [d]		X		X	X (C1,C2)	X (C1,C2)	X		X	X	
Vital signs [e, f]		X		X			X		X	X	
ECOG performance status [g]			X	X			X		X		
Symptom Measurement Questionnaire (English language) [h]		X		X (C2, C3)	X (C1)					X	
Urine or serum pregnancy test[i]			X	X (C2, C3)			X		X	X	
Triplicate 12-lead ECG [fj]		X									
Echocardiography (MUGA) [o]		X									
Ophthalmologic exam [p]		X	A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment (Section 9.4.7)								
Amsler Grid Test [q]		X		X (C2, C3)			X		X	X	
Clinical Laboratory Assessments											
Hematology [fj]			X	X [k]					X [l]	X	
Chemistry [fj]			X	X [k,m]	X(PO4) [n]	X (PO4, PTH)	X	X (PO4)	X	X	

Table 3: REGIMEN 3 Time and Events Schedule (8 mg starting dose, 28 days continuous)

Parameter	Molecular Eligibility Assessment	Full Study Screening		Cycles 1, 2, 3[a]			Cycle 4[a]		Cycle 5+[a]	End of Treatment[a]	Follow-Up[a]
				Day 1	Day 14	Day 21	Day 1	Day 14	Day 1		
Visit Window	N/A	-30 days	-14 days	C2, C3: -2 to +2 days	-1 day	-2 days	-2 to +2 days	-2 to +2 days	-2 to +2 days	+30 days after last dose	every 12 weeks ±7 days
Efficacy Assessments											
Radiological assessment [r]		X		Every 6 weeks for the first 3 months, then every 12 weeks for the next 9 months, then every 4 to 6 months until disease progression[r]							
Pharmacokinetic and Biomarker Assessments											
Tumor biopsy, if feasible, for biomarker research		X		On or around Cycle 2 Day 1 [s]						X	
PK blood sampling [f]				Please see Table 4 - Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations. Additional samples may be collected at any time for assessment of adverse events as clinically appropriate.							
Biomarker blood sampling [f]		X		Please see Table 5 - Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations.						X	
Ongoing Subject Review											
Concomitant medications			X	X							
Adverse events		X		X [t]							X [u]
Survival status, subsequent anticancer therapy											X [v]

Abbreviations: C=Cycle; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FGFR=fibroblast growth factor receptor; ICF=informed consent form; MUGA=multi-gated acquisition scan; PD=pharmacodynamics; PO4=phosphate; PK=pharmacokinetic, PTH= parathyroid hormone

[a] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 11.

[b] Subjects may be presented with a molecular eligibility ICF to allow for the assessment of archived tumor tissue. Subjects who meet the tumor molecular eligibility criteria will be further screened for full study eligibility, for which subjects may be presented a separate Full-Study ICF within 30 days prior to Cycle 1 Day 1.

[c] Archival or fresh biopsy tumor tissue may be sent for molecular screening and biomarker testing.

[d] At Screening, a complete physical examination will be performed including height, weight, and oral/tympanic temperature. During the treatment period, limited physical examination of affected organs will be done, including weight and oral/tympanic temperature.

[e] Including heart rate, systolic and diastolic blood pressure.

[f] On the day of visits with multiple measurements (clinical laboratory testing, ECG, PK/PD, and vital signs), the order of assessments will be per local site standards. An additional biomarker blood collection will be performed on C2 Day 1 for patients providing on-treatment tumor biopsies.

[g] ECOG performance status score of 0, 1, or 2 required within the 14 days prior to Cycle 1 Day 1, up until pre-dose of Cycle 1.

[h] Questionnaire on symptom measurement available in English only, and will be completed by subjects who can read English. Not applicable for existing subjects who switch to Regimen 3.

[i] Urine or serum β-hCG test, for women of childbearing potential and when sexually active: at screening, at Day 1 of each subsequent cycle (following C1D1) and end of treatment. Enrolled subjects should be counselled regarding appropriate contraception as required on Day 1 of every cycle.

[j] Clinical laboratory test results (except PTH) and ECG results must be available in real time prior to dosing with study drug as required in the schedule. Values/results of previous testing should be available for comparison as clinically necessary.
[k] Cycle 1 Day 1 chemistry and hematology may be performed the day prior to Cycle 1 Day 1.
[l] Every third cycle starting on Cycle 6 Day 1: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count
[m] Parathyroid hormone (PTH) will only be assessed pre-dose on Cycle 1 Day 1, Cycle 1 Day 21, Cycle 2 Day 1, and Cycle 3 Day 1.
[n] Decision to up-titrate to 9 mg daily should be determined based on the C1D14 phosphate value, and as per dose up-titration guidelines in Section 6.2
[o] If echocardiogram is not available, MUGA can be used.
[p] Ophthalmological examinations must be performed at Screening by an ophthalmologist and should include assessment of visual acuity, fundoscopy (examination of both central and peripheral zones should be performed), and slit lamp biomicroscopy and Optical Coherence Tomography (OCT).
[q] Amsler grid testing should be performed by study physician or nurse (as directed by specific site instructions); please see Attachment 5 for Amsler grid pictorial
[r] Radiological assessment of response using imaging technology. Identical methodology should be used for disease assessment at baseline and throughout the study whenever possible. Baseline radiological assessment (refer to Section 9.2) will be obtained within 30 days before administration of the first dose of study drug. Radiological assessment will be performed once every 6 weeks (+/-3 days, -14 to +3 days for scans confirming initial response) during the first 3 months, then once every 12 weeks (+/-1week) for the next 9 months, and once every 4 to 6 months until disease progression. All unconfirmed PR/CR require confirmation of response within 4 to 6 weeks of first assessment, as per RECIST 1.1.
[s] Pre-treatment and post-treatment tumor biopsies, if feasible, for patients deemed eligible by investigator (refer to Section 9.1). Not applicable for existing subjects who switch to Regimen 3.
[t] Adverse events will be collected from the day of the full study ICF signing until 30 days after the subject's last dose of study drug. Adverse events may be collected by telephone call, and clinic visits.
[u] Subjects who discontinue study drug due to drug-related toxicity will continue to be monitored for this toxicity until the toxicity resolves to baseline, stabilizes, or is deemed irreversible, the subject dies, or subsequent therapy is started, whichever occurs first.
[v] All subjects are to have a Follow-up Visit every 12 weeks (±7 days) in the Follow-Up Phase. All subjects will enter the Follow-Up Phase to assess survival status and start of alternate anticancer therapy until death, the subject withdraws consent, or the end of study, whichever occurs first. This information may be collected via telephone call. For subjects who discontinue study drug before disease progression, tumor assessment should be continued as if the subject is still on treatment.
[w] Histological documentation of specific tumor type and prior anticancer therapy. Record demographic information.

Table 4: Pharmacokinetic Blood Sample Collection Schedule

Cycle and Day[a]	Number of samples at each time point	Volume (mL)	Predose (within 30 minutes prior to dose)	2 h	4 h
Cycle 1 Day 1	1	3 or 7[b]	X	X[b]	X
Cycle 1 Day 21	1	3	X	X	X
Every other cycle, starting Cycle 3	1	3	X		

[a] 3 mL blood sample will be collected at each time point. The sampling schedule may be adjusted based on pharmacokinetic analysis output generated during the study or in case of vomiting or other safety concerns.

[b] an additional 4 mL blood sample will be collected for determination of FU (fraction of the unbound erdafitinib) and protein levels (total protein, albumin, and alpha-1-acid glycoprotein) on Cycle 1 Day 1, 2 hours post dose

Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations. Additional samples may be collected at any time for assessment of adverse events as clinically appropriate.

Table 5: Biomarker Blood Sample Collection Schedule

Time Point	Number of samples at each time point	Total Volume (mL) [a]
Screening	1+1	22.5 mL
Cycle 1 Day 1 (predose)	1	2.5 mL
Cycle 2 Day 1 (predose) [b]	1+1	22.5 mL
Cycle 3 Day 1 (predose)	1	2.5 mL
Cycle 5 Day 1 (predose) [c]	1+1	22.5 mL
Day 1 of every other cycle (predose) starting Cycle 7	1	2.5 mL
End of Treatment Visit [c]	1+1	22.5 mL

[a] Total volume composed of 2.5 mL sample, and, where applicable, additional 20 mL sample.

[b] Subjects providing post-treatment biopsy only

[c] When possible, additional 20mL sample to be collected.

Note: Routine sample collection will be terminated once protocol Amendment 6 is approved at the site, as required by local regulations.

ABBREVIATIONS AND DEFINITIONS OF TERMS

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	age-related macular degeneration
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
AUC_u	area under the serum concentration versus time curve for unbound drug
BCOP	bovine corneal opacity and permeability
β-hCG	beta human chorionic gonadotropin
BUN	blood urea nitrogen
C_{avg}	average plasma concentrations
CED	the total concentration of erdafitinib in the plasma
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CPK	creatine phosphokinase
CR	complete response
CRF	Case Report Form
CSR	central serious retinopathy
CT	computed tomography
ctDNA	circulating tumor DNA
C_u	unbound concentration of erdafitinib
%CV	coefficient of variation
CYP	cytochrome P
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DRC	Data Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration (United States)
FDG-PET	fluorine 18-fluorodeoxyglucose positron emission tomography
FGFR	fibroblast growth factor receptor
FU	fraction of the unbound erdafitinib
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LC-MS/MS	liquid chromatography-mass spectrometry
LTE	Long-Term Extension
LVEF	left ventricular ejection fraction

MAPK	Ras/mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition scan
MVAC	methotrexate/vinblastine/doxorubicin/cisplatin
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
OCT	Optical Coherence Tomography
OCT2	organic cation transporter 2
ORR	overall response rate
PD	disease progression
PE	Primary Efficacy (analysis population)
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PQC	Product Quality Complaint
PR	partial response
PTH	parathyroid hormone
RANO	Revised Assessment in Neuro-Oncology
RE	Response Evaluable (population)
RECIST	Response Evaluation Criteria in Solid Tumors
RPED	retinal pigment epithelial detachments
RVO	retinal vascular occlusion
SD	stable disease
SMT	Safety Management Team
SPF	skin protection factor
TDI	time-dependent inhibitor
t_{max}	median time to maximum concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell (count)

1. INTRODUCTION

Urothelial carcinoma is a highly prevalent disease, with an estimated 74,700 new cases and 15,600 deaths in the United States (US) in 2014.[27] For metastatic urothelial cancer, platinum-based chemotherapy is the main therapeutic option for front-line therapy and there is no accepted standard of care for second-line therapy.

First-line chemotherapy for metastatic disease includes a combination of gemcitabine and cisplatin or methotrexate/vinblastine/doxorubicin/cisplatin (MVAC).[20] With cisplatin-based treatment, the median survival for patients with surgically unresectable or metastatic urothelial carcinoma is only approximately 14 months,[3] and 5-year survival is 13%.[30] Gemcitabine in combination with cisplatin showed a similar effect on overall survival (median: 14 months versus 15 months) and response rate (49% versus 46%) compared with MVAC with a better safety profile.[24,29]

There is a need to develop new therapeutic options capitalizing on the molecular aberration driving urothelial malignancy. Overexpression of fibroblast growth factor receptors (FGFRs), or aberrant regulation of their activity, has been implicated in many forms of human malignancies including urothelial carcinoma.[22]

Fibroblast growth factor receptors are protein tyrosine kinases and consist of 4 members (FGFR1 to FGFR4).[22] Upon binding to their natural ligand, FGF family members, FGFRs dimerize and autophosphorylate the tyrosine residue in the kinase domain activation loop to become fully activated. Activated FGFR further phosphorylate multiple signaling proteins bound to their intracellular portion, resulting in activation of Ras/mitogen-activated protein kinase (MAPK) and PI3-kinase/Akt signaling pathways. Other downstream signaling components of FGFRs include Src, and Rsk.[11,22] The result is FGFR stimulation of cell growth, survival, migration, and differentiation depending on the cell type.

Fibroblast growth factor receptors are present in many types of normal and tumor cells and have been shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis. Overexpression of FGFRs, or aberrant regulation of their activity, has been implicated in many forms of human malignancies.[13] Fibroblast growth factor receptor activating mutation, gene amplification, and translocation have been associated with neoplastic progression and tumor vascularization in multiple cancer types, including breast, lung, prostate, endometrial, gastric, and urothelial carcinoma.[22] Therefore, targeting FGFRs in urothelial cancer with a small molecule kinase inhibitor is an attractive strategy for the development of a novel cancer treatment.[13]

JNJ-42756493 (erdafitinib) is a selective and potent pan FGFR inhibitor with demonstrated clinical activity in patients with alterations in the FGFR pathway including urothelial carcinoma,[1] indicating the potential to be a new therapeutic option for these patients. In the proposed study, the efficacy and safety of erdafitinib in urothelial carcinomas harboring select FGFR aberrations will be evaluated at 2 dose regimens, and a more favorable dose regimen will be selected. Based on analysis of data up to Interim Analysis 1 (IA1), the Data Review Committee (DRC) decided to

terminate further enrollment to the intermittent schedule and select the continuous schedule with a starting dose of 8 mg and possible up-titration to 9 mg (Regimen 3) for further enrollment.

For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Investigator's Brochure.[13]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Nonclinical Pharmacology

Erdafitinib is an FGFR1, 2, 3, and 4 inhibitor with nanomolar affinity (biochemical half maximal inhibitory concentration [IC_{50}] values of <1 nM for FGFR1, <1 nM for FGFR2, 1.05 nM for FGFR3, and <1 nM for FGFR4). It has demonstrated potent inhibition of cell proliferation with IC_{50} values ranging from <1 nM to 100 nM in cell lines harboring activating FGFR alterations, including squamous non-small cell lung cancer (NSCLC), gastric, breast, and bladder. Non-FGFR driven cell lines require significantly higher drug concentration for inhibition of cell proliferation to be observed. Target inhibition and pathway modulation have been demonstrated in cellular models at the active cellular concentrations. A separate experiment demonstrated rapid lysosomal uptake of erdafitinib, which enables sustained intracellular release and long-lasting target engagement. Brief exposure (1 hour) to erdafitinib has been demonstrated to result in long term (8 to 16 hours) target inhibition due to drug accumulation in the lysosomes.[13] Furthermore, erdafitinib has demonstrated potent inhibition of growth of both xenograft tumors and patient-derived tumor samples implanted in immunodeficient mice and rats, including gastric, breast, lung, and bladder tumors harboring activating FGFR alterations.

1.1.2. Pharmacokinetics and Product Metabolism in Animals

In pharmacokinetic experiments in mice, rats, and dogs, erdafitinib showed high clearance, fast oral absorption, and short elimination half-life; the volume of distribution was higher than the total body water indicating extensive tissue distribution. The highest tissue exposures were observed in lung and liver and the lowest exposures were observed in skin and muscle, resulting in tissue to plasma ratios between 133 and 6.0.[13]

Cytochrome P450 (CYP) 3A4 was identified as the most important CYP enzyme involved in the metabolism of erdafitinib. Other minor routes involved in the microsomal metabolism of erdafitinib were CYP2C8 and CYP2D6.[14] Furthermore, erdafitinib shows weak inhibition potential towards CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A reflected in IC_{50} values >15 µM, suggesting a low drug-drug interaction potential.[13]

Large species differences in unbound fraction in plasma were observed. The free fraction in human samples ranged between 0.55% and 0.74%. In animals, the free fraction ranged between 2.2% (nude rat) to 13.7% (dog). In human blood, erdafitinib was mainly bound to plasma proteins (about

95%). Strong binding of ^{3}H-JNJ-42756493 to human purified alpha-1-acid glycoprotein was observed which was dependent on the protein concentration.[13]

In both rat and dog, less than 5% of the dose was excreted unchanged, indicating extensive metabolism in vivo. Fecal excretion of drug-related material was higher (88% and >75%, respectively) than urinary excretion (2.5% and ≤5.5%, respectively), implying hepatic clearance plays more dominate role than renal clearance.[15]

Toxicology

Toxicology studies were conducted in rats, dogs, and male mice. Cartilage dysplasia and soft tissue mineralization were observed as primary drug-related toxicities in all species. Erdafitinib showed no genotoxic properties in in- vitro genotoxicity screening assays. Soft tissue mineralizations were associated with a disturbance of vitamin D and phosphate homeostasis, characterized by elevated levels of 1,25-dihydroxyvitamin D_3, serum phosphate and, to a much lesser extent, calcium. Chondroid dysplasia and soft tissue mineralization were shown to be slowly and partially reversible, except for the aorta mineralization in dogs that did not show recovery after a 4-week washout period. Additionally mammary gland atrophy was noted in male rats in a 1-month repeated dose study. In the ongoing 3-month repeated dose studies in rats and dogs, at the end of treatment corneal atrophy was seen in rats and lacrimal gland atrophy in rats and dogs. Reversibility was not evaluated. Erdafitinib showed no genotoxic properties in in vitro genotoxicity screening assays. It was classified as a very severe eye irritant at a high concentration in the in-vitro bovine corneal opacity and permeability (BCOP) test. At clinically relevant concentrations it did not induce vascular irritation in the in vitro HET-CAM test. Erdafitinib was evaluated in mice as having a skin sensitizing potential. No phototoxicity was observed in a pigmented rat study.

Erdafitinib is an intrinsic hERG blocker with a proarrhythmia liability which translates into a prolonged repolarization (QTc) after i.v. dosing in the anesthetized dog and guinea pig, and after oral dosing in the conscious dog. A total plasma concentration of 770 ng/mL or unbound concentration of 81 ng/mL is considered to be the cardiovascular threshold for of this liability. In a modified Irwin's test in rats, erdafitinib showed minimal neurofunctional aberrations (impaired wire maneuvers and flaccid body tone) from a mean maximal plasma concentrations (C_{max}) of 12.1 ng/ml, considered an indirect effect of treatment.[13]

Holter monitoring was terminated in Parts 2 and 3 of Study 427856493EDI1001 after no clinically significant cardiovascular findings were noted in 37 consecutive subjects. In addition the concentration of free drug was never recorded above 1/20th of the threshold level for potential cardiac events.[13]

1.2. Clinical Experience

Study 42756493EDI1001 is a Phase 1, first-in-human, open-label, multicenter, 4-part, dose-escalation study to explore the safety, pharmacokinetics, pharmacodynamics, and clinical activity of erdafitinib in subjects 18 years of age or older with advanced or refractory solid malignancies or lymphoma who are not candidates for approved or available therapies. Part 1 is the Dose-

Escalation Phase based on safety and pharmacokinetics. Part 2 is the Dose-Confirmation Phase, consisting of pre- and post-treatment tumor biopsy cohorts to confirm the recommended Phase 2 dose based on the pharmacodynamic effect of erdafitinib on the FGFR signaling pathway in tumors. Part 3 is the first Dose-Expansion Phase, designed to evaluate inclusion biomarkers and preliminary clinical activity at the first recommended Phase 2 dose of 9.0 mg daily, and Part 4 is the second Dose-Expansion Phase, designed to evaluate clinical activity at the second recommended Phase 2 dose of 10 mg intermittent dosing schedule.

Study 42756493EDI1001 has evaluated erdafitinib in daily dosing cohorts from 0.5 mg to 12 mg, and 10 mg intermittent and 12 mg intermittent doses. As of 15 October 2014, 96 subjects have received treatment with erdafitinib in 8 cohorts: 0.5, 2.0, 4.0, 6.0, 9.0, and 12.0 mg daily, and 10.0 mg and 12.0 mg given on an intermittent schedule. One dose-limiting toxicity (DLT) was observed to date in a 40-year-old woman with breast cancer in the 12.0 mg daily dosing cohort. The event was a reversible and asymptomatic Grade 3 hepatic function abnormal/alanine aminotransferase (ALT) increase on Study Day 15 in Cycle 1. Based on the DLT, higher incidence of hyperphosphatemia requiring dose interruption, and overall tolerability, a decision to stop dose escalation beyond 12.0 mg was made and 12 mg was declared the maximum administered daily dose. A true maximum-tolerated dose (MTD) was not established in the Part 1 dose-escalation component. However, based on the safety, pharmacokinetic/ pharmacodynamics and preliminary clinical response data, 9 mg daily was selected as the first recommended Phase 2 dose. Additional doses such as a 6-mg continuous dose and 10-mg and 12-mg intermittent doses were considered possible Phase 2 doses for further evaluation.

1.2.1.1. Safety Experience

Safety data for 96 treated subjects was available at the October 2014 data cut-off. The median drug exposure for all 96 subjects was 2.0 cycles (range: 1 to 13 cycles) or 1.6 months. Across all dose cohorts, the median total number of cycles of treatment ranged from 2.0 to 4.0, and the median total duration of treatment ranged from 1.4 to 2.8 months, suggesting similar tolerability to the drug.

Of the 96 subjects treated with erdafitinib in Study 42756493EDI1001, 91 subjects (94.8%) experienced any treatment-emergent adverse event; 43 subjects (44.8%) experienced a Grade 3 or higher adverse event. Thirty-one subjects (32.3%) experienced a serious adverse event with 8 subjects (8.3%) experiencing a drug-related serious treatment-emergent adverse event. Six subjects (6.3%) discontinued treatment due to an adverse event. Seven subjects (7.3%) experienced adverse events leading to death (Table 6).

Table 6: Overall Summary of Treatment-Emergent Adverse Events: Study 42756493-EDI1001

	6.00 mg (QD)	9.00 mg (QD)	10.00 mg (7d on/7d off)	12.00 mg (QD)	12.00 mg (7d on/7d off)	Total (all doses 0.5-12 mg)
Population: safety	9	47	6	7	13	96
Any adverse event (AE)	9 (100.0%)	44 (93.6%)	5 (83.3%)	7 (100.0%)	13 (100.0%)	91 (94.8%)
Grade 3 or higher	3 (33.3%)	21 (44.7%)	4 (66.7%)	3 (42.9%)	7 (53.8%)	43 (44.8%)
Any drug-related[a] AE	9 (100.0%)	39 (83.0%)	5 (83.3%)	7 (100.0%)	13 (100.0%)	82 (85.4%)
Grade 3 or higher	1 (11.1%)	13 (27.7%)	0	3 (42.9%)	4 (30.8%)	21 (21.9%)
Any serious AE	2 (22.2%)	18 (38.3%)	2 (33.3%)	1 (14.3%)	4 (30.8%)	31 (32.3%)
Drug-related[a]	0	8 (17.0%)	0	0	0	8 (8.3%)
AE leading to treatment discontinuation	1 (11.1%)	3 (6.4%)	0	0	1 (7.7%)	6 (6.3%)
Hyperphosphatemia	7 (77.8%)	30 (63.8%)	4 (66.7%)	4 (57.1%)	10 (76.9%)	60 (62.5%)
Hyperphosphatemia leading to dose interruption	2 (22.2%)	23 (48.9%)	1 (16.7%)	4 (57.1%)	4 (30.8%)	34 (35.4%)
Hyperphosphatemia leading to dose reduction	0	6 (12.8%)	0	3 (42.9%)	0	9 (9.4%)
AE with outcome of death[b]	0	4 (8.5%)	0	0	1 (7.7%)	7 (7.3%)

a Adverse event reported as very likely, possibly or probably related to erdafitinib.
b Death within 30 days of last treatment dose are included.
Note: Adverse events reported any time from the first treatment dose to within 30 days of last treatment dose are included.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Percentages calculated with the number of subjects in safety population of each group as denominator.
Subject PPD was assigned to the liquid group since the subject took only 1 capsule dose then switched to liquid doses.
Sources: TSFAE01S; TSFAE02S; TSFAE42S, TSFAE04S

Treatment-emergent adverse events experienced by at least 10% of subjects in Study 42756493EDI1001 as of October 2014 are summarized in Table 7. The most commonly reported adverse events by preferred terms (>20% of subjects) were hyperphosphatemia (62.5%), dry mouth (44.8%), asthenia (42.7%), constipation (38.5%), stomatitis (33.3%), decreased appetite (29.2%), vomiting (28.1%), dysgeusia (26.0%), and diarrhea (20.8%).

Central serous retinopathy (CSR)/retinal pigment epithelial detachments (RPED) were observed in 3 subjects. One subject (9 mg daily dose) experienced Grade 2 CSR and Grade 1 retinal detachment. This subject had complete resolution of the Grade 2 CSR/Grade 1 RPED within 30 days, however upon study drug reintroduction at a lower dose had recurrent Grade 1 CSR/RPED, which resolved upon on re-interruption. Two other subjects, 1 treated at 12 mg, 7 days on/7 days off, and 1 treated at 9 mg daily, respectively, experienced Grade 1 CSR and Grade 2 retinal edema, which were considered probably related to study drug and resolved after drug interruption.

Prior experiences with CSR with kinase inhibitors, primarily MEK inhibitors have indicated that CSR/RPEDs are generally reversible. In the case of trametinib, a Food and Drug Administration (FDA)-approved MEK inhibitor, instances of CSR have generally resolved completely by withholding drug and required no additional treatment. Permanent ocular sequelae have also not been reported in patients that have experienced CSR due to MEK inhibitors.[18,19,33] Based on

emerging data more stringent eye examination and eye toxicity management guidelines have been instituted in this study.

Thirty-one subjects (32.3%) experienced serious adverse events. The most commonly reported serious adverse events (preferred terms) were general physical health deterioration, abdominal pain, intestinal obstruction, and hyponatremia, experienced by 3 subjects (3.1%) each. Forty-three subjects (44.8%) experienced a Grade 3 or higher adverse event; 21 subjects (21.9%) experienced Grade 3 or higher events considered drug-related (Table 7). These events included 5 events each of onycholysis and Palmar-plantar erythrodysesthesia syndrome; 4 events of fatigue; 3 events each of AST increased, onychalgia, and ALT elevation; 2 events each of onychomycosis and decreased appetite; and 1 event each of acute pancreatitis, stomatitis dyspnea, hyponatremia, atrophic rhinitis, asthenia, anemia, and paronychia.

Eighteen subjects (18.8%) experienced adverse events which led to dose reductions. Adverse events leading to treatment discontinuation were reported for 6 subjects (6.3%): 1 subject in each of the 0.5 mg and 6.0 mg daily dosing groups, 3 subjects in the 9.0 mg daily dosing group, and 1 subject in the 12 mg (7 days on/7 days off) dosing group. Only 1 subject in the 9 mg daily dosing group discontinued treatment due to an adverse event which was considered drug related (Palmar-plantar erythrodysesthesia syndrome).

Dose selection rationale is described in Section 3.1.2.

Table 7: Treatment Emergent Adverse Events in Study 42756493EDI1001 for Dose Levels ≥6 mg (Any Grade, ≥10% Subjects)

Dose	6 mg (QD)	9 mg (QD)	10.00 mg (7 d on/7 d off)	12.00 mg (QD)	12.00 mg (7 d on/7 d off)	Total (all doses 0.5-12 mg)
Total no. of subjects treated	9	47	6	7	13	96
Total no. subjects with adverse events	9 (100.0%)	44 (93.6%)	5 (83.3%)	7 (100.0%)	13 (100.0%)	91 (94.8%)
Hyperphosphataemia	7 (77.8%)	30 (63.8%)	4 (66.7%)	4 (57.1%)	10 (76.9%)	60 (62.5%)
Dry mouth	7 (77.8%)	19 (40.4%)	3 (50.0%)	6 (85.7%)	5 (38.5%)	43 (44.8%)
Asthenia	6 (66.7%)	11 (23.4%)	4 (66.7%)	7 (100.0%)	6 (46.2%)	41 (42.7%)
Constipation	3 (33.3%)	20 (42.6%)	0	4 (57.1%)	5 (38.5%)	37 (38.5%)
Stomatitis	3 (33.3%)	19 (40.4%)	2 (33.3%)	5 (71.4%)	2 (15.4%)	32 (33.3%)
Decreased appetite	2 (22.2%)	11 (23.4%)	3 (50.0%)	2 (28.6%)	7 (53.8%)	28 (29.2%)
Vomiting	4 (44.4%)	15 (31.9%)	1 (16.7%)	1 (14.3%)	3 (23.1%)	27 (28.1%)
Dysgeusia	1 (11.1%)	12 (25.5%)	3 (50.0%)	4 (57.1%)	4 (30.8%)	25 (26.0%)
Diarrhoea	3 (33.3%)	10 (21.3%)	1 (16.7%)	1 (14.3%)	2 (15.4%)	20 (20.8%)
Dry skin	1 (11.1%)	8 (17.0%)	0	6 (85.7%)	3 (23.1%)	19 (19.8%)
Nausea	3 (33.3%)	10 (21.3%)	0	1 (14.3%)	2 (15.4%)	19 (19.8%)
Alopecia	1 (11.1%)	8 (17.0%)	0	5 (71.4%)	2 (15.4%)	16 (16.7%)
Anaemia	1 (11.1%)	4 (8.5%)	3 (50.0%)	0	5 (38.5%)	16 (16.7%)
Abdominal pain	1 (11.1%)	7 (14.9%)	0	2 (28.6%)	0	14 (14.6%)
Dry eye	1 (11.1%)	8 (17.0%)	0	2 (28.6%)	3 (23.1%)	14 (14.6%)
Arthralgia	2 (22.2%)	8 (17.0%)	0	0	0	12 (12.5%)
Hepatic function abnormal	1 (11.1%)	2 (4.3%)	1 (16.7%)	1 (14.3%)	4 (30.8%)	12 (12.5%)
Fatigue	0	9 (19.1%)	0	0	1 (7.7%)	11 (11.5%)
Hypomagnesaemia	3 (33.3%)	4 (8.5%)	1 (16.7%)	1 (14.3%)	1 (7.7%)	11 (11.5%)
Abdominal pain upper	2 (22.2%)	4 (8.5%)	1 (16.7%)	0	2 (15.4%)	10 (10.4%)
Dyspnoea	0	5 (10.6%)	0	1 (14.3%)	4 (30.8%)	10 (10.4%)
Pyrexia	2 (22.2%)	6 (12.8%)	0	1 (14.3%)	0	10 (10.4%)
Urinary tract infection	2 (22.2%)	3 (6.4%)	2 (33.3%)	1 (14.3%)	0	10 (10.4%)

AE=adverse event; QD=once daily
Note: Adverse events reported any time from the treatment dose to within 30 days of last treatment dose are included.
Note: Incidence is based on the number of subjects, not the number of events.
Note: Percentages calculated with the number of subjects in safety population of each group as denominator.
Note: Recurring events are counted only once for each subject.
Subjetc PPD was assigned to liquid group since the subject took only one capsule dose then switched to liquid doses.
Source: [TSFAE02ES.rtf] [JNJ-42756493\EDI1001\DBR_FDA_BB_2014\RE_FDA_BB_2014\TSFAE02es.sas] 15OCT2014, 15:28

The overall safety profile for Study 42756493EDI1001 at the time of the final report was essentially identical to the safety reported for the primary analysis. There were no new safety signals observed after the cut-off date for the primary CSR. The most commonly reported AEs, after hyperphosphatemia (65%), were dry mouth (46%), asthenia (45%), stomatitis (39%), constipation (37%), decreased appetite (34%), and diarrhea (30%). One hundred sixteen subjects (62%) experienced a Grade 3 or higher AE. Twenty-three subjects (12%) discontinued treatment due to an AE.

Erdafitinib for the treatment of patients with metastatic urothelial carcinoma that harbor select FGFR alterations received accelerated approval in the United States based on the primary analysis of Study BLC2001. At the time of the primary analysis (clinical cutoff of 15 March 2018), 210 subjects had been treated: 33 subjects in the 10 mg intermittent dosing regimen, 78 subjects in the 6 mg daily regimen, and 99 subjects in the 8 mg daily regimen (selected dose regimen). The most frequently reported adverse events in the 8 mg once daily regimen, most of which were Grade

1 or 2 in severity, were hyperphosphatemia (77%), stomatitis (58%), diarrhea (51%), and dry mouth (46%). Twenty-one subjects (21%) discontinued treatment due to adverse events. The most common reason for discontinuation was general physical health deterioration. The frequency of reported adverse events and discontinuations across all dose regimens combined was similar to that seen in the 8 mg once daily regimen.

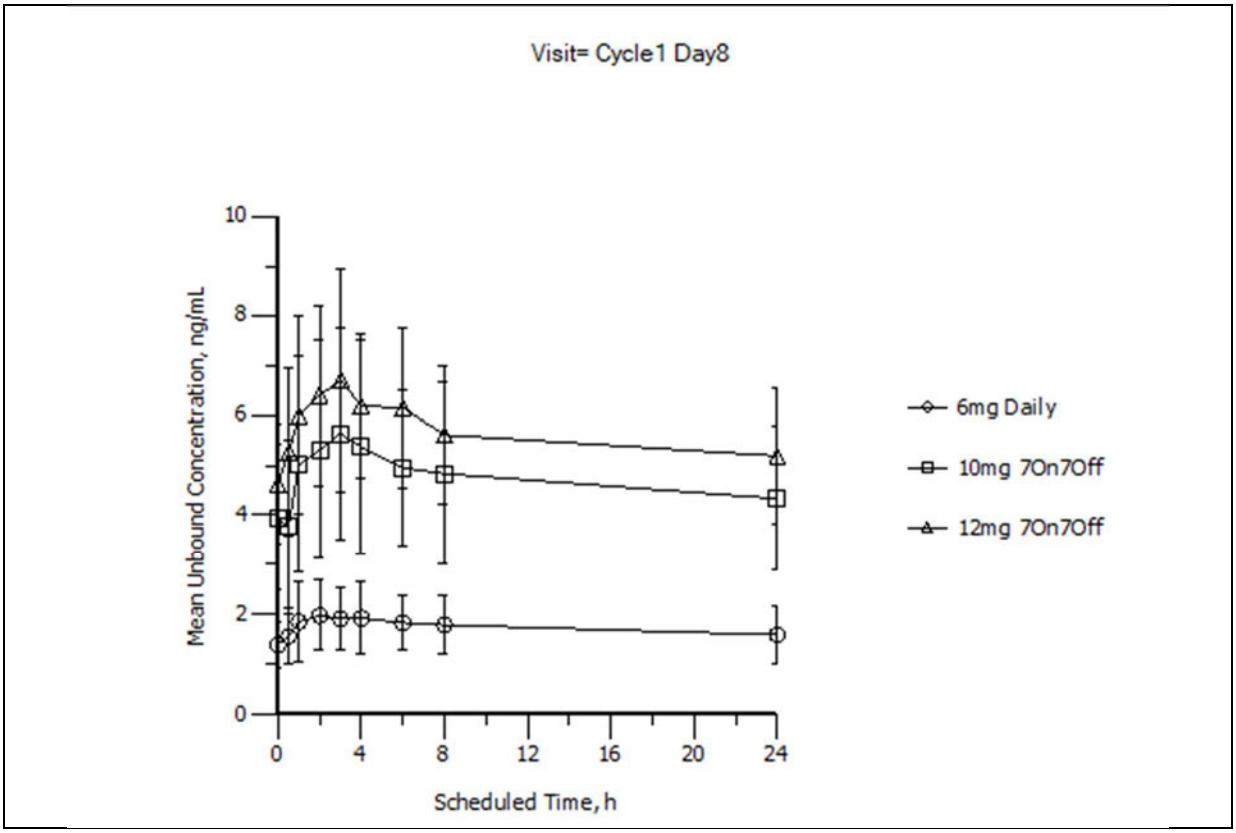
An updated analysis has also been completed for Study BLC2001 (clinical cutoff of 09 August 2019). The median follow-up for 101 subjects treated in the erdafitinib 8 mg regimen was approximately 24 months. The erdafitinib safety profile was consistent with the primary analysis. No new treatment-emergent adverse events were seen with longer follow-up. Central serious retinopathy events occurred in 27% (27/101) of subjects; 85% (23/27) were Grade 1 or 2. Dosage was reduced in 13 subjects with CSR, interrupted in 8 subjects, and discontinued for 3 subjects. On the data cutoff date, 63% (17/27) CSR events had resolved; 6 of 10 of the ongoing CSR events were Grade 1. There were no treatment-related deaths.

Also, please refer to the current Erdafitinib Investigator's Brochure for recent safety information.

1.2.1.2. Clinical Pharmacokinetics

Erdafitinib plasma pharmacokinetics has been assessed in Study 42756493EDI1001 with oral doses ranging from 0.5 mg to 12 mg. Erdafitinib is highly and tightly bound to alpha-1-acid glycoprotein (orosomucoid) leading to low and variable free-drug fraction in cancer-patient circulation (mean: 0.0035; range: 0.0012 to 0.0083). Unbound drug is detailed here as this is the relevant pharmacologically active moiety. Erdafitinib absorption is fast following oral intake of oral solution or immediate-release capsule formulation. Maximal plasma concentrations (C_{max}) and area under the serum concentration versus time curve (AUC) values increased approximately linearly with increasing doses across the dose range tested, after both single- and multiple-dosing (Select doses are shown in Figure 1 and CCI). There is no indication of time-dependent pharmacokinetics on multiple dosing of erdafitinib.

Figure 1: Mean (SD) Unbound JNJ-42756493 Plasma Concentration-time Profiles Following Oral Administrations of Drug at Indicated Doses (Study JNJ-42756493-EDI1001)



The apparent terminal half-life of erdafitinib is variable and ranges from 50 to 60 hours and possibly up to 3 days. Oral clearance (based on total plasma drug concentrations) of the drug is low in the range of 0.3 (L/h) and central volume of distribution (based on total drug concentrations) is also low at approximately 20 (L).

Based on a population-based approach, analysis of current clinical exposure data demonstrates 2 significant co-variates in the determination of pharmacokinetic parameters. Erdafitinib is highly protein bound including plasma alpha-1-acid glycoprotein. Alpha-1-acid glycoprotein plasma levels and bodyweight have influence on the pharmacokinetics of erdafitinib.

CCI

With a median drug exposure at the October 2014 data cut-off for the total population of 1.6 months (2.0 cycles), there does not appear to be substantial differences in mean or median drug exposure in dose cohorts comparing higher doses with lower doses considering the number of subjects who are continuing treatment, suggestive of tolerability to the drug.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

2.1.1. Primary

The primary objective of the study is:

- To evaluate the objective response rate (complete response [CR]+ partial response [PR]) of the selected dose regimen in subjects with metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations.

2.1.2. Secondary

The secondary objectives of the study are:

- To evaluate the objective response rate of the selected dose regimen in chemo-refractory subjects
- To evaluate the progression-free survival (PFS), duration of response, and overall survival of the selected dose regimen in all and in chemo-refractory subjects
- To evaluate the response rate in biomarker-specific subgroups (translocations versus mutations) with the selected dose regimen
- To evaluate the objective response rate, PFS, duration of response, and overall survival of the other dose regimens tested
- To evaluate the safety and pharmacokinetics of erdafitinib of all dose regimens

CCI

[redacted]

2.2. Hypotheses

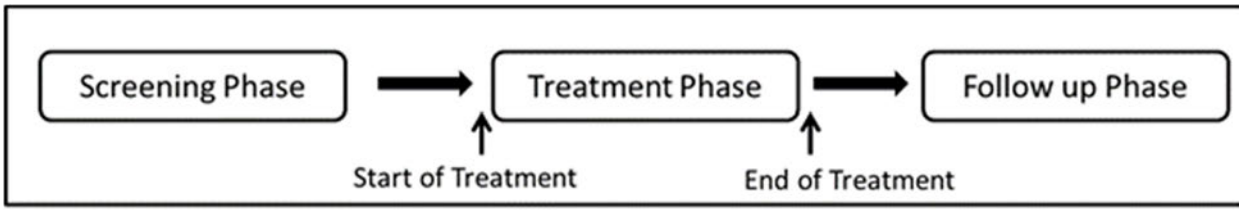
The primary hypothesis is that the selected dose regimen of erdafitinib has an overall response rate (ORR) >25% in subjects with metastatic or surgically unresectable urothelial cancer harboring select FGFR alterations.

2.3. Overview of Study Design

This is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of single-agent erdafitinib in subjects with metastatic or surgically unresectable urothelial cancer harboring select FGFR genetic alterations.

The study comprises a Screening Phase (both molecular screening and full-study screening), a Treatment Phase, and a post-treatment Follow-up Phase (Figure 2). Molecular screening will occur any time prior to the first dose; the full-study Screening Phase will be up to 30 days prior to the first dose. The Treatment Phase will extend from the administration of the first dose until the End-of-Treatment Visit. The post-treatment Follow-up Phase will extend from the End-of-Treatment Visit until the subject has died, withdraws consent, is lost to follow-up, or the end of study, whichever comes first. The end of study is defined as the date when all subjects have completed the study treatment (Regimens 1 to 3) and all subjects enrolled under the drug-drug interaction (DDI) substudy are no longer receiving treatment with erdafitinib.

Figure 2: Study Phases

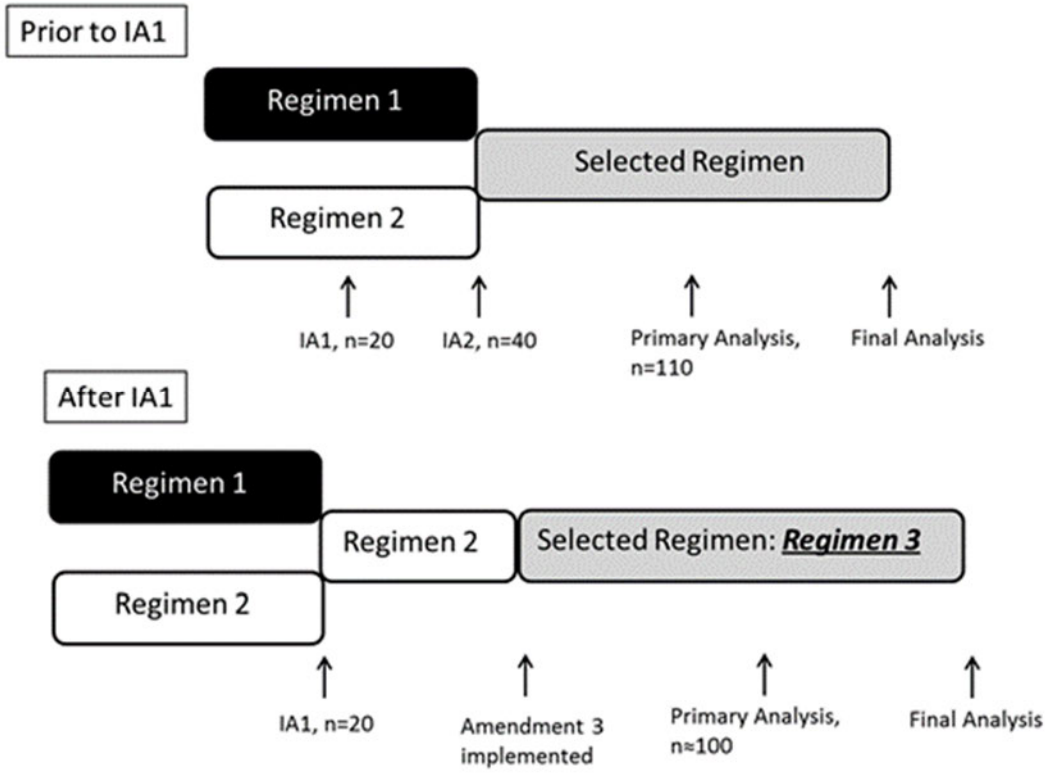


Study treatment will be administered on a 28-day cycle. Prior to IA1, there were 2 treatment regimens: Regimen 1 (10 mg once daily, 7 days on/7 days off); Regimen 2 (6 mg once daily for 28 days). Following IA1 and implementation of Amendment 3, Regimen 3 (8 mg once daily for 28 days) will be instituted. It is expected that approximately 180 subjects with specified FGFR genetic alterations will be enrolled in the study, of which about 30 subjects will be treated with Regimen 1, about 50 subjects will be treated with Regimen 2, and approximately 100 subjects will be treated with Regimen 3. When approximately 88 subjects have been treated in Regimen 3, if less than 80 subjects are chemo-refractory, then enrollment of chemo-naïve subjects in Regimen 3 will be stopped but enrollment of chemo-refractory subjects will continue until at least 80 chemo-refractory subjects are treated in Regimen 3 or a total of approximately 100 subjects are treated with Regimen 3.

Dose up-titration and dose reductions for each treatment group are described in Sections 6.2 and 6.3, respectively. Prior to IA1, randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0-1 versus 2), hemoglobin value (<10 g/dL versus ≥10 g/dL), FGFR alteration type (translocation versus mutation), pretreatment status (chemo-refractory versus chemo-naive), and disease distribution (presence or absence of visceral metastases: lung, liver, and bone). Covariate-adaptive randomization method was used to allocate subjects into treatment regimens. Randomization continued until a preferred dose regimen was selected on the basis of activity and tolerability.

A diagram of the study design is provided below in Figure 3.

Figure 3: Study Design



The study will be conducted in an outpatient setting. Subjects will be seen at the study center on the pre-specified days for safety monitoring, pharmacokinetic sample collection, and provision of clinical supplies. More frequent study center visits may be scheduled, if deemed necessary, on the basis of emerging safety observations. Subjects will be issued diary cards to record study drug dosing time and meal time.

Subjects will be assessed for disease response every 6 weeks during the first 3 months. Thereafter, scans will be performed every 12 weeks for the next 9 months, then every 4 to 6 months until disease progression.

All subjects are to have a Follow-up Visit (telephonic or in person) every 12 weeks (±7 days) for survival status update and start of subsequent anticancer therapy in the Follow-up Phase. The post-treatment Follow-up Phase will extend from the End-of-Treatment Visit until the subject has died, withdraws consent, is lost to follow-up, or the end of study, whichever comes first. Additional information may be gathered in the Follow-up Phase in the following 2 situations:

- If a subject discontinues study drug due to drug-related toxicity which has not resolved by the End-of-Treatment Visit, the subject will continue to be monitored for this toxicity as clinically appropriate until the toxicity resolves to baseline, stabilizes, or is deemed irreversible; the subject dies; or subsequent therapy is started; whichever occurs first.
- If a subject discontinues study drug before disease progression, tumor assessments should be continued as usual, as if the subject is still on study treatment until disease progression is documented, subsequent therapy is started, the subject dies, or the end of study, whichever occurs first.

The entire duration of the main study will be approximately 60 months to completion (first subject's first visit to end of study), while the duration of the DDI substudy will be approximately 16 months.

Safety will be monitored by the sponsor's medical monitor or study responsible physician throughout the study. In addition, the sponsor's Safety Management Team (SMT), a multi-disciplinary team including an internal safety physician will review the safety data routinely and will investigate specific safety queries. The SMT will review all serious adverse events. In the event a significant safety issue is identified, both the internal safety team and the responsible investigators will convene to discuss the safety data and to make a recommendation on the future conduct of the study. All decisions will be documented and will be distributed to investigators. The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) will be notified if required.

Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 11.

3. STUDY DESIGN AND RATIONALE

For subjects enrolled under the DDI substudy (with continued erdafitinib treatment until disease progression), follow Attachment 12; DO NOT USE the eligibility criteria or the Time and Events Schedules in the main protocol.

3.1. Overall Rationale for the Study

3.1.1. Rationale for the Study in the Target Indication

Urothelial carcinoma of the bladder is a common malignancy causing approximately 165,000 deaths per year worldwide.[12] The median survival for patients with recurrent or metastatic urothelial carcinoma is only 14 to 15 months.[24] Treatments for muscle-invasive urothelial carcinoma have not improved beyond cisplatin-based combination chemotherapy and surgery in the past 30 years, and no new drugs making a significant impact on the disease have been approved in that time. In fact, there is no approved standard of care therapy for surgically unresectable or metastatic patients who have disease recurrence after treatment with a platinum-containing therapy (in the US). Objective response rates ranging from 10% to 20% have been observed with single-agent and combination therapies in patients who have progressed following platinum-based chemotherapy regimens.[6,16,17,28,32]

Vinflunine is approved only in Europe for treatment of metastatic urothelial cancer in the second line setting, based upon results of a Phase 3 study in which subjects were randomized to either vinflunine plus best supportive care or best supportive care alone, and demonstrated a 9% objective response rate and increase in median overall survival (6.9 versus 4.3 months) in the vinflunine arm.[2,4] Vinflunine has not been evaluated for efficacy and safety in patients with a performance status of ≥2.[23]

Moreover, a significant proportion of patients have poor performance status and compromised renal function and need targeted therapies with relatively benign safety profiles.[20] Due to age, disease-associated impairment in renal function, as well as comorbidities and specific treatment related toxicities, approximately 30 to 50% of patients are ineligible for treatment with cisplatin.[9]

For patients unfit to receive cisplatin-containing chemotherapy in the first line, 2 carboplatin-based regimens (gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine) demonstrated objective response rates as low as 26% and 20% in patients with a glomerular filtration rate less than 60 and a performance status of 2.[7]

Thus far, no molecularly targeted agents have been approved for the treatment of the disease. However, recent advances in genomic profiling of urothelial carcinomas have identified potential therapeutic molecular targets in 69% of the tumors. The genomic alterations identified involve the PI(3)K/AKT/mTOR, CDKN2A/CDK4/CCND1 and RTK/RAS pathways, including ERBB2, ERBB3, and FGFR3, most of which are potentially targetable.[5]

Of the molecular alterations identified, FGFR signaling in particular is altered in a high proportion of bladder tumors in both muscle invasive and non-invasive tumors. The FGFR pathway is thought to play an important role in promoting cancer. Multiple alterations have been identified in this

pathway including FGFR gene translocations, activating mutations, gene amplifications, and overexpression of FGFRs or their ligands. Mutations in FGFR3 are found in 12% of all patients with high-grade muscle-invasive urothelial bladder carcinomas.[5] Translocations of FGFR reported in urothelial carcinoma have been demonstrated to play a key role in transforming normal cells.[31] Our internal data and external data have indicated the presence of multiple FGFR translocations in bladder cancer such as, FGFR2-BICC1, FGFR2-AFF3, FGFR2-CASP7, FGFR2-CCDC6, FGFR2-OFD1, FGFR3-TACC3, and FGFR3-BAIAP2L1. Based on a small sample size, approximately 50% of urothelial carcinomas could potentially harbor these translocations. However, the clinical sensitivity of all these alterations to an FGFR inhibitor is not yet fully known. Pre-clinical studies have demonstrated that urothelial carcinoma cell lines RT-4 and RT-112 carrying the FGFR3-TACC3 translocation are sensitive to erdafitinib, with IC_{50} values of 0.1 and 0.01 nM, respectively. The ability of each translocation to respond to erdafitinib is currently being investigated.

The ongoing Phase 1 study of erdafitinib has demonstrated anti-tumor activity in subjects with urothelial carcinoma. Of the 12 subjects with urothelial carcinoma who were treated at doses ≥9 mg, 4 had confirmed or unconfirmed partial response (PR), 6 had stable disease (SD), 1 had progressive disease (PD), and the results for 1 subject were not applicable (Table 9). All the responses occurred in subjects with FGFR aberrations and included subjects with FGFR3-TACC3, FGFR2-BICC1 translocations or FGFR3 mutations such as S249C, R248C and G370C. Another FGFR inhibitor, BGJ 398, has been reported to produced responses in patients with urothelial carcinoma with FGFR3 mutations; a response rate of 40% was observed in the 5 FGFR3-mutant patients treated.[26] All of these factors emphasize the importance of targeting the FGFR pathway in urothelial carcinomas with a potent pan FGFR inhibitor such as erdafitinib. Therefore, a clinical study to test the efficacy of erdafitinib in urothelial carcinomas is merited

Table 9: Clinical Activity of JNJ-42756493 in Subjects with Urothelial Cancer (±FGFR Abnormality) Treated at 6 mg or Higher Dose (Study 42756493EDI1001)

Dose	Molecular Status	Activity
9 mg daily	FGFR3-TACC3	PR (-39%)
9 mg daily	FGFR2-BICC1/FGFR2-CASP7	PR (-79%)
9 mg daily	FGFR3 mut	SD (-19%)
9 mg daily	FGFR3 mut (R248C)	SD (-21%)
9 mg daily	FGFR3 mut (G370C)/FGF3,4,19 amp	PR (-45%)
9 mg daily	FGFR3 mut (S249C)	PR (-73%)
9 mg daily	FGFR3 (S249C)	NA
9 mg daily	FRS2 amp/MDM2 amp	SD (-25%)
10 mg, 7 days on 7 days off	FGFR3:BIAP2L1/ FGFR2:BICC1/ FGFR2:CASP7/ FGFR2:OFD1	SD (+7)
10 mg, 7 days on 7 days off	Unknown	PD
12 mg, 7 days on 7 days off	FGFR3-TACC3/FGFR3 amp	SD (-10%)
12 mg daily	No FGFR alteration	SD (FDG-PET complete response)

Abbreviations: PD=progressive disease; PR=partial response; NA=not applicable; SD=stable disease
Total (n=12): PR 4, SD 6, PD 1, NA 1; FGFR+ (n= 9): PR 4, SD 5

Study 42756493BLC2001 was designed to confirm the significance of selecting FGFR fusions and activating mutations as predictive markers when treated with erdafitinib in the metastatic urothelial carcinoma population. This study prospectively screens and evaluates the significance of these FGFR aberrations when subjects are treated with erdafitinib. Erdafitinib for the treatment of this population received accelerated approval in the United States based on the primary analysis. At the primary analysis (clinical cutoff of 15 March 2018), 210 subjects had been treated: 33 subjects in the 10 mg intermittent dosing regimen, 78 subjects in the 6 mg daily regimen, and 99 subjects in the 8 mg daily regimen (selected dose regimen). Of the 99 subjects in the primary efficacy population in the 8 mg regimen, 87 (90%) subjects were chemo-refractory and 12 (10%) subjects were chemo-naïve. Confirmed ORR based on investigator assessment (CR+PR), was 40.4% in the 8 mg once daily regimen. CCI [redacted]

An updated analysis has also been completed for Study BLC2001 (clinical cutoff of 09 August 2019), the median follow-up for 101 subjects treated in the erdafitinib 8 mg regimen was approximately 24 months. The confirmed ORR by investigator assessment was 40%. The median duration of response (DOR) was 5.98 months. Thirty-one percent of responders had DOR of 1 year or more. The median PFS was 5.52 months. The median OS was 11.3 months. The 12- and 24-month survival rates were 49% and 31%, respectively. Median treatment duration was 5.4 months.

The rationale for the treatment of subjects with advanced solid tumors in the DDI substudy is provided in DDI Substudy Section 1.2.

3.1.2. Rationale for Phase 2 Dose Selection

In the proposed erdafitinib Phase 2 study, the sponsor will explore 3 different active dosing regimens, in 28-day cycles.

1. Sustained Inhibition Regimen: 6 mg once daily continuously for 28 days
2. Intermittent High-Dose Regimen: 10 mg once daily 7 days on 7 days off
3. Sustained Inhibition Regimen: 8 mg once daily continuously for 28 days

The first 2 dose regimens were selected to test whether high exposure levels with intermittent dosing could maximize antitumor effects while minimizing drug-related toxicities as compared with moderate exposures sustained over a longer period. A randomized comparison of the safety and clinical activity of these regimens allowed for the selection of an optimal regimen for an expansion cohort of patients. After IA1, a third regimen is instituted to evaluate 8 mg once daily continuous dosing.

Recent data with targeted therapies indicate that intermittent dosing may enhance efficacy, delay the emergence of resistance, and improve safety profiles.[10,16,26,27] The dose and schedules of these 3 different regimens are supported (as described below) by emerging pharmacokinetic, pharmacodynamic, safety, and clinical activity data.

Choice of the Sustained Dosing Regimen: 6 mg Daily with Flexibility to Up-titrate to 8 mg Daily

Pharmacokinetics: The 6 mg daily regimen is the lowest dose that achieves sustained exposures in the efficacious range, CCI [redacted]. At the 6 mg dose, based on pharmacokinetic simulations, the expected mean unbound C_{avg} plasma concentrations in patients during the 28 day cycle period is CCI [redacted]. The mean unbound average plasma concentration of urothelial cancer patients with clinical activity (partial responses) in the Phase 1 study was CCI [redacted], which is also consistent with the preclinical target window. Antitumor activity is anticipated to correlate with preclinical AUC for unbound drug (AUC_u), and at the 6 mg dose level, 90% of patients will have unbound trough plasma concentrations and AUC_u levels within the target window by day 2. At doses lower than 6 mg daily, trough plasma concentrations will fall below the effective range in approximately 50% or more of patients. Thus, 6 mg daily is the lowest sustained dose that is predicted to generate continuously efficacious drug concentrations for the majority of patients.

Pharmacodynamics: Hyperphosphatemia is a common drug-induced toxicity due to renal tubular FGFR inhibition and, thus, it can serve as a pharmacodynamic marker of drug activity. Dose-dependent elevations in serum phosphate occurred in all patients starting at 4 mg daily. Because this represents a target-mediated drug effect, one of the Phase 1 study goals was to select a dose regimen that consistently induced manageable hyperphosphatemia but did not exceed a critical level requiring cessation of therapy, which in the Phase 1 study was 7 mg/dL. Emerging data from the ongoing Phase 1 study indicates that a phosphate increase of at least 35% over baseline level may be required for anti-tumor response. Therefore a pharmacodynamic objective of 50% increase in phosphate level over baseline was felt to be appropriate. Considering the median phosphate level of 3.6 mg/dL in the Phase 1 study, a 50% increase would correspond to an absolute phosphate level of 5.5 mg/dL (which is also 35% over the phosphate ULN). Subjects achieving a phosphate level of less than 5.5mg/dL by the end of first cycle dosing period (day 28) would be considered to have had inadequate PD effect and be subject to dose escalation to 8 mg daily to achieve an optimum PD effect (phosphate range 5.5-7mg/dL).

Overall, 6 mg is the lowest sustained dose that achieves, in 77.8% of subjects in the Phase 1 study, hyperphosphatemia consistent with a biologically significant inhibition of FGFR. Emerging pharmacokinetic/pharmacodynamic modeling suggests that 40% of subjects would have serum phosphate levels < 5.5 mg/dL (on Day 28) and would potentially benefit from dose up-titration. Additionally, approximately 25% may reach a phosphate level >7 mg /dL and thus need an unscheduled interruption of up to 7 days to maintain the phosphate level in the target range of 5.5 to 7 mg/dL. A 3-weeks on/1-week off regimen may be suitable at the 6 mg starting dose, but such scheduled dose interruption might well be unnecessary when the dose is reduced to below 6 mg daily. The latter was observed in Phase 1 at the 4 mg dose level, and further confirmed in modeling. Thus, continuous dosing is attainable for the proposed 6 mg, 5 mg, and 4 mg dose levels.

Clinical safety: The 6 mg daily dose is the highest continuous regimen that was well tolerated without treatment interruptions. In the Phase 1 study at this dose level, there were no dose reductions and only one subject (11%) was removed from the study due to a non-drug-related AE

of abdominal pain. However, 44.4% of subjects treated with 6 mg daily continuously required treatment interruptions, generally after several weeks of dosing. Escalation of dose from 6 mg to 8 mg in 40% of subjects with suboptimal pharmacodynamic effect, ie, phosphate below 5.5 mg/dL at the end of the first treatment cycle and who do not have any significant drug related toxicity (Grade ≥2 toxicity or Grade ≥1 central serious retinopathy or retinal pigment epithelial detachments) is unlikely to significantly change the overall tolerability profile.

Clinical activity: Assessment of clinical activity at the 6 mg dose has been limited by the paucity of treated subjects with tumors bearing FGFR aberrations. To date, the only subject treated at this dose with a known FGFR aberration had an adrenal cortical carcinoma that harbored both CCI [redacted]. This patient achieved stable disease for 9 months on erdafitinib. Clinical activity has been noted at 9 mg daily, but 70% of the subjects treated at this dose needed unscheduled treatment interruptions. Selective dose escalation to 8 mg for optimization of the pharmacodynamic effect in approximately 40% of subjects is likely to increase the potential for clinical activity without significantly increasing dose interruptions or toxicity. In addition, the mean dose intensity of this continuous 6 mg regimen (with flexibility to up-titrate) is likely to be closer to the 6.8 (± 2.37) mg/day as observed with the 9 mg daily schedule in Phase 1 as compared to the observed 5.4 (± 0.63) mg/day reported with the 6 mg daily schedule in Phase 1, thereby increasing the potential for clinical activity.

Choice of the Intermittent Dosing Regimen: 10 mg on a 7 Days-on/7 Days-off Schedule with Flexibility to Up-titrate to 12 mg 7 days-on/7 days-off

Pharmacokinetics: An intermittent regimen of 10 mg is expected to generate a mean unbound C_{avg} plasma concentration of CCI [redacted] during the 28-day cycle period. This is in the upper range of exposures associated with preclinical efficacy and similar to geometric mean observed in clinical urothelial partial responders. In simulation studies, 100% of patients after Day 1 will have unbound trough plasma concentrations and AUC_u values within the target window. Doses lower than 10 mg intermittently are associated with plasma concentrations below the minimum thresholds needed to inhibit FGFR in preclinical models in approximately 35% or more of patients. Therefore, 10 mg is the lowest intermittent dose given for a 1 week on/1 week off schedule that generates drug exposures continuously in the efficacious range for most patients.

Pharmacodynamics: Nearly 70% of patients on the 10 mg intermittent regimen developed hyperphosphatemia consistent with FGFR target engagement. This was the lowest intermittent dose that achieved serum phosphate levels that rapidly approached but did not consistently exceed the critical threshold of 7 mg/dL. Only 16% of the subjects required treatment interruptions due to hyperphosphatemia and none needed dose reductions. However, based on emerging pharmacokinetic/pharmacodynamic modeling, 35% of subjects are likely to have a phosphate level <5.5mg/dL at the end of the Cycle 1 dosing period (Day 21), indicating the need to optimize the dose by up-titrating the dose to 12 mg in these selected subjects.

Clinical safety: The 10 mg dose is the highest intermittent regimen with acceptable tolerability proposed for further evaluation in Phase 2 and 3 studies. At the 10 mg dose, drug-related interruptions occurred in 33.3% of subjects; however, only 16.7% required dose reduction and

none (0%) were terminated from the study. In contrast, the 12 mg intermittent regimen was less well tolerated, with 46.2% of patients requiring treatment interruptions, 15.4% requiring dose reductions, and 7.7% requiring complete discontinuation due to drug-related AEs.

Additional toxicities were also more common on the 12 mg intermittent schedule as compared with the 10 mg dose. In the 12 mg and 10 mg intermittent dose cohorts, eye toxicities occurred in 38.5% (one case of Grade 1 central serous retinopathy) and 16.7%, respectively, liver function abnormalities were noted in 38% and 16.7%, respectively, nail disorders/ onychodystrophy/onycholysis were present in 30.8% and 16.7%, respectively, and alopecia was reported in 15.4% and 0% of subjects, respectively. However, escalation of dose from 10 mg to 12 mg in approximately 35% of subjects with suboptimal pharmacodynamic effect and who do not have any significant drug related (≥Grade 2 toxicity or ≥Grade 1 CSR/RPED) toxicity is unlikely to significantly change the overall tolerability profile. This approach is safer than starting at 12 mg in all subjects and de-escalating to 10 mg based on toxicity. Thus, the 7 days on/7 days-off schedule at 10 mg (with the flexibility to up-titrate) is a regimen with acceptable clinical tolerability.

Clinical activity: It is clear that an intermittent regimen can be active. At 12 mg on the intermittent schedule, a subject with glioblastoma harboring an CCI achieved a PR (-58% tumor reduction) by RANO criteria, and a second subject with a uterine neuroendocrine tumor (FGFR status unknown) demonstrated a PR (-70% tumor reduction). Clinical activity evaluation in patients treated with the 10 mg intermittent regimen is ongoing; however, early but as yet unconfirmed assessments suggest that this regimen will also be clinically active. Further optimization of the dose with up-titration to 12 mg in approximately 35% of subjects with suboptimal pharmacodynamic effect is likely to increase the potential for clinical activity.

Selected dose regimen: Choice of the Sustained Dosing Regimen: 8 mg Daily with Flexibility to Up-titrate to 9 mg Daily

Pharmacokinetics: At the 8 mg dose, based on pharmacokinetic simulations, the expected mean unbound C_{avg} plasma concentrations in patients during the 28 day cycle period is CCI. The mean unbound average plasma concentration of urothelial cancer patients with clinical activity (partial responses) in the Phase 1 study was CCI, which is also consistent with the preclinical target window. Antitumor activity is anticipated to correlate with preclinical AUC for unbound drug (AUC_u), and at the 8 mg dose level, 90% of patients will have unbound trough plasma concentrations and AUC_u levels within the target window CCI by Day 3. Thus, 8 mg daily is predicted to generate continuously efficacious drug concentrations for the vast majority of patients.

Pharmacodynamics: Hyperphosphatemia is a common drug-induced toxicity due to renal tubular FGFR inhibition and, thus, it can serve as a pharmacodynamic marker of drug activity. Dose-dependent elevations in serum phosphate occurred in all patients starting at 4 mg daily. Because this represents a target-mediated drug effect, one of the Phase 1 study goals was to select a dose regimen that consistently induced manageable hyperphosphatemia but did not exceed a critical level requiring cessation of therapy, which in the Phase 1 study was 7 mg/dL. Emerging

data from the ongoing Phase 1 study indicates that a phosphate increase of at least 35% over baseline level may be associated with anti-tumor response. Therefore a pharmacodynamic objective of 50% increase in phosphate level over baseline was felt to be appropriate. Considering the median phosphate level of 3.6 mg/dL at baseline in the Phase 1 study, and of 3.3 mg/dL at baseline in the Phase 2 study (IA1 data) an increase of at least 50% for the majority of subjects would correspond to an absolute phosphate level of around 5.5 g/dL (which is also 35% over the phosphate ULN). Subjects achieving a phosphate level of less than 5.5mg/dL by the end of first cycle dosing period (day 28) would be considered to have had inadequate PD effect and would be candidates for dose escalation to 9 mg daily to achieve an optimum PD effect (phosphate range 5.5-7mg/dL).

Overall, emerging pharmacokinetic/pharmacodynamic (PK/PD) modeling suggests that approximately 60% of subjects would have serum phosphate levels < 5.5 mg/dL (on Day 28) when dosed with 6 mg and would potentially benefit from dose up-titration. Additionally, by Day 28 approximately 13% of subjects may reach a phosphate level ≥7 mg /dL and thus need an unscheduled interruption of up to 7 days to maintain the phosphate level in the target range of 5.5 to <7 mg/dL.

Clinical safety: The 8 mg daily dose is the continuous regimen that, based on modelling, would likely be well tolerated without significant treatment interruptions (approximately 10% to 15% anticipated early interruptions) and for which the majority of subjects would tolerate the sustained dose of 8 mg once daily. Escalation on Day 15 of the first treatment cycle of daily dose from 8 mg QD to 9 mg QD in the subjects with both phosphate below 5.5 mg/dL (suboptimal pharmacodynamic effect; about 40% of subjects), and without significant drug related toxicity (Grade ≥2 toxicity or Grade ≥1 central serious retinopathy or retinal pigment epithelial detachments) is unlikely to significantly change the overall tolerability profile.

Clinical activity: Assessment of clinical activity at the 6 mg dose and in up-titrated subjects at IA1 is limited by the paucity of treated subjects, but 3 PR were observed in 14 subjects with phosphate level below 5.5 mg/dL and 4 PR in 7 subjects with phosphate level over 5.5 mg/dL, pointing to the potential importance of attaining full pharmacodynamic effect. Hence the aim is to bring a maximal number of subjects within the target phosphate range of 5.5 mg/dL to less than 7 mg/dL in order to attain maximal sustained inhibition of target, and thereby allow for potential optimization of efficacy, given the observed correlation thus far between clinical response and the pharmacodynamic effect on phosphate. Selective dose escalation to 9 mg for optimization of the pharmacodynamic effect in approximately 40% of subjects is likely to increase the potential for clinical activity without significantly increasing dose interruptions or toxicity. In addition, the mean dose intensity of the continuous 8 mg regimen (with flexibility to up-titrate) based on PK/PD model based simulations is likely to be 6.7 mg /day, which would be close to the 6.8 (±2.37) mg/day as observed with the 9 mg daily schedule in Phase 1 as compared to the observed 5.4 (± 0.63) mg/day reported with the 6 mg daily schedule in Phase 1, thereby increasing the potential for clinical activity.

4. SUBJECT POPULATION (For DDI Substudy – see Attachment 12)

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

Potential subjects must meet all of the inclusion criteria to be eligible to participate in the study:

1. Must be 18 years of age or older

2. Must have histologic demonstration of metastatic or surgically unresectable urothelial cancer CCI Minor components (<50% overall) of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable.

3. Must have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at baseline.

4. Must have shown disease progression according to RECIST, version 1.1, following prior chemotherapy for metastatic or surgically unresectable urothelial cancer. Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease recurrence or progression according to RECIST, version 1.1, within 12 months of the last dose are considered to have received chemotherapy in the metastatic setting. These subjects will be referred to as chemo-refractory subjects. (Subjects who have shown disease progression according to RECIST, version 1.1 following prior treatment with anti-PDL1/PD1 antibodies are also eligible).

   OR

   Subjects who have not yet received chemotherapy for metastatic or surgically unresectable urothelial cancer, and are ineligible for cisplatin based upon impaired renal function defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 by 24-hour urine measurement or calculated by Cockcroft-Gault (Attachment 2), or Grade 2 or higher peripheral neuropathy per CTCAE version 4.0.[9,10] These subjects will be referred to as chemo-naïve subjects.

5. Subjects must meet 1 of the following molecular eligibility criteria based on evaluation of appropriate tumor tissue (only available tumor tissue should be sent for analysis; please see Section 9.1.2 for details):

   - Tumors must have at least 1 of the following translocations:, FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or
   - One of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C.

6. Must have an ECOG performance status score 0, 1, or 2 (Attachment 1).

7. Must have adequate bone marrow, liver, and renal function as described below:

   - Bone marrow function (without the support of cytokines and/or erythropoiesis-stimulating agent [ESA] in preceding 2 weeks):

- Absolute neutrophil count (ANC) >1500/mm^3
- Platelet count >75,000/mm^3
- Hemoglobin >8.5 g/dL (without transfusion or demonstrate stability, i.e., no significant decline in hemoglobin, for 2 weeks after transfusion)

- Liver function:
  - Total bilirubin ≤1.5 x institutional upper limit of normal (ULN), unless know to have Gilbert's disease.
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x institutional ULN.
  - Albumin ≥2.0 g/dL
- Renal function: Creatinine clearance ≥40 mL/min/1.73 m^2 either directly measured via 24-hour urine collection or calculated using Cockroft-Gault. (Attachment 2)
- Electrolytes: Magnesium within 0.85 to 1.25 x institutional normal limits; sodium ≥130 mEq/L; and potassium within institutional normal limits.

8. Female subjects (if of child bearing potential and sexually active) must use medically acceptable methods of birth control before study entry, during the study, and until 3 months after taking the last dose of study drug. Male subjects must use a condom with spermicide when sexually active and must not donate sperm from the first dose of study drug until 5 months after the last dose of study drug. Medically acceptable methods of contraception that may be used by the subject and/or his/her partner include hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, true sexual abstinence, and surgical sterilization (e.g., confirmed successful vasectomy or tubal ligation). True sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, including up to 3 months for females and 5 months for males after the last dose of study drug is given. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not considered an acceptable contraceptive method.
9. Negative pregnancy test (urine or serum beta human chorionic gonadotropin [β-hCG]) at Screening for women of child bearing potential who are sexually active.
10. Subject (or his/her legally acceptable representative) must sign the informed consent documents indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participation in the study:

1. Received chemotherapy, targeted therapies, definitive radiotherapy, or treatment with an investigational anticancer agent within 2 weeks (in the case of nitrosoureas and mitomycin C, within 6 weeks; in the case of immunotherapy, within 4 weeks) before the first administration of study drug.

Localized palliative radiation therapy (but should not include radiation to target lesions) and ongoing bisphosphonates and denosumab, are permitted.

2. Has persistent phosphate level >ULN during screening (within 14 days of treatment and prior to Cycle 1 Day 1) and despite medical management
3. Has a history of or current uncontrolled cardiovascular disease including:
   - unstable angina, myocardial infarction, or known congestive heart failure Class II-IV (Attachment 3) within the preceding 12 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months, pulmonary embolism within the preceding 2 months.
   - any of the following: sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, cardiac arrest, Mobitz II second degree heart block or third degree heart block; known presence of dilated, hypertrophic, or restrictive cardiomyopathy.
   - Left ventricular ejection fraction (LVEF) <50% as assessed by echocardiography (or multi-gated acquisition scan [MUGA]) performed at screening.
   - QTc prolongation as confirmed by triplicate assessment at screening (Fridericia; QTc >480 milliseconds).
4. Any reason that in the view of investigator would substantially impair the ability of the subject to comply with study procedures and increase the risk to the subject. Examples include poorly controlled diabetes (HbA1c >8), and ongoing active infection requiring IV antibiotics.
5. Females who are pregnant, breast-feeding, or planning to become pregnant within 3 months after the last dose of study drug and males who plan to father a child while enrolled in this study or within 5 months after the last dose of study drug
6. Has not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, or Grade 1 neuropathy).
7. Has impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions
8. Had major surgery within 4 weeks before enrollment
9. Has known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection (subjects with history of hepatitis C infection but negative hepatitis C virus polymerase chain reaction (PCR) test and subjects with hepatitis B with positive hepatitis B surface antibody are allowed.)
10. Has active, symptomatic, or untreated brain metastases (subject with prior brain metastases treated at least 3 weeks prior to signing the full-study Informed Consent Form (ICF) or that are clinically and radiographically stable for at least 1 month prior to Cycle 1 Day 1 and do not require chronic corticosteroid treatment are allowed to be enrolled).
11. Received prior FGFR inhibitor treatment or if the subject has known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients.[13]
12. Any corneal or retinal abnormality likely to increase the risk of eye toxicity, i.e.:
    - History of or current evidence of CSR or retinal vascular occlusion (RVO)

- Active wet, age-related macular degeneration (AMD)
- Diabetic retinopathy with macular edema
- Uncontrolled glaucoma (per local standard of care)
- Corneal pathology such as keratitis, keratoconjunctivitis, keratopathy, corneal abrasion, inflammation or ulceration.

13. Subjects with evidence of active malignancies other than urothelial cancer (except definitively treated early stage cancer such as resected skin cancers and/or completely resected prostate cancer)

Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after Screening but before the first dose of study drug is given such that the subject no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

5. TREATMENT ALLOCATION AND BLINDING

As this is an open-label study, blinding procedures are not applicable.

Before IA1, central randomization was implemented in this study. Subjects were randomly assigned to treatment Regimen 1 or 2 via a web-based and computer-generated randomization method. Subjects were randomized to receive Regimen 1: 10 mg of oral study drug once daily on Days 1 through 7 and Days 15 through 21 of a 28-day cycle; or Regimen 2: 6 mg of oral study drug once daily on Days 1 through 28 of a 28-day cycle. Randomization was stratified according to ECOG performance status (0-1 versus 2), hemoglobin level (<10 g/dL versus ≥10 g/dL), FGFR alteration type (translocation versus mutation), pretreatment status (chemo-refractory versus chemo-naive), and disease distribution (presence or absence of visceral metastases: lung, liver, and bone). Covariate-adaptive randomization was used to allocate subjects between Regimens 1 and 2 until a favorable dose was selected. The interactive web response system (IWRS) assigned a unique treatment code, which dictated the treatment assignment for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and then gave the relevant subject details to uniquely identify the subject.

After IA1, all subjects will be assigned to Regimen 2. After implementation of Amendment 3, all subjects will be assigned to Regimen 3.

6. DOSAGE AND ADMINISTRATION

6.1. Administration of Study Drug

The study drug will be provided as a tablet for oral administration. Subjects assigned to Regimen 1 will be instructed to take 10 mg of the study drug orally each day on an intermittent dosing schedule of 7 days on and 7 days off on a 28-day cycle. Subjects assigned to Regimen 2 will be instructed to take 6 mg of study drug orally once daily for 28 days on a 28-day cycle. Subjects assigned to Regimen 3 will be instructed to take 8 mg of study drug orally once daily for 28 days on a 28-day

cycle. The study drug is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact and subjects should not attempt to dissolve them in water. Each dose should be taken at approximately the same time each day with or without food. Subjects should avoid consuming grapefruit or Seville oranges due to CYP450 3A4/5 inhibition.

If a dose is missed, it can be taken up to 6 hours after the scheduled time; the subject may return to the normal schedule the following day. If it has been more than 6 hours since the missed dose, then that dose should be skipped and the subject should continue treatment at the scheduled time the next day.

The study drug will be dispensed at the first visit of each cycle. All study drug doses dispensed must be captured in the source documents, including the subject's diary card, and the electronic case report form (eCRF). Unused study drug in the issued bottles and empty bottles must be returned to the site at each study visit. Study drug must be returned to the site when a subject discontinues study treatment. Returned tablets cannot be re-issued in this study or outside the study (follow study drug accountability guidelines in the Site Investigational Product Manual). Missed doses will not be replaced and the next dose will remain unchanged. If vomiting occurred with drug administration, no replacement dose will be taken and any such event that occurs up to 4 hours following dose administration must be recorded on the subject's diary card and the eCRF.

The exposure of erdafitinib is predicted to increase by 50% in subjects with the CYP2C9 *3/*3 genotype, estimated to be 0.4% to 3% of the population among various ethnic groups. Therefore, monitor for increased adverse reactions in subjects who are known or suspected to have the CYP2C9*3/*3 genotype. Dose titration is guided by serum phosphate levels in all subjects irrespective of genotype; therefore, the implications of higher exposures of erdafitinib including safety may be addressed.

6.2. Dose Up-titration Guidelines

Subjects in Regimen 1 and Regimen 2 followed dose up-titration guidelines as specified in Attachment 8 (Regimen 3 moved in this attachment).

For subjects enrolled under the DDI Substudy, the erdafitinib dose may be up-titrated to 9 mg or maintained at 8 mg based on the Cycle 1 Day 14 phosphate level taking into account observed toxicity to that day.

- Subjects with serum phosphate levels higher than 9.00 mg/dL (>2.91 mmol/L) will withhold erdafitinib treatment, with at least weekly assessment of serum phosphate until it returns to less than 7.00 mg/dL (<2.25 mmol/L) while initiating treatment with a phosphate binder such as sevelamer. Use of phosphate binder must be recorded as concomitant medication in the eCRF. (See Section 6.3.2 for detailed guidelines regarding further treatment).
- Subjects with serum phosphate levels between 7.00 to 9.00 mg/dL (2.25 mmol/L to 2.90 mmol/L) should increase the erdafitinib dose to 9 mg once daily, while concurrently initiating treatment with a phosphate binder such as sevelamer (see Section 6.3.2 for details).

- Subjects with serum phosphate level less than 7.00 mg/dL (<2.25 mmol/L) will increase the erdafitinib dose to 9 mg once daily. No concomitant treatment is required for these subjects.

6.3. Dose Modifications and Dose Delays

Treatment can be modified or terminated based on toxicity as described in Table 10. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines are provided in Sections 6.3.1 through 6.3.7.

Table 10: Dose Modification Guidelines

Toxicity Grade	Action	Dose Modification After Resolution of Adverse Event
1	None	Continue same dose
2	None or consider interruption	If interrupted, restart at same dose or 1 dose lower, if necessary.
3	Interrupt drug	Restart at 1 or 2 doses lower if recovery (to ≤Grade 1 or back to baseline for non-hematologic toxicity) is within 28 days. Discontinue drug if unresolved for >28 days.
4	Interrupt drug or discontinue	Discontinue*

For general toxicity management:

- Subjects with any grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment when applicable.
- Subjects should follow the guidelines in Table 11 or Table 12 or Table 13 for dose reduction recommendations and may have more than 1 dose reduction.
- If erdafitinib must be withheld for more than 28 days for a drug-related adverse event that fails to resolve to acceptable level (e.g., ≤Grade 1 non-hematologic toxicity or back to baseline), treatment with erdafitinib should be discontinued with the exception noted below.*
- If the subject achieves calcium-phosphate product >70 mg^2/dL^2 for 2 consecutive weeks despite phosphate lowering therapy or >90 mg^2/dL^2 any time during treatment despite phosphate lowering therapy, erdafitinib should be withheld until recovery to calcium-phosphate product <55 mg^2/dL^2. Treatment may be reintroduced at the first reduced dose level.
- In all cases of clinically significant impaired wound healing or imminent surgery or potential bleeding complications, it is recommended that dose administration be interrupted, appropriate clinical laboratory data be carefully monitored, and supportive therapy administered, where applicable. Dose administration may be restarted when it is considered safe and at an appropriate dose, according to the investigator's assessment.

*Exception: if a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. Please see Section 16.2.3 for details.

Dose reduction levels for each regimen are provided in Table 11 or Table 12 or Table 13.

Table 11: Dose Schedule and Dose Reductions - Regimen 1: Once Daily (QD) dosing, 7 days on / 7 days off in 28-day cycles

Category	No up-titration	With up-titration
	Dose	Dose
Starting dose	**10 mg**	**10 mg**
Up-titration	None	12 mg
1st dose reduction	8 mg	10 mg
2nd dose reduction	6 mg	8 mg
3rd dose reduction	4 mg	6 mg
4th dose reduction	**stop**	4 mg
5th dose reduction		**stop**

Table 12: Dose Schedule and Dose Reductions - Regimen 2: 6 mg Once Daily (QD) dosing, continuous daily dosing in 28-day cycles

Category	No up-titration	With up-titration
	Dose	Dose
Starting dose	**6 mg**	**6 mg**
Up-titration	None	8 mg
1st dose reduction	5 mg	6 mg
2nd dose reduction	4 mg	5 mg
3rd dose reduction	**stop**	4 mg
4th dose reduction		**stop**

Table 13: Dose Schedule and Dose Reductions - Regimen 3: 8 mg Once Daily (QD) dosing, continuous daily dosing in 28-day cycles		
Category	No up-titration	With up-titration
	Dose	Dose
Starting dose	**8 mg**	**8 mg**
Up-titration	None	9 mg
1st dose reduction	6 mg	8 mg
2nd dose reduction	5 mg	6 mg
3rd dose reduction	4 mg	5 mg
4th dose reduction	**stop**	4 mg
5th dose reduction		**stop**

6.3.1. Liver Event Safety Stopping Criteria

Liver chemistry threshold stopping criteria have been established to provide safety to the subjects and to better assess the etiology of the liver event during the development of new investigational products. The liver chemistry stopping criteria include any of the following:

- ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin) (or ALT ≥3 x ULN and international normalized ratio [INR] >1.5, if INR measured). Exception to the bilirubin elevation is made if the subject has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.
- ALT ≥5 x ULN for 2 weeks or ALT >8 ULN.
- ALT ≥3 x ULN if associated with the appearance or worsening of symptoms of liver injury, hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
- Persistent elevation of ALT ≥3 x ULN for ≥4 weeks or if ALT elevation cannot be monitored.

The liver chemistry should be repeated within 2 to 3 days. If any of the chemistry stopping criteria are met and there is no other explanation for the abnormalities, the study drug must be STOPPED, the medical monitor must be contacted as soon as possible, and the event reported as a serious adverse event if applicable. If Hy's law criteria (ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin) with no evidence of ALP elevation or ALT≥3 x ULN and INR >1.5 and no alkaline phosphatase [ALP] elevation) are met, then the event should be reported as a serious adverse event.

Liver Event Follow-Up Requirements

For subjects meeting any of the liver chemistry stopping criteria, the following procedures should be followed:

- Re-assess liver chemistries within 72 hours. Monitor liver chemistries (ALT, AST, alkaline phosphatase, bilirubin, including bilirubin fractions and INR) 1 to 2 times weekly until

resolution, stabilization, or return to subject's baseline values. Monitor clinical condition closely.

- Draw blood samples for random pharmacokinetic analysis.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins.
- Record alcohol use on the liver event alcohol intake Case Report Form (CRF).
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Check the viral hepatitis serology as appropriate and include:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM);
  - Hepatitis C RNA;
  - Hepatitis E IgM antibody (appropriate for subjects traveling outside North America);
  - Cytomegalovirus IgM antibody; and
  - Epstein-Barr viral capsid antigen IgM antibody (or equivalent test).
- Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease

Liver Event Re-challenge Requirements

If a subject meets the liver event stopping criteria, the study drug should not be re-administered. In the case in which Hy's law (refer to Section 6.3.1) is not met and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. Prior to re-introduction, the investigator should obtain written permission from the study medical monitor and the IRB. The investigator should also have the subject re-consent, explaining that re-introduction of study drug could lead to liver damage, which may be serious and/or may even result in death (please see Section 16.2.3 for details).

6.3.2. Guidelines for the Management of Elevated Phosphate Levels

Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 14.

Table 14: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Medical Management
<5.50 mg/dL (<1.75 mmol/L) (Grade 0)	Continue erdafitinib treatment.	None
5.50-6.99 mg/dL (1.75-2.24 mmol/L) (Grade 1)	Continue erdafitinib treatment.	Restriction of phosphate intake to 600 – 800 mg/day.
7.00-8.99 mg/dL (2.25-2.90 mmol/L) (Grade 2)	Continue erdafitinib treatment. A dose reduction will be implemented for persistent[a] hyperphosphatemia (defined as serum phosphate ≥7.00 mg/dL for a period of 2 months) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances)	Restriction of phosphate intake to 600 – 800 mg/day. Start sevelamer 800 to 1,600 mg 3 times a day with food until phosphate level is <7.00 mg/dL.
9.00-10.00 mg/dL (2.91-3.20 mmol/L), (Grade 3)	Withhold[b] erdafitinib treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Re-start treatment at the same dose level. A dose reduction will be implemented for persistent[a] hyperphosphatemia (defined as serum phosphate ≥9.00 mg/dL for a period of 1 month) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances)	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer up to 1,600 mg 3 times a day with food until serum phosphate level returns to <7.00 mg/dL
>10.00 mg/dL (>3.20 mmol/L) (Grade 4)	Withhold[b] erdafitinib treatment until serum phosphate level returns to 7.00 mg/dL (weekly testing recommended). Re-start treatment at the first reduced dose level. If persistent[a] hyperphosphatemia (≥10.00 mg/dL) for >2 weeks, erdafitinib should be discontinued permanently.	Medical management as clinically appropriate.
Significant alteration in baseline renal function and/or Grade 3 hypocalcemia	Erdafitinib should be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the sponsor's medical monitor agree that continuation of treatment is in the best interest of the subject, the drug may be re-started at 2 dose levels lower if appropriate. Follow other recommendations described above, Section 6.3)	Medical management as clinically appropriate.

Note: These are general guidelines that are based on emerging data and consensus experience of participating investigators or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If sevelamer hydrochloride (Renagel®) is not available, use of other phosphate binders (non-calcium containing) based on the local standard is recommended, including sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol®). These guidelines will be updated based on emerging data. Additional information on phosphorous in foods by class of food can also be found at www.permanente net/homepage/kaiser/pdf/42025.pdf. Additional information for phosphate management and diet can be found the National Kidney Foundation website (http://www kidney.org/atoz/content/phosphorus.cfm)

a Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value above the cut-off.

b Study drug interruptions for hyperphosphatemia suggested to be 7 days duration.

6.3.3. Guidelines for the Management of Dry Mouth and Stomatitis

General prophylaxis for dry mouth and oral mucositis:

- Good oral hygiene
- Use a soft toothbrush
- Avoidance of spicy, acidic, hard, and hot food and beverages
- Use of mild-flavored toothpastes
- Use of salt and baking soda mouthwashes 3 or 4 times per day
- Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)

Table 15: Guidelines for Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1: symptomatic (eg, dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	Continue erdafitinib at current dose.	Sorbitol lozenges as needed
Grade 2: moderate symptoms; oral intake alterations (eg, copious water, other lubricants, diet limited to purees or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue erdafitinib at current dose.	Sorbitol lozenges as needed and Cevimeline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 3: inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva less than 0.1 mL/min	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Sorbitol lozenges as needed and Cevimeline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated

Table 16: Guidelines for the Management of Oral Mucositis

Grade	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1	Continue erdafitinib at current dose.	• Continue general prophylaxis recommendations • Dexamethasone solution (0.5 mg/ 5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2%-5% jelly or solution. • Consider clotrimazole/nystatin if subjects are at risk of developing oral candidiasis.
Grade 2	• Consider holding erdafitinib if the subject has other study-drug related concomitant Grade 2 AEs. • Hold erdafitinib if the subject was already on symptom management (dexamethasone solution swish and spit and lidocaine 2%-5% jelly or solution) for more than a week. • If the erdafitinib is withheld, reassess in 1-2 weeks. • If this is the first occurrence of toxicity and resolves to ≤ Grade 1 or baseline within 2 weeks, restart at same dose. • If recurrent event or takes > 2 weeks to resolve to ≤ Grade 1 or baseline, then restart at 1 dose level below.	• Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2%-5% jelly or solution. • Consider concomitant etiologies such as oral candidiasis, oral herpes and recommend appropriate anti-fungal or anti-viral agents.
Grade 3	• Hold erdafitinib, with reassessments of clinical condition in 1-2 weeks. • When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	• Dexamethasone solution (0.5 mg/ 5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2%-5% jelly or solution. • Consider pain management strategies. • Consider IV hydration.
Grade 4	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated.
AE=adverse event; QID= four times a day.		

6.3.4. Guidelines for the Management of Dry Skin and Skin Toxicity

Guidelines for the management of dry skin are provided in Table 17.

General prophylaxis for dry skin and skin toxicity:

- Avoid unnecessary exposure to sunlight and excessive use of soap.
- Avoid bathing in excess; use tepid rather than hot water.
- Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
- Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
- Use broad spectrum sunscreen with a skin protection factor (SPF) ≥15.
- Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
- Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
- For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

Table 17: Guidelines for Management of Dry Skin

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus	Continue erdafitinib at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10% to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue erdafitinib at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13%-40% at night for areas with fissures.
Grade 3: Dry skin covering >30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL)	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Use topical steroid ointment or cream* BID and zinc oxide 13%-40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated
*Topical Steroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%		

6.3.5. Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)

Guidelines for management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) are provided in Table 18. Guidelines for the management of paronychia are provided in Table 19.

General prophylaxis for nail toxicity:

- Good hygienic practices, keep fingers and toes clean
- Keep nails trimmed but avoid aggressive manicuring
- Use gloves for housecleaning and gardening to minimize damage and prevent infection
- Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal
- Wearing comfortable shoes (wide sized shoes with room for the toes)

Table 18: Guidelines for Management of Nail Toxicity (Onycholysis/ Onychodystrophy)

Grade	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1	Continue erdafitinib at current dose.	• Continue general prophylaxis recommendations • Over the counter nail strengthener OR polyurea-urea urethane nail lacquer (Nuvail™) OR diethylene glycol monoethylether nail lacquer (Genadur) daily. • Use non-alcohol-containing moisturizing creams.
Grade 2	Consider holding erdafitinib with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes > 2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below in consultation with the medical monitor.	• Manage as per Grade 1 • For signs of infection (periungual edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: o treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim BID) AND o topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) • Silver nitrate application weekly AND topical antibiotics AND vinegar soaks[a]
Grade 3	Hold erdafitinib, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks.[a] For signs of infection (periungual edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.
Grade 4	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated.

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixins B
BID=bis in die (two times each day).

Table 19: Guidelines for Management of Paronychia

Grade	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1	Continue erdafitinib at current dose.	Topical antibiotics AND vinegar soaks[a]
Grade 2	Continue erdafitinib at current dose. Consider erdafitinib holding if no improvement in 1 to 2 weeks. When resolves to ≤Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor	Topical antibiotics AND vinegar soaks[a] AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) For signs of infection (periungual edema/erythema/tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim [Bactrim™ DS BID).
Grade 3	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or base line, restart at one dose level below in consultation with the medical monitor.	Vinegar soaks[a] AND consider nail avulsion For signs of infection (periungual edema/erythema/tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim [Bactrim DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

6.3.6. Guidelines for Eye Toxicity Associated With Vision Changes

If a subject experiences an event of confirmed new corneal or retinal abnormality while on study drug, the event should be reported as an adverse event (if Grade 1 or 2) or a serious adverse event (if Grade 3 or higher) as appropriate. Any new and clinically significant symptoms, such as but not limited to, blurred vision, partial or complete loss of vision, double vision, floaters or color spots or halos around light, change in color or night vision, photophobia, ocular pain or stinging sensation, or foreign body sensation should be further evaluated and managed per the guidelines below.

Amsler grid (illustrated in Attachment 5) testing will be performed (by the study physician or nurse) at Screening, at the beginning of every new cycle from Cycle 2 onwards and at the End-of-Treatment Visit. For any positive Amsler grid test, the subject should be referred for a full ophthalmologic examination within 7 days. However, if the subject has an abnormal Amsler grid test and otherwise normal ophthalmologic examination at baseline (during Screening), a repeat

ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler grid test at Screening, or the subject has developed new clinical symptoms.

Table 20: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only Or abnormal Amsler grid test	Refer for an ophthalmologic examination. If an ophthalmologic exam cannot be performed within 7 days, withhold treatment of erdafitinib until an examination can be performed. If there is no evidence with of eye toxicity on ophthalmologic examination, continue erdafitinib at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (RPED), withhold erdafitinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level after consultation with the sponsor's medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the medical monitor.	Refer the subject for an ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Immediately withhold erdafitinib. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold erdafitinib until signs and symptoms have resolved. Resume erdafitinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved, stabilized, or subject is lost to follow-up or withdraws consent (which ever happens first). If toxicity is reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level after consultation with the sponsor's medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
	recurrence, then re-escalation can be considered in consultation with the medical monitor.	
Grade 3: Severe or medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	If the toxicity is Grade 3, report as a serious adverse event and withhold erdafitinib. If the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that continuation of treatment is in the best interest of the subject, then erdafitinib may be resumed at 2 dose levels lower if appropriate. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence, consider permanent discontinuation.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with erdafitinib. Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (which ever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.
ADL=Activities of Daily Living, OCT= Optical Coherence Tomography		

6.3.7. Guidelines for the Management of Dry Eye

- **General considerations:** Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- **Prophylactic management:** Frequent use of artificial tear substitutes and ocular demulcents are strongly recommended, ie, every 2 hours during awake time.
- **Reactive management**:
  - Withhold erdafitinib for Grade 3 toxicity
  - Artificial tear substitutes if not started, every 2 hours during awake time
  - Ocular demulcents
  - Severe treatment-related dry eye should be evaluated by an ophthalmologist

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of the amount of study drug dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study.

Subjects will receive instructions on compliance with study treatment at the screening visit. A diary card will be given to the subject to record intake at home. On days when the subject visits the study center for dose administration or pharmacokinetic sampling, the investigator or designee

will supervise administration of the study drug and the exact time of administration will be recorded in the eCRF. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instruction to reeducate any subject who is not compliant with the study drug schedule.

8. CONCOMITANT THERAPY

Concomitant therapies are to be recorded at the time of screening (within 14 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the eCRF.

All therapies (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the eCRF. Caution should be exerted for subjects taking anti-coagulant therapies. Frequent monitoring for international normalized ratio (INR) is allowed at the treating physician's discretion.

The sponsor must be notified in advance, or as soon as possible thereafter, of any instances where prohibited medications are administered.

8.1. Permitted Medications

Permitted medications are to be recorded at the time of screening (within 14 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the eCRF.

Symptomatic treatment: Supportive care, such as antibiotics, analgesics, transfusions, diet, etc., and concomitant medications for the symptomatic treatment of related toxicities (Grade 1 to 4) may be administered according to the standard of care at the site, and at the treating physician's discretion, as clinically indicated.

Prophylactic medications: Appropriate prophylactic antiemetic regimens may be provided if required, in accordance with institutional practice and current European Society of Medical Oncology guidelines.

Chronic supportive therapies: Ongoing bisphosphonates and denosumab or other supportive therapies are permitted.

Palliative radiotherapy: Localized radiotherapy for symptomatic control is permitted, but should not include definitive radiation to target lesions.

COVID-19 vaccination: Administration of non-live vaccines approved or authorized for emergency use by local health authorities are allowed before or during this study. (For additional information, please refer to Attachment 11.)

8.2. Prohibited Medications

The following concomitant medications are prohibited during the study. The sponsor must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

- Concurrent investigational agents
- Concurrent antineoplastic agents or hormonal anticancer therapy

8.3. Precautions for Concomitant Medications

- Based on in vitro data, erdafitinib is metabolized by cytochrome CYP3A4 and CYP2C9. A clinical drug-drug interaction study showed that on average, erdafitinib exposure (C_{max} and AUC) was increased 5% to 34% when co-administered with itraconazole (a strong inhibitor of CYP3A4) and 21% to 49% when co-administered with fluconazole (a moderate inhibitor of CYP2C9). For this reason, strong CYP3A4 and moderate CYP2C9 inhibitors should be used with caution (see Attachment 4). Consider alternative therapies that are not strong CYP3A4 or moderate CYP2C9 inhibitors during treatment with erdafitinib. If co-administration of strong CYP3A4 or moderate CYP2C9 inhibitors is unavoidable, monitor the subject closely for adverse reactions and consider dose modifications accordingly. If the strong inhibitor is discontinued, the erdafitinib dose may be increased in the absence of drug-related toxicity.

  Based on in vitro data, erdafitinib is metabolized by cytochrome CYP2C9 and CYP3A4. The impact of moderate CYP2C9 inducers and strong CYP3A4 inducers (such as rifampin) on erdafitinib was not clinically studied. The concomitant use of these agents with erdafitinib should be avoided (see Attachment 4).

  Co-administration of erdafitinib with moderate CYP3A4 inducers may decrease erdafitinib exposure. Caution should be exercised for concomitant administration of erdafitinib and these agents. A comprehensive list of CYP450 isoenzymes and CYP3A4/2C9 inhibitors and inducers is provided in Attachment 4 and in http://medicine.iupui.edu/CLINPHARM/ddis/main-table; however, both these references may not be exhaustive and up-to-date at any given time. Please consult the product information of ongoing and new concomitant medications for the most accurate information on potential strong inducers of CYP3A4 and CYP2C9.

- Until further data become available, concomitant use of erdafitinib with CYP3A4 substrates with narrow therapeutic indices should be avoided (Attachment 4).

  In in vitro experiments, erdafitinib was shown to inhibit human P-glycoprotein (P-gp) at concentrations achieved at therapeutic doses in humans. If the compound is administered with drugs that are substrates of P-gp, there is the potential for observing increased concentrations of the substrate drug. Therefore, caution should be exercised for co-administered drugs that are P-gp substrates, such as digoxin, dabigatran, and fexofenadine (https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf); in addition, drugs with a narrow therapeutic index should only be used where the benefit outweighs the potential risk.

- Erdafitinib was shown to be an OCT2 inhibitor in vitro. PBPK simulations with metformin, an OCT2 substrate, predicted a lack of clinically relevant interaction with erdafitinib.

However, until further data are available, consider reducing the dose of OCT2 substrates or consider alternative agents based on tolerability.

- For subjects taking erdafitinib: medications known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) thought to increase serum phosphate levels.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules (Table 1, Table 2, Table 3, Table 4, and Table 5) summarize the frequency and timing of safety, efficacy, pharmacokinetic, biomarker, and other measurements applicable to this study.

Pre-treatment and post-treatment tumor biopsies will be collected where feasible. Feasibility may include but is not limited to: accessible tumor location; subject deemed clinically appropriate by investigator; subject is willing to comply with the procedure.

The number of blood samples, volume of blood, and amount of tissue that will be required from each subject for the various study procedures is outlined in the Laboratory Manual. The number of samples and the blood volume will vary depending on the number of cycles of the study drug that the subject receives. Unscheduled blood samples may be required for safety issues of individual subjects.

9.1.2. Screening Phase

The Screening Phase will consist of a molecular eligibility assessment period and a study screening period. The molecular eligibility assessment period starts with the signing of a molecular eligibility Informed Consent Form (ICF) and can occur at any time prior to administration of study drug. During this period, a central laboratory will evaluate subjects for molecular eligibility by analyzing appropriate tumor specimens.

The Sponsor will communicate results of the testing to the site. If a subject meets the molecular eligibility criteria, the subject can continue full-study screening under the full-study ICF for determination of full-study eligibility.

Subjects must meet all of the inclusion and none of the exclusion criteria in Section 4, as well as the molecular eligibility criteria. During the Screening Phase, prior to IA1, subjects were randomly assigned to Regimen 1 or 2. After IA1, newly enrolled subjects will be assigned to Regimen 2. After implementation of Amendment 3, all newly enrolled subjects will be assigned to Regimen 3. All information required for randomization purposes must be available at the time of randomization including: ECOG performance status, hemoglobin value, FGFR alteration type, disease distribution (presence or absence of visceral metastases: lung, liver, and bone) based upon

baseline radiographic imaging performed during screening window, and pretreatment status (chemo-refractory versus chemo-naive) obtained by subject history/medical records.

9.1.3. Treatment Phase

The Treatment Phase will begin with the administration of the first dose of erdafitinib and will continue until disease progression or unacceptable toxicity (based on investigator assessment) occurs. Subjects with progressive disease or unacceptable toxicity will be withdrawn from treatment. If a subject has progressive disease per RECIST version 1.1, but the treating physician strongly believes that continuation of study treatment is in the best interest of the subject, then, in consultation with the medical monitor, the subject may be allowed to continue on the study drug. The subject may receive treatment until such time as the treating physician and the medical monitor agree that further continuation of treatment is no longer thought to benefit the subject. The subject must follow the procedures as outlined in the Time and Events Schedule (Table 1, Table 2, and Table 3) as if the subject has not progressed.

Subjects who have been treated on Regimens 1 or 2 (and who have not already been up-titrated to 8 mg in Regimen 2) may be considered for treatment in Regimen 3 (8 mg, without the provision for up-titration), based on fulfillment of specific clinical elements as determined by the sponsor, and furthermore based upon agreement between the sponsor and treating physician. These subjects will follow the Time and Events schedule for Regimen 3, and will start treatment at the new dose at the start of their next subsequent cycle based on approval by the medical monitor in discussion with the treating physician.

Adverse events occurring any time after the subject signs the full-study ICF and up to 30 days after the last dose of erdafitinib are to be recorded for all subjects (no adverse events will be collected for subjects signing the molecular ICF only). Adverse event information will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. See Section 12 for complete details on adverse event reporting. Concomitant medications used will also be recorded throughout this time period.

Throughout the Treatment Period, the investigator will assess subject response to therapy using the RECIST Version 1.1.[8] Efficacy evaluations are described in Section 9.2.

9.1.4. End-of-Treatment Visit

The End-of-Treatment Visit will be performed after the last dose of erdafitinib is administered and will include End-of-Treatment procedures as outlined in the Time and Events Schedule (Table 1, Table 2, and Table 3). All subjects should have the End-of-Treatment Visit completed within 30 days after the last dose of study drug, and prior to starting any subsequent cancer treatment, except for those who have withdrawn consent, died, or have been lost to follow-up.

Additional information on reporting of adverse events can be found in Section 12.

9.1.5. Follow-Up Phase

The Follow-up Phase is the time between the End-of-Treatment Visit and the end of study participation or end of study. All subjects who enter the Follow-up Phase will have a Follow-up

Visit every 12 weeks (±7 days) after the End-of-Treatment Visit to assess survival status and start of alternate anticancer therapy until death, the subject withdraws consent, or the end of study, whichever occurs first as outlined in the Time and Events Schedules (Table 1, Table 2, and Table 3). Assessments of survival status and alternate anticancer therapies must be recorded in the eCRF. If necessary, this visit can occur telephonically.

9.2. Efficacy

Disease assessments will be performed according to the Time and Events Schedules (Table 1, Table 2, and Table 3). Assessment of responses for solid tumors will be performed according to RECIST (version 1.1)[8] by investigators. For subjects who discontinue study drug before disease progression, tumor assessments should be continued per this schedule, as if the subject is still on study treatment.

More frequent radiological assessments are allowed, if clinically indicated/desirable. Identical methodology (computed tomography [CT] scan or magnetic resonance imaging [MRI]) should be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document disease status. Ultrasound, fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET), and plain x-rays are not acceptable methods of evaluating disease response in the absence of CT or MRI scans.

If symptomatic deterioration (on the basis of global deterioration of health status) occurs without documentation of radiographic progression, the clinical findings used to make this determination must be specified in the eCRF and documented in the source documents. Every effort should be made to document the objective progression even after discontinuation of treatment for symptomatic deterioration. Tumor response will be reported by the investigator in the eCRF.

9.2.1. Evaluations

9.2.1.1. Radiographic Images Assessment

Computed tomography (CT) scans of the chest, abdomen, pelvis, and any other location where disease is present will be performed at Screening. During the study, disease response will be assessed using CT scans of the locations of known disease. Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations or in cases where use of CT scan is clinically contraindicated). For all other sites of disease, MRI studies do not replace the required chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

All unconfirmed PR/CR results require confirmation of response within 4 to 6 weeks of first assessment of response, as per RECIST 1.1.

After disease progression is documented, subjects will be monitored as outlined in Section 9.1.5.

9.2.1.2. Definition of Measurable Disease

Subjects will have response assessments performed by radiographic image assessments (CT or MRI) as described in Section 9.2.1.1. Disease assessment procedures must be consistent with RECIST version 1.1 guidelines for radiographic assessment, as outlined in Attachment 6. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination alone.

9.2.2. Endpoints

Primary Endpoint

The primary endpoint is the best objective response.

Secondary Endpoints

- Progression-free survival, defined as the duration from the date of the first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever comes first. Data from subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Duration of response (CR or PR), calculated from the date of initial documentation of a response to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. Data from subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Overall survival, measured from the date of first dose of study drug to the date of the subject's death. If the subject is alive or the vital status is unknown, the subject's data will be censored at the date the subject was last known to be alive.
- The safety profile of erdafitinib
- The response rate in biomarker-specific subgroups
- Pharmacokinetics of erdafitinib: population (typical) and individual pharmacokinetic parameters of JNJ 42756493 (for instance, plasma clearance, volumes of distribution, etc.) will be estimated from the available JNJ 42756493 plasma concentration-time observations

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9.2.3. Pharmacokinetics Evaluations

Venous blood samples will be collected for determination of plasma concentrations of erdafitinib at the time points specified in the Pharmacokinetic Time and Event Schedule (Table 4). On Cycle 1 Day 1, a 4-mL venous blood sample will be taken together with the 2-hour postdose pharmacokinetic blood sample for the determination of the plasma protein binding of erdafitinib. Total protein, albumin, and alpha-1-acid glycoprotein levels will be determined as well. If indicated by the emerging safety findings or if the scheduled pharmacokinetic samples are not collected due to treatment interruption, unscheduled blood samples may be collected to study the relationship between drug exposure and adverse events to support the decision of dose reduction or modification. The total number of samples and blood volume will not be substantially increased without IEC approval. The estimated volume of blood required for the pharmacokinetic evaluations is summarized in Table 4. The dates and times of venous blood sample collection will be recorded on the laboratory requisition form or in the eCRF. At the time of implementation of Amendment 6 at the local site level, routine PK samples will no longer be collected; PK samples may still be collected for assessment of adverse events as clinically appropriate.

The Laboratory Manual provides further information regarding handling and shipment of blood/plasma samples.

9.2.4. Analytical Procedures

Blood samples will be processed to obtain plasma for measurement of erdafitinib by validated analytical methods under the direction of the sponsor. For total plasma concentrations of erdafitinib, the samples will be analyzed using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method under the direction of the sponsor. Plasma protein binding will be determined by equilibrium dialysis. The Cycle 1 Day 1, 2-hour plasma samples will be subjected to equilibrium dialysis against phosphate buffer. After dialysis, the buffer and plasma samples will be analyzed for erdafitinib content using a qualified LC-MS/MS method by the sponsor's Bioanalytical Laboratory. The fraction of the unbound erdafitinib (FU) will be calculated as the ratio of the unbound concentration (C_u) in the buffer, to the total concentration (CED) in the plasma (formula: FU = Cu/CED).

Based on the metabolite profiling data, the need for further metabolite assessment in the clinical samples will be evaluated. If further metabolite quantification is needed it will be done by a qualified method. After these analyses, the remaining plasma will be retained and may be used for future metabolite identification, or profiling (to be reported either together with or separate from the clinical study report).

9.3. Pharmacodynamic and Predictive Biomarker Evaluations

9.3.1. Pharmacodynamic Biomarker Evaluations

For pharmacodynamic biomarker evaluation, serum phosphate levels will be monitored in subjects treated with the study drug. The Phase 1 Study EDI1001 demonstrated that the phosphate levels tend to correlate with the activity of erdafitinib.

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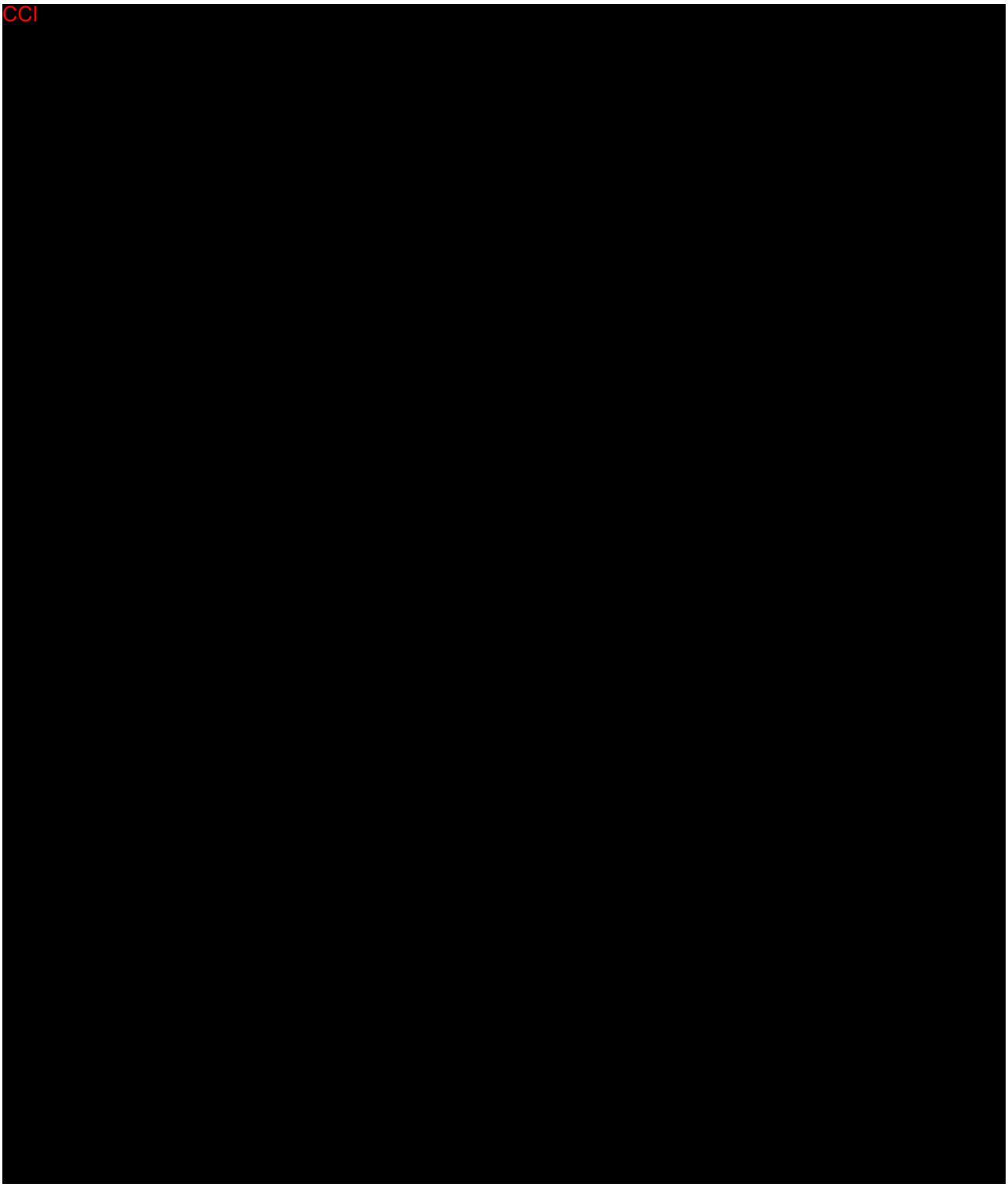

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9.4. Safety Evaluations

This study will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse event and serious adverse event data will be reviewed internally on an ongoing basis to identify safety concerns by the study medical monitor. In addition, the sponsor's SMT will review the safety data routinely and will investigate specific safety queries. The SMT will review all serious adverse events. Periodic conference calls with the study investigators will be conducted to discuss study progress, obtain investigator feedback, and discuss study-specific issues including adverse events and serious adverse events.

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, clinical laboratory tests, ECOG performance status, and other safety evaluations at specified time points as described in the Time and Events Schedules (Table 1, Table 2, and Table 3).

Any clinically significant abnormalities or toxicities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable condition. For adverse events such as skin/nail and mucosal toxicity, upon subjects consent, photographs may be taken for assessment and monitoring of the toxicity.

9.4.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Adverse events will be graded according the NCI-CTCAE, Version 4.0. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.4.2. Clinical Laboratory Tests

- Blood samples for serum chemistry and hematology will be collected according to the Time and Events Schedules (Table 1, Table 2, and Table 3). More frequent clinical laboratory tests may be performed, as indicated by the overall clinical condition of the subject and for abnormalities that warrant more frequent monitoring.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

- Laboratory test results completed on Cycle 1 Day 1 should be reviewed prior to dosing and subjects should continue to meet eligibility requirements per the Inclusion/Exclusion criteria.
- The following tests will be performed locally:
  - **Hematology Panel**
    - -hemoglobin
    - -platelet count
    - -white blood cell (WBC) count and ANC only
  - **Serum Chemistry Panel**
    - -alanine aminotransferase (ALT)
    - -albumin
    - -alkaline phosphatase
    - -aspartate aminotransferase (AST)
    - -blood glucose
    - -blood urea nitrogen (BUN)
    - -total bilirubin
    - -calcium
    - -creatinine
    - -magnesium
    - -alpha-1-acid glycoprotein[1]
    - -phosphate
    - -potassium
    - -sodium
    - -total protein
    - -parathyroid hormone (PTH)

1. Testing of alpha-1-acid glycoprotein will be performed by a central lab using the 2-hour post dose blood sample from Cycle 1 Day 1. This test is not performed locally. Please refer to Table 4 for additional details.

Potential Hy's Law case reporting requirements are defined in Section 6.3.1.

9.4.3. Renal Toxicity Evaluation

Serum creatinine clearance will be calculated according to Cockcroft-Gault Formula (Attachment 2) or measured by 24-hour urine collection.

9.4.4. Urine or Serum Beta-hCG Pregnancy Test

A urine or serum sample will be obtained for a pregnancy test in sexually active female subjects of child-bearing potential at pre-specified time points (β-hCG). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

9.4.5. Electrocardiogram

Electrocardiograms will be performed according to the Time and Events Schedule at the study site. Subjects should reside in a quiet setting for the duration of serial ECG recordings, without distractions, at each scheduled time point for ECG measurements. The subject should rest in a supine position for at least 5 minutes before each serial ECG recording, and should refrain from talking or moving arms or legs. Skin preparation should be optimal to obtain high quality of ECGs; if deemed appropriate, the chest should be shaved and prepped with light abrasion. Serial triplicate ECGs should be performed with 5 minute intervals between each assessment, at approximately the

same time of day for each required study visit (as outlined in the Time and Events Schedules). Serial triplicate 12-lead ECGs will be recorded and 1 printout produced and stored in the subject's source documents. The data will also be stored digitally and sent to the central laboratory for storage (as described in the ECG manual) periodically. All 12-lead ECG recorder devices should have been recently serviced and calibrated. The following variables should be measured: heart rate, RR, QT, PR, QRS, QTc (Fridericia) intervals. QTcF (Fridericia) will be used for assessment of QTc interval prolongation. The investigator will review the results, including ECG morphology, for immediate management. A description of the overall assessment (i.e., normal or abnormal plus reason) will be made along with the clinical investigator's signature and date.

Abnormal and clinically significant ECG results will be reported to the Sponsor within 72 hours. Screening ECG results will be used to determine subject eligibility. The investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings). Any clinically significant worsening from baseline or new finding after the first study drug administration will be recorded as an adverse event and will be followed up to resolution or until an adequate explanation for the abnormality is found.

9.4.6. Echocardiography Evaluation

Echocardiography (ECHO) will be conducted and assessed by a local cardiologist during the full-study Screening. Echocardiography may be repeated at any time during the study at the discretion of investigators to assess for any potential cardiovascular toxicity. Screening ECHO results will be used to determine subject eligibility. In the event that ECHO is not available or not interpretable, MUGA is an acceptable alternative.

9.4.7. Ophthalmic Examination

All subjects must have an ophthalmological examination performed at Screening by an ophthalmologist, which should include assessment of visual acuity, fundoscopy (examination of both central and peripheral zones should be performed), slit lamp biomicroscopy and an Optical Coherence Tomography (OCT). The Amsler grid test will also be administered by the treating study physician or nurse at screening and other timepoints, as indicated in the Time and Events Schedule. A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment.

When Central Serous Retinopathy (CSR)/Retinal Pigment Epithelial Detachments (RPED) is suspected, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected Retinal Vein Occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the subject's records for future reference. In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered.

Amsler grid testing will be administered by the treating physician or nurse according to the Time and Events Schedules (Table 1, Table 2, and Table 3). Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days.

However, if the subject has an abnormal Amsler grid test at baseline (during Screening), then a repeat ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler Grid test at Screening, or the subject has developed new clinical symptoms (specific guidelines outlined in Section 6.3.6).

9.4.8. Vital Signs

Blood pressure (systolic and diastolic) and heart rate measurements will be assessed with a completely automated device consisting of an inflatable cuff and an oscillatory detection system according to the Time and Events Schedules (Table 1, Table 2, and Table 3).

9.4.9. Physical Examination

A full physical examination will be performed at screening according to the Time and Events Schedule. Limited physical examinations of involved organs will be performed at subsequent visits as outlined in the Time and Events Schedules (Table 1, Table 2, and Table 3).

9.4.10. ECOG Performance Status

Eastern Cooperative Oncology Group performance status score will be determined at pre-specified time points listed in the Time and Events Schedules (Table 1, Table 2, and Table 3). Eastern Cooperative Oncology Group scoring information is provided in Attachment 1.

9.4.11. Symptomatic Measurement Questionnaire

An abbreviated set of self-reported questions will be administered to rate the subject's experience focusing on disease- and treatment-related symptoms. Symptoms reflect a subject's experience of treatment-related side effects and disease-related symptoms that may impact treatment decisions. Subjects will be asked to rate their symptoms on a scale ranging from 0 to 10, with higher scores indicating a more severe degree of symptoms. The Symptom Measurement Questionnaire (e.g. pain, fatigue, cough, breathing) was developed by reviewing clinical reports from the subjects treated thus far in BLC2001. The questionnaire time recall period for this instrument is 1 week (the past week) and it will be administered in this study to perform Patient-Reported Outcomes (PRO) analysis. The Symptom Measurement Questionnaire will be completed by the subject at the timepoints specified in the Time and Events Schedule (Table 3). The Symptom Measurement Questionnaire will be provided as part of the CRF. The Symptom Measurement Questionnaire will be analyzed by measuring change from baseline to determine if response to therapy and side effects of therapy are accompanied by measurable changes in the symptoms reported.

This questionnaire will be in English only, and will be completed only by subjects who can read English. Subjects who switch to Regimen 3 from Regimen 1 or 2 are not required to complete the questionnaire.

9.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form/source documentation. Refer to the Time and Events Schedules for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if the subject has died.

10.2. Discontinuation of Study Treatment

A subject's study treatment will be discontinued for any of the following reasons:

- Concurrent medical conditions or unmanageable disease–related events for which the investigator believes that it is in the best interest of the subject to stop treatment
- The subject becomes pregnant
- Disease progression (Exception: if the investigator and medical monitor agree that continuation of treatment is acceptable and in the best interest of the subject considering the terminal nature of the underlying disease, he/she may receive treatment until such time as the treating physician and the medical monitor agree that further continuation of treatment is no longer beneficial to the subject.)
- Unacceptable toxicity (Exception: If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator (please see Section 16.2.3 for details.)
- The subject refuses further treatment with the study drug
- The sponsor terminates the study
- Investigator decision approved by the sponsor

If a subject discontinues treatment, an End-of-Treatment visit should be conducted within 30 days of the subject’s last dose of study drug. The primary reason for treatment discontinuation will be clearly documented in the subject’s medical record and recorded in the eCRF. Once a subject discontinues treatment with the study drug, the subject will not be permitted to be retreated.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

A subject may be replaced if the subject withdraws prior to study drug administration or prior to the first disease assessment for reasons other than toxicity or disease progression.

10.3.1. Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the full study ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

In the original protocol, 2 interim analyses were planned. After Interim Analysis 1 was completed and Amendment 3 written, no further interim analyses were needed. The original protocol sections describing the interim analyses and dose selection criteria were moved to Attachment 9, along with the original sample size calculations.

11.1. Sample Size Determination

Sample size determination prior to IA1 is described in Attachment 9.

After IA1, it is expected that approximately 180 subjects with specified FGFR genetic alterations will be enrolled in the study. Of these, about 30 subjects will be treated with Regimen 1, about 50 subjects will be treated with Regimen 2, and approximately 100 subjects will be treated with Regimen 3. When approximately 88 subjects have been treated in Regimen 3, if less than 80 subjects are chemo-refractory, then enrollment of chemo-naïve subjects in Regimen 3 will be stopped but enrollment of chemo-refractory subjects will continue until at least 80 chemo-refractory subjects are treated in Regimen 3 or a total of approximately 100 subjects are treated with Regimen 3.

The number of subjects to be treated with Regimen 3 (at least 88) was based on sample size calculations using the following assumptions:

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After a total of approximately 88 subjects are treated with Regimen 3, enrollment will be stopped if at least 80 chemo-refractory subjects have been treated with Regimen 3. However, if the number of chemo-refractory subjects treated with Regimen 3 is less than 80, then the enrollment will change as follows:

1. Enrollment of chemo-naïve subjects will be stopped.
2. Enrollment of chemo-refractory subjects will continue until a total of at least 80 chemo-refractory subjects are treated or a total of 100 subjects are treated with Regimen 3.

Enrollment of at least 80 chemo-refractory subjects will provide at least 80% power to reject the null hypothesis within the chemo-refractory subgroup under the above assumptions.

11.2. Analysis Populations

The analysis populations for this study are defined as the following:

- The Primary Efficacy (PE) analysis population will consist of all subjects who are treated by at least 1 dose of study drug in Regimen 3.
- The Treated Population will consist of all subjects who receive at least 1 dose of study drug. All safety analyses will be performed using the Treated Population.
- The Response-Evaluable (RE) population will include all subjects who satisfy all of the following:
  - Met all eligibility criteria for the study;
  - Received at least 1 dose of study drug;
  - Had a baseline and at least 1 adequate post-treatment disease evaluation, have had clinical signs and/or symptoms of disease progression or died prior to the first post-treatment disease evaluation (these subjects will be considered non-responders). Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred.

  The efficacy analyses at IA1 and IA2 will be performed using the RE population.

- The Pharmacokinetic/Pharmacodynamic Population will consist of all subjects who received at least 1 dose of erdafitinib and had at least 1 sample collected during treatment to determine the drug concentration or pharmacodynamic biomarker response.

11.3. Efficacy Analyses

Efficacy will be evaluated using the RECIST version 1.1 and current disease specific solid tumor response criteria.[8] Response may be assessed by investigators and by an Independent Radiologic Review Committee (IRRC). Independent Radiologic Review Committee assessment may not be performed if the investigator assessments indicate that the primary objective has not been met (IRRC assessment will not be performed for IA1 and IA2). If response is assessed by an IRRC,

the IRRC assessment of response will be used for the primary and final analyses, and the response assessed by the investigators will be used for supportive analyses.

11.3.1. Primary Analysis

The primary analysis will be conducted 6 months after enrollment of the last subject in the selected dose regimen. The primary efficacy analyses will be based on the PE analysis population.

The response rate for both the chemo-naïve and chemo-refractory subjects will be analyzed at the time of primary analysis. The null hypothesis will be rejected using normal approximation to the binomial distribution. The response rate and its 95% 2-sided confidence interval will be calculated using normal approximation to the binomial distribution as well.

The response rate of the chemo-refractory subgroup in Regimen 3 will be analyzed at the time of the primary analysis. Only chemo-refractory subjects who have received at least 1 dose of study drug will be included in this analysis. The null hypothesis for the chemo-refractory subjects is that the response rate is less than or equal to 25%; this will be rejected using normal approximation to the binomial distribution. Efficacy on response rate within the chemo-refractory subgroup will be claimed if the null hypothesis on response rate on the combined chemo-naive and chemo-refractory group is rejected and the null hypothesis on response rate on the chemo-refractory subgroup is also rejected.

Analysis of duration of response, PFS, and overall survival will be conducted at the same cutoff date of the primary analysis. The distribution (median and Kaplan-Meier curves) of duration of response will be provided using Kaplan-Meier estimates for subjects who achieved a response during the study. Biomarker-specific response rates will also be evaluated, including differences between translocations and mutations.

Exploratory analyses will be performed on response rate, duration of response, PFS, overall survival based on the treated population.

Similar exploratory efficacy analyses on Regimen 1 and Regimen 2 will be performed as well.

11.3.2. Final Analysis

The final analysis will be performed 12 months after last subject is enrolled. All analyses on efficacy endpoints will be updated based on the treated population. For subjects still on study treatment after the planned final analysis the study Sponsor will continue to provide access to erdafitinib and collect safety data (eg, AEs, SAEs) until the end of study (see Section 2.3 for the end of study definition).

11.4. Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analyses

Population pharmacokinetic analysis of plasma concentration-time data of erdafitinib will be performed using nonlinear mixed-effect modeling. Data from this study may be combined with those from a selection of Phase 1 studies to support a relevant structural model. This model will be used to predict pharmacokinetic parameters at steady-state. Descriptive statistics, including

mean, standard deviation, coefficient of variation (%CV), median, minimum, and maximum will be applied for estimated pharmacokinetic parameters. Graphical exploration of data may be performed if deemed useful. In addition, available subjects' characteristics (demography, such as body weight; laboratory data, such as alpha-1-acid glycoprotein; and genotype) may be tested as potential covariates affecting pharmacokinetic parameters.

Relationships between plasma concentrations or metrics of systemic exposure and markers of pharmacological activities, efficacy or treatment-emergent adverse events could also be explored as data allow using population approaches (e.g., non-linear mixed effects approaches). For example, Pharmacokinetic-phosphate relationships will be explored, also evaluating the potential effect of baseline phosphate level as influential covariate.

11.5. Biomarker Analyses

All FGFR alterations in tumor will be tested at the central laboratory and biomarker eligibility will be determined using the accepted criteria developed in the central laboratory.

Blood samples will be collected as outlined in Table 5. Blood samples will be tested for the presence of the FGFR translocations or mutations to determine if they correlate with sensitivity to the compound. A laboratory-developed test will be used for this exploratory endpoint.

Phosphate will be tested at local laboratories using the test developed there. Analysis will be performed and total levels of phosphate in serum will be determined for each subject.

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11.6. Safety Analyses

Safety analyses will be performed using the treated population. Safety will be evaluated using the NCI-CTCAE, Version 4.0. All safety analyses will be performed using data from the safety population. The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

Treatment-emergent adverse events are adverse events that occur after the first dose of study drug, through the Treatment Phase, and for 30 days following the last dose of study drug; any adverse event considered study drug-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI-CTCAE, Version 4.0) and drug relationship as well as categorized by System Organ Class and preferred term by treatment group.

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (i.e., treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be included in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline.

Parameters with predefined NCI-CTCAE Version 4.0 toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Electrocardiogram

The effects of erdafitinib on ECGs (QT, QTc, PR, QRS, heart rate) will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the Day 1 pre-dose ECG will be used as baseline) to allow detection of clinically relevant changes in individuals.

Vital Signs

Descriptive statistics of pulse/heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with clinically important changes from baseline will be summarized.

11.7. Data Review Committee

The DRC will be conducting all interim analyses (IA1 and IA2 prior to Amendment 3, please refer to Attachment 9) and further safety analyses. Details of the composition of the DRC and their operational procedures will be specified in the DRC charter.

11.8. Safety Monitoring Team

Safety will be monitored by the sponsor's medical monitor or study responsible physician throughout the study. In addition, the sponsor's SMT, a multi-disciplinary team including an internal safety physician, will review the safety data and will investigate specific safety queries. In addition, the SMT will review all serious adverse events. In the event a significant safety issue is identified, both the internal safety team and the responsible investigators will convene to discuss the safety data and to make a recommendation on the future conduct of the study. All decisions will be documented and will be distributed to investigators. The IRB or IEC will be notified if required.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For erdafitinib, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

The attribution definitions (ie, assessment of causality) have been updated for the DDI Substudy and are provided in DDI Substudy Attachment 12, Section 12.

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

The severity criteria have been updated for the DDI Substudy and are provided in the DDI Substudy Attachment 12, Section 12; the DDI Substudy will be using the NCI-CTCAE, Version 5.0.

Adverse event severity is a clinical determination of the intensity of an adverse event. The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE, Version 4.0. Any adverse event or serious adverse event not listed in the NCI-CTCAE, Version 4.0 will be graded according to the investigator clinical judgment by using the standard grades as follows:

Grade 1, Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities

Grade 2, Moderate: Sufficient discomfort is present to cause interference with normal activity

Grade 3, Severe: Extreme distress causing significant impairment of functioning or incapacitation; prevents normal everyday activities

Grade 4, Life-threatening: Requires urgent medical intervention

Grade 5, Death: Death

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g., laboratory abnormalities).

Hyperphosphatemia and adverse events related to nails are to be graded using Table 21.

Table 21: Grading of Hyperphosphatemia and Nails Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nail Changes (onychodystrophy)	Nail discoloration, asymptomatic separation of the nail bed from the nail plate or nail loss	Nail/finger tips pain, symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	Severe nail finger tips pain, symptomatic separation of the nail bed from the nail plate or nail loss; significantly limiting instrumental ADL	Life-threatening consequences, urgent intervention indicated
Hyperphosphatemia	5.5-6.9 mg/dl 1.8-2.2 mmol/L	7.0-8.9 mg/dl 2.3-2.9 mmol/L	9.0-10.0 mg/dl (>2.9-3.2 mmol/L), or asymptomatic soft tissue calcification with any phosphate level	>10 mg/dl (>3.2 mmol/L), or symptomatic soft tissue calcification with any phosphate level

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

Corneal or retinal abnormalities for subjects receiving erdafitinib should be reported as adverse events (if Grade 1 or 2) and or as serious adverse events if the severity is Grade 3 or higher.

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated full-study ICF (no adverse events will be collected for subjects signing the molecular ICF only) is obtained until 30 days after last dose of study drug. Subjects who discontinue study drug due to drug-related toxicity will continue to be monitored for this toxicity until the toxicity resolves to baseline, stabilizes, or is deemed irreversible, the subject dies, or subsequent therapy is started, whichever occurs first. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information

that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Adverse events that occur between after signing the ICF for assessment of the molecular eligibility and before signing the full study eligibility screening ICF will not be collected.

All events that meet the definition of a serious adverse event will be reported as such.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the following:

- Subject's name
- Subject number
- Subject's date of birth
- Study site number
- Investigator's name and 24-hour contact information
- Local sponsor's name and 24-hour contact information
- Statement that the subject is participating in a clinical trial.

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the End-of-Treatment Visit, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs (whichever occurs first):

- The event resolves;
- The event stabilizes;
- The event returns to baseline, if a baseline value/status is available;
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct;
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts); or
- The subject dies.

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. (Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event).
- Administration of blood or platelet transfusion. (Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.)
- Procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling) (Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event).
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- Planned procedures (i.e., planned prior to starting of treatment on study; must be documented in the eCRF). (Prolonged hospitalization for a complication considered to be at least possibly related to the study drug remains a reportable serious adverse event.)

Anticipated Events

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, the following SAEs will be considered anticipated events:

- Cauda equina syndrome
- Haematuria
- Urinary incontinence
- Lymphedema
- Pathological fracture
- Spinal cord compression
- Urinary hesitation
- Ureteric obstruction
- Hydronephrosis
- Urine flow decreased, including oliguria
- Urinary retention
- Urinary tract obstruction
- Urinary tract stoma complication
- Urinary tract pain
- Urinary tract infection
- Urosepsis

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, stillbirth, and congenital anomaly) are

considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Disease-related Events or Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

Progression of disease should not be considered nor should be reported as an adverse event (or serious adverse event). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Section 12.1.1).

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to

Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

The erdafitinib study drug supplied for this study is formulated as 3-, 4-, and 5-mg tablets for oral use. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

The tablets for oral use in this study will be packaged in child-resistant bottles.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. No medication can be relabeled without prior approval from the sponsor.

14.4. Preparation, Handling, and Storage

The tablets for oral use should be stored at room temperature. Dosing instructions are provided in by the investigator and on the study drug labeling.

The study drug must be stored as specified at delivery and in the original packaging.

14.5. Drug Accountability

The clinical investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects (or, when appropriate, by a caregiver or surrogate) must be instructed to return all original containers, whether empty or containing study drug. Study drug returned by study subjects will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Protocol
- Investigator's Brochure
- Electronic CRFs and electronic data capture (eDC) manual
- Site Investigational Product Manual
- Laboratory manual
- ECG manual
- Kits for pharmacokinetic, pharmacodynamics/biomarker, safety, and tissue sample assessments
- Subject diary card and information booklet
- Investigator binder to store all documents concerning the study. This is a confidential binder and only personnel involved in the study should have access to it.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of 2 different dose regimens (Regimen 1: 10 mg oral study drug once daily on an intermittent schedule [Days 1 through 7 and Days 15 through 21 of a 28-day cycle]; Regimen 2: 6 mg oral study drug once daily on a continuous schedule [Days 1 through 28 of a 28-day cycle]), and selection of a more favorable dose regimen for erdafitinib in subjects with metastatic or surgically unresectable urothelial cancer with select FGFR genetic alterations. Based on analysis of data up to Interim Analysis 1 (IA1), the Data Review Committee (DRC) decided to terminate further enrollment to the intermittent schedule and select the continuous schedule with a starting dose of 8 mg and possible up-titration to 9 mg (Regimen 3) for further enrollment.

The collective experience from both the Phase I and current ongoing global Phase 2 trials, in addition to emerging pharmacokinetic/pharmacodynamic (PK/PD) modeling, suggest that the 8 mg daily

dose as the continuous regimen is likely to be well tolerated without significant treatment interruptions. In addition, the majority of subjects would tolerate the sustained 8 mg daily dose, while maximizing the chance for potential efficacy, based on observations to date of responses being most associated with reaching the target therapeutic window for serum phosphate (5.5 - 7mg/dL). Selective dose up-titration to 9 mg for optimization of the pharmacodynamic effect based on individual tolerance in subjects is likely to increase the potential for clinical activity without significantly increasing dose interruptions or toxicity.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the trial, as outlined in the Time and Events Schedules.

The total blood volume to be collected is considered to be within the normal range allowed for this adult subject population over this time frame.[21]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials

- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF text must be obtained from the IEC/IRB.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The re-approval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care they will receive. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject, or legally acceptable representative, is authorizing such access, including permission to obtain information about his or her survival status. agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, subsequent disease-related treatments, or to obtain information about his or her survival status.

Each subject (or legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's (or his or her legally acceptable representative's) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

Subjects will be asked for consent to provide optional samples for research where local regulations permit.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

If the subject (or legally acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.

When prior consent of the subject is not possible (and the subject's legally acceptable representative is not available), enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject (or legally acceptable representative) must be informed about the study as soon as possible and give consent to continue.

In the event of re-introduction of study drug after drug has been withdrawn due to an adverse event requiring drug discontinuation, the investigator must demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, and the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. Prior to re-introduction, the investigator should obtain written permission from the study medical monitor and the IRB. The investigator should also have the subject re-consent using the appropriate re-challenge ICF, explaining that re-introduction of study drug could lead to increased risk of recurrent toxicities or death. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. Subjects who are already being treated at the lowest dose level are not permitted to have re-introduction of study drug at this level. Also cross-over to a different dose regimen is not permitted.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related

monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory pharmacodynamics, biomarker, and pharmacokinetics research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand erdafitinib, to understand differential drug responders, and to develop tests/assays related to erdafitinib. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal from the Study).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

16.2.7. Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be

obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g., curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (e.g., curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

17.2.3. Financial Disclosure

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

Refer to Required Prestudy Documentation in Section 17.2.2 and contracts for details on financial disclosure.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and age at initial informed consent. In cases where the subject is not randomized (subjects enrolled under the DDI substudy will not be randomized) into the study, the date seen and age at initial informed consent will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Inclusion Criteria and Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure

manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (e.g., pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed when all subjects have completed the study treatment or 12 months after last subject is enrolled, whichever is later. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject follow-up survival assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if the subject has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding erdafitinib or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of erdafitinib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived

from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed the study have been submitted for publication, within 18 months after the study end date or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the design of the work, or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

REFERENCES

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Attachment 1: ECOG PERFORMANCE STATUS SCORES

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

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;596):649-655.

Attachment 2: Cockcroft-Gault Formula For Estimated Creatinine Clearance (Crcl)

$$eCR = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dLl)}}$$

OR

$$eCcr = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in µmol/L)}}$$

Where Constant = 1.23 for men and 1.04 for women

http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

Attachment 3: The Stages of Heart Failure – New York Heart Association (NYHA) Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath) .
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Heart Failure Society of America The Stages of Heart Failure – NYHA Classification. Available at http://www.abouthf.org/questions_stages.html. Accessed October 6, 2008.

Attachment 4: Drugs Classified as Strong or Moderate In Vivo Inhibitors and Inducers of CYP3A4/2C9 Enzymes

Strong CYP3A4 Inhibitors

Boceprevir	Conivaptan
Clarithromycin	Indinavir
Grapefruit juice	Itraconazole
Lopinavir	Ketoconazole
Mibefradil	Ritonavir
Nefazodone	Nelfinavir
Posaconazole	Erythromycin
Saquinavir	Troleandomycin
Telaprevir	
Telithromycin	
Voriconazole	
Fluconazole	

Strong Inhibitors: ≥5-fold increase in AUC or >80% decrease in CL.

Moderate to Strong CYP3A4 Inducers

Moderate CYP3A4 Inducers	
Bosentan	Efavirenz
Etravirine	Modafinil
Nafcillin	Lersivirine
Talviraline	Tipranavir
Lopinavir	
Strong CYP3A Inducers	
Avasimibe	Carbamazepine
Barbiturates eg, phenobarbital	Phenytoin
Rifabutin	Rifampin
St. John's wort	Mitotane
Enzalutamide	Apalutamide

Strong Inducers: ≥80% decrease in area under the curve (AUC). Moderate Inducers: 50% to 80% decrease in AUC.

Moderate CYP2C9 Inhibitors

Fluconazole	Amiodarone
Miconazole	Piperine
Oxandrolone	Ataciguat
Tienilic acid	Azapropazone
Bucolome	Sulfaphenazole
Benzbromarone	

Moderate CYP2C9 Inducers

Carbamazepine	Rifampin
Enzalutamide	Aprepitant

Reference: University of Washington's Drug Interaction Database
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#4

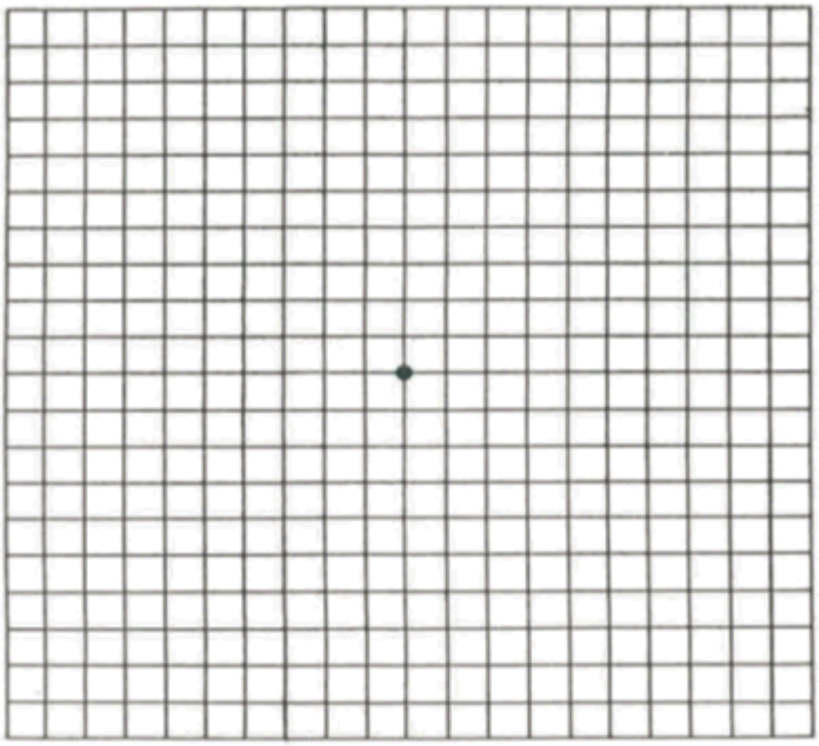
Both these references may not be exhaustive and up-to-date at any given time. Please consult the product information of ongoing and new concomitant medications for the most accurate information on potential moderate to strong inhibitors or inducers of CYP3A4 and CYP2C9.

Attachment 5: Amsler Grid

R.J.'s

AMSLER RECORDING CHART

A replica of Chart No. 1, printed in black on white for convenience of recording



Name _____

Address _____

Date _____ Examiner _____

Attachment 6: RECIST GUIDELINES

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The following information was extracted from Section 3, Section 4, and Appendix I of the New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009). Refer to the European Journal of Cancer article (2009;45(2):228-247) for the complete publication.

Measurability of tumor at baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable:

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Lymph nodes to be considered pathologically enlarged and measurable. A lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness is recommended to be a maximum of 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

Non-measurable:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Specifications by methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response (CR).

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

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

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

Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

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

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

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Timepoint response

It is assumed that at each protocol specified timepoint, a response assessment occurs. Table 22 on the next page provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 23 is to be used.

Best overall response: all timepoints

The *best overall response* is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 22: Timepoint response: patients with Target (+/- non-target) disease

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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable.

Table 23: Timepoint response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; NE = inevaluable.

[a] Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 22 and Table 23.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of progressive disease).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Summary of major changes RECIST 1.0 to RECIST 1.1[a]

	RECIST 1.0	RECIST 1.1	Rationale
Minimum size measurable lesions	CT: 10 mm spiral; 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable.
	Lymph node: not mentioned	CT: ≥15 mm short axis for target ≥10 - <15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive.
Special considerations on lesion measurability	-	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions.
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site.
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes.
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error.
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding.
New lesions		New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD).
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline.
		Special notes: How to assess and measure lymph nodes; CR in face of residual tissue; Discussion of 'equivocal' progression	Frequently asked questions on these topics.

Summary of major changes RECIST 1.0 to RECIST 1.1[a] (Continued)

	RECIST 1.0	RECIST 1.1	Rationale
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint.
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint. Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III; 9 categories collapsed into 5; In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently.
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomized studies where response is not the primary endpoint makes separate 'rules' unnecessary.
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT. Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience.
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1; Appendix III: frequently asked questions	

PD = progressive disease

[a] See publication for references applicable to this table.

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[redacted]

CCI

[redacted]

CCI

[redacted]

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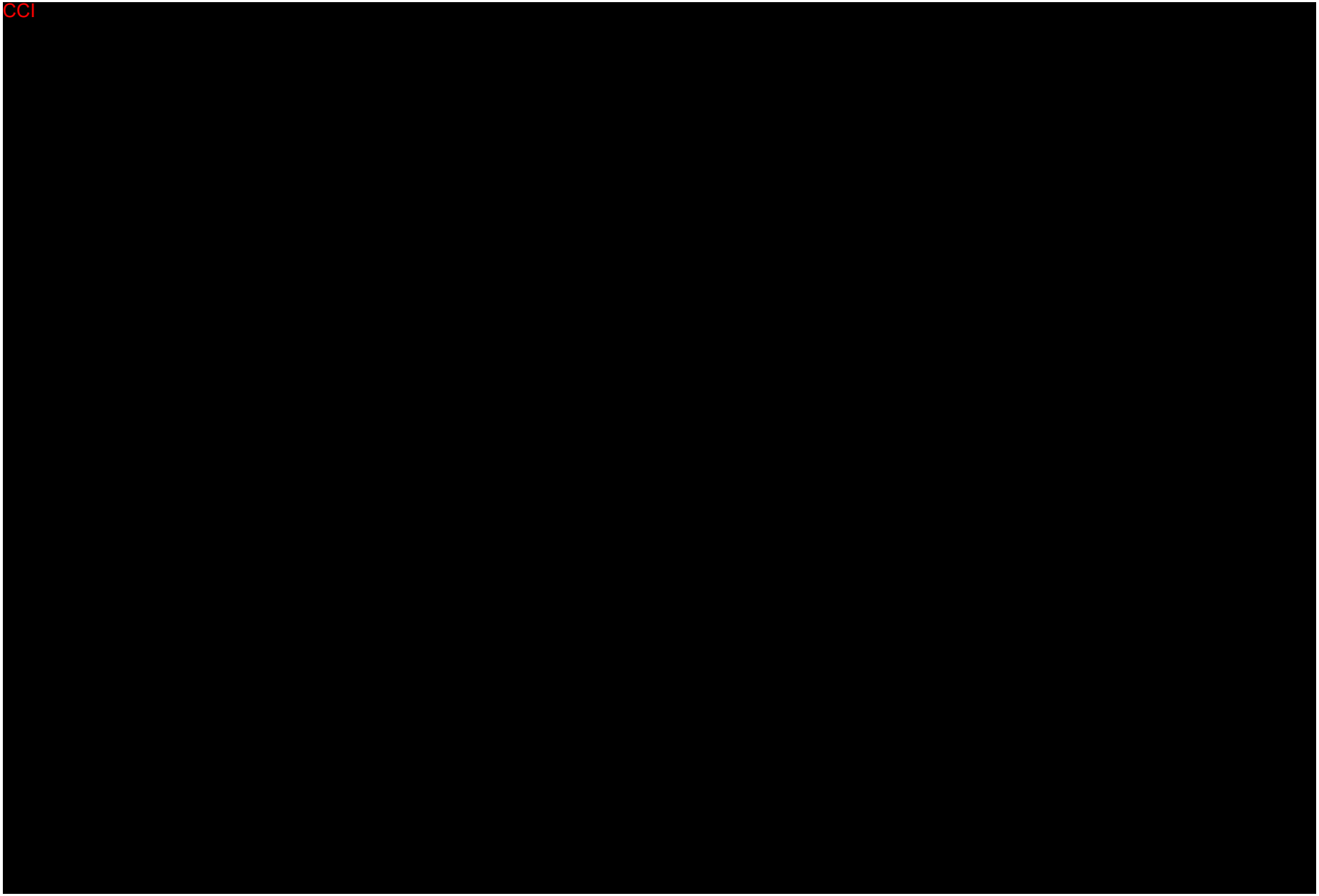
[redacted]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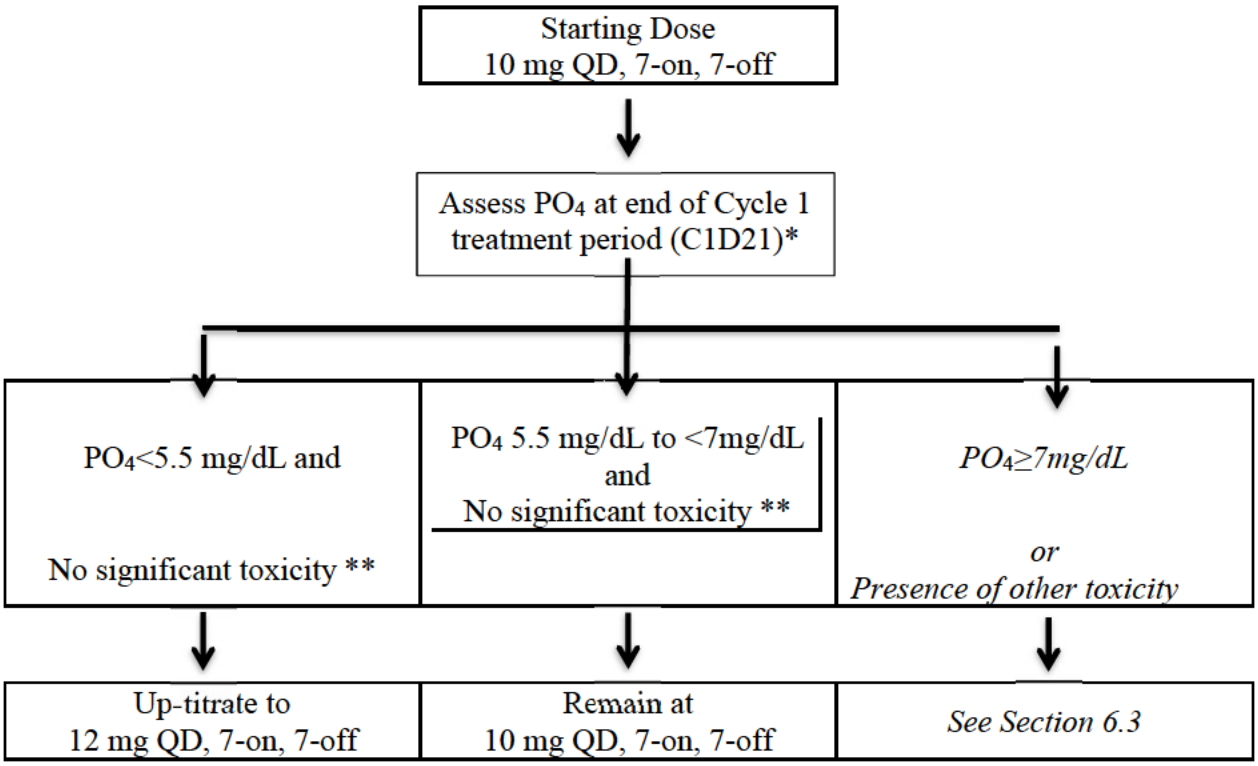
Attachment 8: Dose Up-titration Guidelines Made Obsolete by Amendment 3 and Regimen 3

Guidelines Prior to Amendment 3 (Regimens 1 and 2)

Treatment can be up-titrated or maintained based on phosphate level measured on Cycle 1 Day 21 for Regimen 1, or Cycle 2 Day 1 for Regimen 2, and taking account of observed toxicity to that day, as described in Figure 4 (Regimen 1) and Figure 5 (Regimen 2). The up-titrated dose would be given starting on Cycle 2 Day 1 for both regimens.

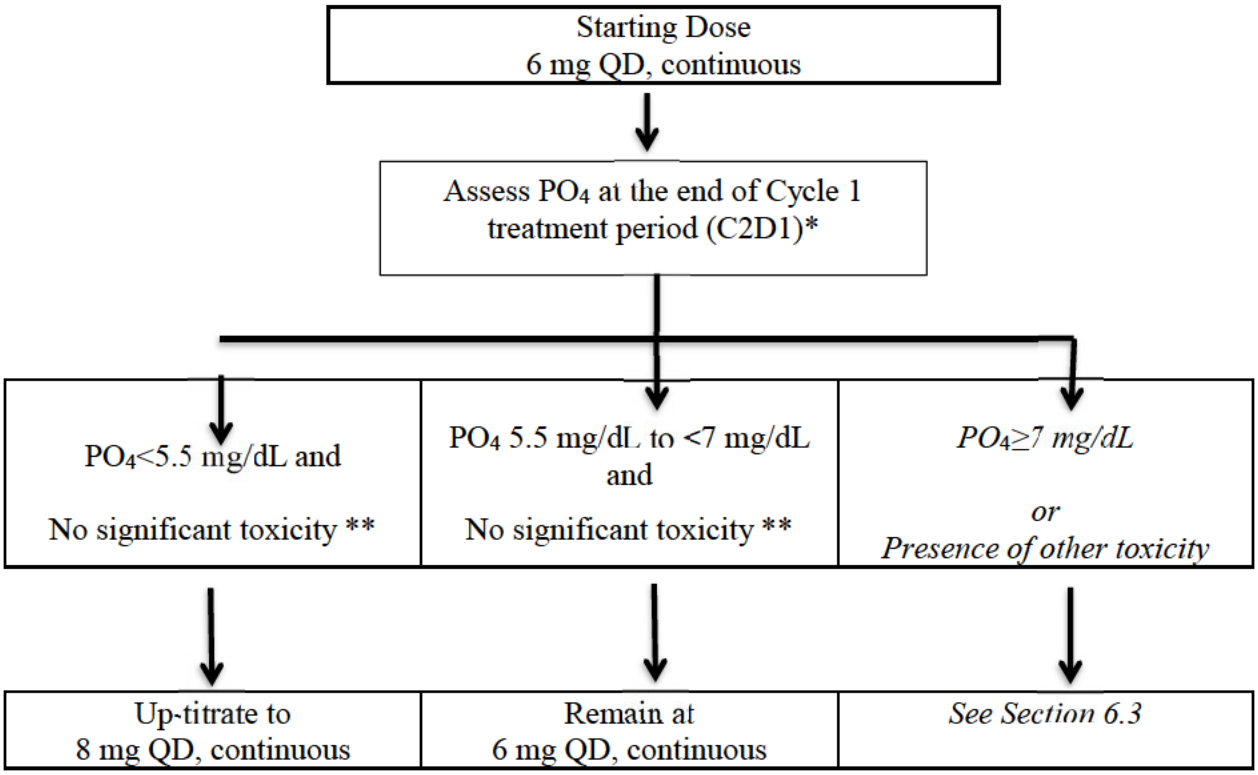
Figure 4: Dose Up-titration for Regimen 1



* Routine phosphate (PO_4) assessments are done as per T&E; dose up-titration decision is based on C1D21 assessment

** Any Grade ≥2 drug-related; any Grade ≥1 Central serous retinopathy (CSR)/retinal pigment epithelial detachments (RPED)

Figure 5: Dose Up-titration for Regimen 2



* PO_4 assessments are done as per T&E; dose up-titration decision is based on C2D1 assessment

** Drug related toxicity during Cycle 1 as determined by investigator. At any time during treatment with study drug, dose interruptions/modifications would be managed by investigator as clinically indicated; specific recommendations on dose reductions and toxicity management are provided throughout Section 6.)

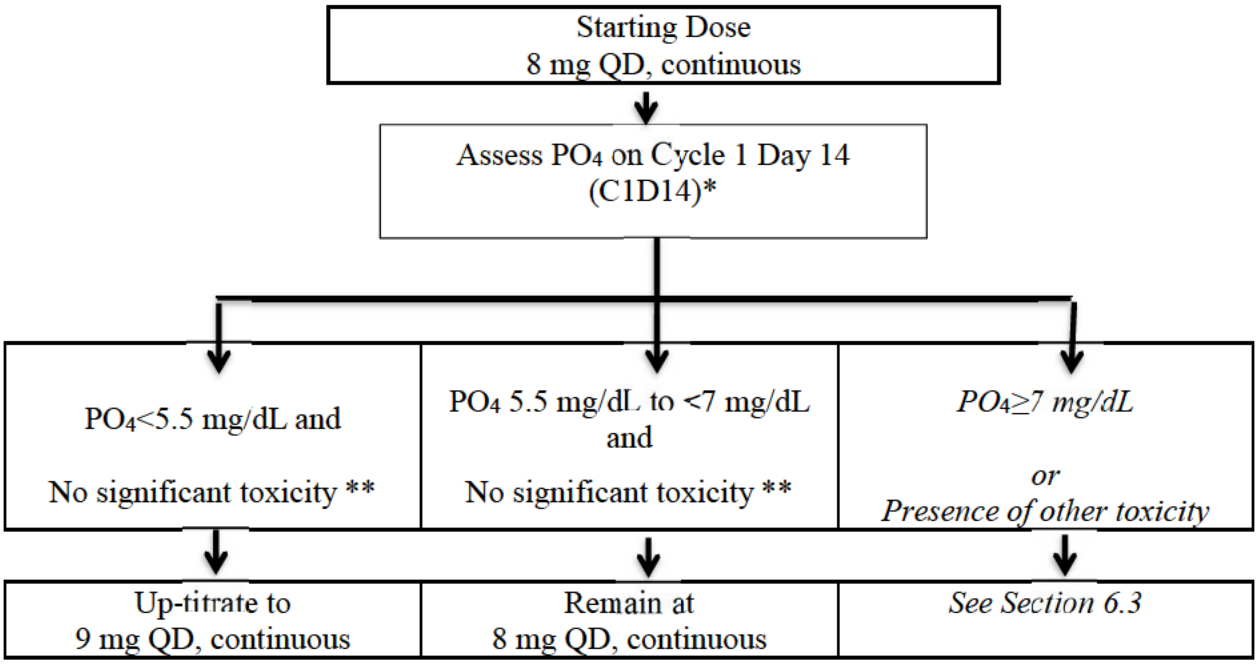
If dose up-titration is achieved for either treatment regimen, further treatment modification or termination will be based on toxicity as described in Table 10. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines are provided in Sections 6.3.1 through 6.3.7.

Guideline for Regimen 3

For subjects in Regimen 3, treatment will be up-titrated or maintained based on phosphate level measured on Cycle 1 Day 14, and taking into account observed toxicity to that day, as described in Figure 6. The up-titrated dose would be given starting on Cycle 1 Day 15 for in Regimen 3.

Further treatment modification or termination will be based on toxicity as described in Table 10. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines are provided in Sections 6.3.1 through 6.3.7.

Figure 6: Dose Up-titration for Regimen 3



* PO_4 assessments are done as per T&E; dose up-titration decision is based on C1D14 assessment and up-titrated dose to be administered starting C1D15

** Drug related toxicity during Cycle 1 as determined by investigator. At any time during treatment with study drug, dose interruptions/modifications would be managed by investigator as clinically indicated; specific recommendations on dose reductions and toxicity management are provided throughout Section 6.)

Attachment 9: Statistical Methods Sections Made Obsolete by Amendment 3

Section 11.1, Sample Size Determination

Approximately 165 subjects with select FGFR genetic alterations may be enrolled in the study on treatment Regimen 1 or 2. There are 2 planned interim analyses (IA1 and IA2), which will be performed for safety, futility, and dose selection. Approximately 110 subjects will be treated at the selected dose regimen and up to 55 subjects may be treated at the dropped dose regimen.

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After a total of 110 subjects are treated at the selected dose regimen, enrollment will be stopped if at least 80 chemo-refractory subjects have been treated at the selected dose regimen. However, if the number of chemo-refractory subjects treated at the selected dose regimen is less than 80, then the enrollment will change as follows:

1) Enrollment of chemo-naïve subjects will be stopped.

2) Enrollment of chemo-refractory subjects may continue until a total of 80 chemo-refractory subjects are treated.

Enrollment of at least 80 chemo-refractory subjects will provide at least 79% power to reject the null hypothesis within the chemo-refractory subgroup under the above assumptions.

At IA1, a sample size of at least 20 response-evaluable subjects per treatment regimen will have at least an 80% probability of selecting the preferred dose regimen, assuming the following: 1) the true response rates of one or both regimens is at least 10%; 2) the preferred dose has at least a 30% higher response rate than the other dose; and 3) the dose selection criteria as specified in Section 11.8 are followed.

If both dose regimens are continued until IA2, a sample size of at least 40 response-evaluable subjects will be enrolled in each regimen and will have at least an 80% probability of selecting the preferred dose regimen if 1 dose regimen has at least a 15% greater response rate than the other regimen and both dose regimens have at least a 20% response rate.

The statistical technical details are described in Attachment 7.

Subjects will be randomly assigned to treatment Regimen 1 or 2. Covariate-adaptive randomization will be used to allocate subjects between Regimen 1 and Regimen 2 until a favorable dose is selected. Randomization will be stratified according to ECOG performance status (0-1 versus 2), hemoglobin level (<10 g/dL versus ≥10 g/dL), FGFR alteration type (translocation versus mutation), pretreatment status (chemo-refractory versus chemo-naive), and disease distribution (presence or absence of visceral metastases: lung, liver, and bone). Randomization will continue until a favorable dose regimen is selected (up to a maximum of 110 subjects total).

Section 11.7, Interim Analysis

There will be 2 planned interim analyses (IA1 and IA2), which will be performed for safety, futility, and dose regimen selection.

The interim safety analyses will be based on the Treated Population (as defined in Section 11.2). The interim analyses for futility and the efficacy portion of dose regimen selection will be based on the RE population (as defined in Section 11.2).

In IA1 and IA2, subjects with unconfirmed response (CR or PR) will be considered responders for futility and dose selection only. However, subjects who have initially demonstrated a CR or PR but on subsequent evaluation have shown PD will not be considered responders. Response will be assessed by the investigators. The Sponsor's Data Review Committee (DRC) will be conducting the interim analyses.

The interim futility boundary will be derived using East® software version 5.3 to control the 1-sided Type-2 error of 0.14. The Type-2 error spending function is from Rho family with parameter of 1.8. Enrollment may be stopped if the pre-specified futility boundary is crossed. However, enrollment will not be stopped for efficacy at these interim analyses (IA1 and IA2).

The interim futility boundaries at IA1 and IA2 are listed in Table 27 below.

Table 27: Interim Futility Boundaries

N (number of subjects in the response-evaluable population)	Declare futility if the number of responders is less than or equal to (≤)
20 – 22	3
23 – 25	4
40 – 41	10
42 – 43	11
44 – 45	12

IA1 will be conducted after at least 20 subjects have been treated per dose regimen and are considered evaluable. The enrollment may continue until 30 subjects per dose regimen have been

treated. The enrollment will be held pending the outcome of the interim analysis, unless the decision is already clear based on available data prior to the interim analysis.

IA2 will be conducted after at least 40 subjects have been treated per dose regimen and considered evaluable (if both dose regimens continue at IA1) or in the selected dose regimen only. The enrollment may continue until 55 subjects have been treated per dose regimen. The enrollment will be held pending the decision of the interim analysis unless the decision is already clear based on available data before the interim analysis.

Section 11.8, Dose Selection Criteria

The Sponsor's DRC will make dose selection decisions, taking into consideration elements of safety, tolerability, and efficacy. Safety and tolerability of each dose regimen will be assessed by consideration of the following (including but not limited to): overall and Grade 3 or higher adverse events, any and Grade 3 or higher drug-related adverse events, any and drug-related serious adverse events, adverse events leading to treatment interruption, dose reduction or treatment discontinuation, percent of planned dose administered, overall tolerability, and mean exposure.

If a dosing regimen is deemed unsafe or intolerable by the DRC, further enrollment into that dosing regimen will be discontinued, and that dose regimen will not be considered for further dose regimen selection.

1. If only 1 dose regimen is safe and tolerable, that dose regimen will be evaluated by efficacy parameters (including, but not limited to, response rate, PFS, and overall survival) to decide if the enrollment into that dose regimen should continue.

2. If both dose regimens are considered to be safe and tolerable, then further evaluation will be made based on efficacy parameters (including, but not limited to, response rate, PFS, and overall survival). The guidelines for dose selection based on response rate alone are outlined in the study CCI [redacted].

Attachment 10: Statistical Methods Sections Made Obsolete by Amendment 3

Attachment 11: Guidance on Study Conduct During a National Disaster for Enrolled Subjects

It is recognized that a national disaster, eg, pandemic, may have an impact on the conduct of this clinical study. In alignment with the recent health authority guidances, the Sponsor is providing guidance for study-related patient management in the event of disruption to the per-protocol conduct of the study as outlined throughout the protocol. These measures are to be followed on a temporary basis. Once the national situation allows, the usual study conduct methods will resume. This guidance does not supersede any local or government requirements or the clinical judgement of the Investigator to protect the health and well-being of patients and site staff. If at any time a subject's safety is considered to be at risk, study drug will be discontinued, and study follow-up will be conducted, as outlined in the protocol. (Note: These measures do not apply to subjects who have not initiated study treatment.)

Scheduled visits for safety monitoring and other protocol required assessments that cannot be conducted in-person will be performed remotely/virtually (eg, telephone contact, telemedicine, remote nursing, remote administration of study drug), where feasible, or delayed until the time at which access is determined to be appropriate by the Investigator and Sponsor. Study assessments requiring investigator judgement, should be conducted by the investigator. At each contact, subjects will be interviewed to collect adverse events data and any changes to concomitant medications. Subjects will also be questioned regarding general health status to fulfill the physical examination requirement.

Flexibility for all protocol-required assessments will be provided on a case by case basis, and with agreement between the Sponsor and Investigator. However, every effort should be made to adhere to protocol-specified assessments, including follow-up, if it is in the best interest of the subject. The Sponsor will continue to monitor the conduct and progress of the clinical study and any changes (eg, delay or discontinuation in recruitment) will be communicated to the sites and health authorities.

Guidance specific to this protocol:

- Missed assessments or change to protocol assessments will be documented in the source documentation and in the case report form. All study conduct performed outside of the protocol should be documented in the source documentation.

- If a site visit is not feasible, the Investigator may discuss with the Sponsor other mechanisms for the subject to receive study drug (eg, direct to patient shipment, obtain from another Investigative Site participating in the study). Any change in dispensing study drug must be documented in the source documentation and eCRF.

- Safety assessments may be conducted at a local facility after discussion with the Sponsor.

- Critical laboratory tests, imaging or other diagnostic tests may be done at an authorized/certified (as legally required nationally) local laboratory or clinical facility. A

copy of the laboratory report must be reviewed by the Investigator and retained, along with the reference ranges, for the source documentation and provided with the eCRF.

- Consenting of subjects for full study screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent. (Remote consenting for molecular eligibility screening is described in the DDI substudy attachment.)

Note: administration of non-live vaccines approved or authorized for emergency use (eg, COVID 19) by local health authorities are allowed before or during this study. For guidance on vaccination, please refer to National Comprehensive Cancer Network. Preliminary recommendations of the NCCN COVID-19 Vaccination Advisory Committee* Version 1.0 1/22/2021. NCCN https://www.nccn.org/covid-19/pdf/COVID-19_Vaccination_Guidance_V1.0.pdf (2021), Garassino, M. C. et al. The ESMO call to action on COVID-19 vaccinations and patients with cancer: Vaccinate. Monitor. Educate. Ann. Oncol. https://doi.org/10.1016/j.annonc.2021.01.068 (2021), and Desai et al COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials Nature Reviews Vol18; 313 https://doi.org/10.1038/s41571-021-00487-z.

Attachment 12: Drug-drug Interaction Substudy

Drug-drug Interaction Substudy to Assess the Effect of Repeated Doses of Erdafitinib on the Single-dose Pharmacokinetics of Midazolam and Metformin in Subjects with Advanced Solid Tumors that Harbor Target FGFR Mutations or FGFR Gene Fusions at Selected Sites

DRUG-DRUG INTERACTION (DDI) SUBSTUDY SUMMARY

This drug-drug interaction (DDI) substudy will assess the effect of repeated doses of erdafitinib on the single-dose pharmacokinetics (PK) of midazolam and metformin in subjects with advanced solid tumors including those with metastatic or surgically unresectable urothelial cancer that harbor target fibroblast growth factor receptor (FGFR) mutations or FGFR gene fusions. This substudy is designed to fulfill the Food and Drug Administration (FDA) post-marketing requirement to evaluate the interaction of repeated doses of erdafitinib with a sensitive cytochrome 450 (CYP) 3A substrate, as well as the post-marketing commitment to evaluate the interaction of repeated doses of erdafitinib with an organic cation transporter 2 (OCT2) probe substrate.

The DDI substudy is described in this attachment, as well as continued treatment with erdafitinib until disease progression or unacceptable toxicity. The Time and Events Schedule for subjects enrolled at the time of the DDI substudy are provided in this attachment (DDI Table 28), as well as the Time and Events Schedule for subjects in the DDI Substudy Long-Term Extension (LTE) Phase (DDI Table 29, Section 9.1.5), with reference to the main study protocol for specific additional information.

Detailed introductory information regarding erdafitinib (nonclinical pharmacology, PK, and clinical experienced) is provided in the Main Protocol Section 1.

DDI Table 28: Time and Events Schedule (For Subjects Enrolled Under the DDI Substudy)

(Note: Upon re-consenting in the Long-term Extension Phase, subjects should follow DDI Table 29. This Time and Event Schedule Should Not be Used)

Visit window	NOTES	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle) Day -2 to C1D15: DDI Treatment Phase			
					Cycles 1, 2, 3		Cycle 4+	EoT Visit[b]
					Day 1	Day 14	Day1	
		N/A	- 35 days	- 14 days	C1:0 days C2, C3: ±2 days	±2 days	±2 days	+7 days after last dose
Screening/Administrative: Check clinical status again before first dose of study drug.								
Molecular Eligibility ICF	Only required before assessing archived tumor tissue tor testing FGFR alterations. See Section 3. Consent for molecular eligibility screening (but not full study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.	X						
Study ICF (For those enrolled under the DDI substudy)	Required before collection of fresh biopsy for FGFR assessment and for subjects meeting molecular eligibility before any other study-related activity. See Section 3.		X					
Inclusion/exclusion criteria	Confirm inclusion/exclusion criteria on Day -3 (See Section 4). The radiological assessment will be done within 35 days of C1D1.		X	X (Day -3) See Note				
Telephone contact	Day -3 Reminder: No food/drink 8 hour before clinic visit on Day -2. Day 12: No food/drink 8 hours before clinical visit on Day 13 AND Not take erdafitinib at home, bring to study site Day 13 (or while at the study site): No food/drink 8 hours before clinical visit on Day 14 AND Not take erdafitinib at home, bring to study site Day 14 (or while at the study site): Not take erdafitinib at home, bring to study site on Day 15			Day -3		D12, 13, 14 (see Notes)		
Medical history including smoking history	Record histological documentation of specific tumor type, prior anticancer therapy, demographic information.		X					
ECOG	See Section 9.3.7.		X					
Optional tumor biopsy for biomarker research	Optional See Section 9.1.	Any time before first dose (Tissue should be from biopsy done after most recent progression prior to enrollment)			C1D15 and at time of disease progression			
Study Drug and Probe Drug Administration								
Erdafitinib	Start with 8 mg on C1D1. Erdafitinib administration will take place after the 24-hour postdose PK sample of metformin is collected.				C1D14 and C1D15 (see Notes)			

	Erdafitinib will be taken at home, except at Cycle 1 on Days 1, 13, 14, and 15 when it will be administered in the clinic. C1D14 and C1D15: Erdafitinib administration will take place after the 24-hour postdose PK sample of midazolam and metformin is collected, respectively. The erdafitinib dose may be up-titrated to 9 mg or maintain at 8 mg based on C1D14 phosphate value. (See Section 6)				Once daily until disease progression, unacceptable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or study termination, whichever occurs first (See Sections 10.2 and 10.3)			
Midazolam, 2.5 mg	Orally administered syrup, solution, or suspension dosage forms are permitted (including pre-filled oral syringes) provided the total dose of midazolam is 2.5 mg. In the case of severe sedation, intravenous flumazenil may be used.		Day -2		C1D13			
Metformin, 1,000 mg	On Day -1: Metformin (1 tablet of metformin, 1000-mg strength) administration will take place after the 24-hour postdose PK sample of midazolam is collected. On C1D14: Erdafitinib and metformin administrations will take place after the 24-hour postdose PK sample of midazolam and the predose PK sample of erdafitinib are collected		Day -1		C1D14			
Safety Assessments: On visit days with multiple measurements (clinical laboratory testing, ECG, PK, and vital sign measurements), the order of assessments will be per local site standards								
Physical examination	See Section 9.3.1		X		X		X C4D1, C5D1, C6D1, then every 3 cycles	X
Vital Sign Measurements	See Section 9.3.2.		X		X	X	X	X
12-lead ECG	ECGs should be performed at approximately the same time of day when possible. See Section 9.3.3.		X		X C2D1 only (predose)		X C4D1 only (pre-dose)	
Ophthalmologic exam	To be performed by an ophthalmologist, for exact assessments see Section 9.3.5		X	A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment , or at regular intervals as deemed necessary by the screening ophthalmologist.				
Amsler Grid Test	To be performed by treating study physician or nurse (as directed by specific site instructions). see Section 9.3.5.		X		X (C2, C3)		X	X
Review adverse events	Collected from the day the DDI Substudy ICF is signed until 30 days after last dose of study drug (see Main Protocol, Section 12).		X					
Concomitant medications	See Section 8 and Main Protocol Section 8.		X					
Urine or serum β-hCG pregnancy test	Women of childbearing potential only. Screening test within 7 days before enrollment. See Section 9.3.6.			-7 days	X predose C1		X	X
Clinical Safety Laboratory Assessments: Clinical laboratory test results (except parathyroid hormone) must be available before the start of treatment at C1D1. Results of previous testing should be available for comparison as clinically necessary. Clinical laboratory testing will be performed at a local laboratory.								

Hematology	If screening sample is drawn within 3 days before C1D1, C1D1 measurement does not have to be repeated. For exact assessment see Section 9.3.4.			X Day -3	X		X	X
Comprehensive metabolic panel	If screening sample is drawn within 3 days before C1D1, C1D1 measurement does not have to be repeated. For exact assessment see Section 9.3.4.			X Day -3	X	X	X	X
Phosphate	Before dosing on C1D1. See Section 9.3.4.			X Day -3	X	X	X	
Parathyroid hormone	After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12 (see Section 9.3.4).			X Day -3	X C2, C3 only	X C1 only	X	
Efficacy and other assessments: The 30-day Safety Follow-up Visit should occur before the start of any subsequent anticancer therapy, if such therapy starts within 30 days after last dose of study drug.								
Radiological assessment	Radiological assessment of response is conducted every 3 months for the first 6 months and then per standard of care thereafter. See Attachment 12, Section 9.5.			X	Every 3 months for the first 6 months and then per standard of care thereafter			
Drug-drug Interaction Assessments								
PK blood sampling for erdafitinib					C1D14: predose C2D1: predose and 3h (±1 h) postdose			
PK blood sampling for midazolam	The time window for the scheduled PK sampling of midazolam is described as follows: ±5 min for 0.5 hr timepoints; ±15 min for 1, 2, 4 and 6 hr timepoints; ±30 min for 8 hr timepoint; ± 2 hr for 24 hr timepoint.			Timing relative to midazolam dosing: Day -2: 0 hr (taken prior to administration of midazolam) Day -2: 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr Day -1: 0 hr (or 24 hr post-dose from Day -2) Taken before metformin predose PK sample and before administration of metformin C1D13: 0 hr (taken prior to the administration of erdafitinib and midazolam) C1D13: 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr C1D14: 0 hr (taken prior to the administration of erdafitinib and metformin)				
PK blood sampling for metformin	The time window for the scheduled PK sampling of metformin is described as follows: ±5 min for 0.5 hr timepoint; ±15 min for 1, 1.5, 2, 3 and 5 hr timepoints; ±30 min for 8 and 10 hr timepoints; ± 2 hr for 24 hr timepoint.			Timing relative to metformin dosing: Day -1: 0 hr (taken prior to administration of metformin) Day -1: 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 5 hr, 8 hr, 10 hr C1D1: 0 hr (taken prior to the administration of erdafitinib) C1D14: 0 hr (taken prior to the administration of erdafitinib and metformin) C1D14: 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 5 hr, 8 hr, 10 hr C1D15: 0 hr (or 24 hr post-dose from Day 14, prior to the next administration of erdafitinib)				
Biomarker Assessments								

Blood (plasma) for ctDNA	See Main Protocol, Section 9.3.2.		X		C2D1, C5D1	X

β-hCG=beta-human chorionic gonadotropin; C=cycle; ctDNA=circulating tumor DNA; CXDX=Cycle X Day X; D=day; DDI=drug-drug interaction; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=End of Treatment; FGFR=fibroblast growth factor receptor; ICF=informed consent form; LTE=long-term extension; PK=pharmacokinetic; SoA=Schedule of Activities;

[a] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 11.

[b] Subjects who re-consent to LTE Phase will not be required to complete EoT visit.

DDI Table 29: Time and Events Schedule (For Subjects Enrolled Under the DDI Substudy): Long-Term Extension Phase
(Note: No data are collected in the eCRF. The clinical database will be closed at this time.)

Visit window	NOTES	Treatment Phase[a]
		Long-term Extension Phase
Informed Consent		
Informed Consent	Subjects will be required to re-consent to participate in the LTE phase.	Prior to Entry
Erdafitinib	Once daily until disease progression, unacceptable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or study termination, whichever occurs first (See Sections 10.2 and 10.3)	Once daily
Safety Assessments		
Physical examination	See Section 9.3.1	Investigator Discretion
Vital Sign Measurements	See Section 9.3.2.	Investigator Discretion
Ophthalmologic exam including Amsler Grid Test	A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment, or at regular intervals as deemed necessary by the screening ophthalmologist. To be performed by an ophthalmologist, for exact assessments see Section 9.3.5. The Amsler Grid Test to be performed by treating study physician or nurse (as directed by specific site instructions). See Section 9.3.5	Per the Investigator's Brochure
Review adverse events	Assessment and management of adverse events per investigator discretion.	X Only serious adverse events will be captured (via the company safety repository)
Concomitant medications	Refer to Investigator's Brochure for precautions and drug interactions.	Investigator Discretion
Urine or serum β-hCG pregnancy test	Women of childbearing potential only. See Section 9.3.6.	Per the Investigator's Brochure
Clinical Safety Laboratory Assessments		
Hematology	To be done per Investigator Discretion.	Investigator Discretion
Comprehensive metabolic panel	To be done per Investigator Discretion.	Investigator Discretion
Phosphate	To be done per Investigator Discretion.	Investigator Discretion
Efficacy and Other Assessments		
Radiological assessment	To be performed at the discretion of the investigator based. See Attachment 12, Section 9.5	Investigator Discretion

β-hCG=beta-human chorionic gonadotropin; DDI=drug-drug interaction; eCRF=electronic case report form; ICF=informed consent form; LTE=Long-Term Extension

[a] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 11.

DEFINITION OF PHARMACOKINETIC PARAMETERS

The definition of the PK parameters is as follows:

C_{max}	maximum observed analyte concentration
C_{trough}	observed analyte concentration just prior to the beginning or at the end of a dosing interval
t_{max}	the actual sampling time to reach the maximum observed analyte concentration
AUC_{last}	area under the analyte concentration versus time curve (AUC) from time 0 to the time of the last measurable (non-below quantification limit [BQL]) analyte concentration
AUC_{∞}	AUC from time 0 to infinite time
λ_z	apparent terminal elimination rate constant, estimated by linear regression using the terminal log-linear phase of the log-transformed concentration versus time curve
$t_{1/2term}$	apparent terminal elimination half-life
CL/F	total apparent clearance
Ratio C_{max}, metabolite /parent	ratio of individual C_{max} values between metabolite and parent
Ratio AUC_{last}, metabolite/ parent	ratio of individual AUC_{last} values between metabolite and parent
Ratio AUC_{∞}, metabolite/ parent	ratio of individual AUC_{∞} values between metabolite and parent
Ratio C_{max}, test/reference	ratio of individual C_{max} values between test and reference treatment
Ratio AUC_{last}, test/reference	ratio of individual AUC_{last} values between test and reference treatment
Ratio AUC_{∞}, test/reference	ratio of individual AUC_{∞} values between test and reference treatment

1. INTRODUCTION

1.1. Erdafitinib

Nonclinical Studies

Erdafitinib has been shown to have high affinity and low nanomolar inhibitory activity for all FGFR family members, FGFR 1, 2, 3 and 4. It has demonstrated activity in FGFR pathway-activated cancer cell lines including squamous non-small cell lung cancer (NSCLC), gastric, breast, hepatocellular cancer, endometrial, bladder, multiple myeloma, and acute myeloid leukemia. Target inhibition and pathway modulation have been demonstrated in cellular models at active cellular concentrations. Brief exposure to erdafitinib has been demonstrated to result in long-term target inhibition. Erdafitinib has been shown to have in vivo antitumor activity in mouse xenograft models of FGFR-driven gastric, bladder, and squamous NSCLC tumor models, and in patient-derived xenografts from squamous NSCLC, gastric, breast, and hepatocellular tumors.

An in vitro metabolism study in human liver microsomes and hepatocytes showed major involvement of cytochrome 450 (CYP) enzymes CYP2C9 and CYP3A4. Long terminal phase half-life of erdafitinib (>50 hours) in plasma was observed resulting in approximately 3-fold accumulation of C_{max} and area under the curve (AUC) following multiple daily dosing.

Clinical Studies

In humans, erdafitinib exhibited dose-related increase in C_{max} and AUC and time-independent PK within the dose range of 0.5 mg to 12 mg, both after single- and multiple-daily dosing. The observed median time to maximum concentration (t_{max}) ranged from 2 to 4 hours (erdafitinib as capsule). Relative bioavailability was comparable under fed and fasted conditions. Erdafitinib is highly bound to plasma proteins such as α1-acid glycoprotein (α1-AGP). Free fractions of erdafitinib in human plasma were small (average ~0.36%). Erdafitinib is a P-glycoprotein (P-gp) substrate.

In a Phase 1 study (Study 42756493EDI1001, n=187), the antitumor effect of erdafitinib was observed in subjects with urothelial cancer with selected FGFR aberrations, as well as other solid tumors. CCI [redacted] The most frequently reported treatment-emergent adverse events (TEAEs) were hyperphosphatemia (65%), dry mouth (46%), asthenia (45%), stomatitis (39%), constipation (37%), and decreased appetite (34%).

In Study BLC2001 (n=210, based on the primary analysis), the antitumor effect of erdafitinib was further demonstrated in subjects with relapsed/refractory advanced urothelial cancer with defined FGFR mutations and gene fusions. Subjects received a starting dose of erdafitinib 8 mg once daily with a dose increase to 9 mg once daily for subjects whose serum phosphate levels were below the target of 5.5 mg/dL between days 14 and 17; a dose increase occurred in 41% of subjects. The ORR (CR + PR) was 32.2% as assessed by a blinded independent review committee, and duration

of response was 5.4 months. The most frequently reported adverse events were hyperphosphatemia (76%), stomatitis (56%), diarrhea (47%), and dry mouth (45%). The follow-up efficacy analysis (cut-off date of 09 August 2019) was consistent with the primary analysis, ie, the time-to-event outcomes such as median DOR (5.98 months), median PFS (5.52 months) and median overall survival (11.30 months) indicate that the efficacy outcomes overall were robust.

For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Erdafitinib Investigator's Brochure.

1.2. Substudy Rationale

The purpose of this DDI substudy is to evaluate the potential inhibition or induction effects of erdafitinib on the CYP3A-mediated metabolism of the probe drug midazolam and the potential inhibition effect on the OCT2-mediated transport of the probe drug metformin as discussed in the following section.

The DDI substudy expands the population to patients with advanced or metastatic solid tumors who have exhausted standard-of-care options. As described in the introduction above, these patients have a dismal prognosis and a high unmet medical need for new therapies. The rationale for the use of erdafitinib as treatment for patients with metastatic urothelial carcinoma provided in the Main Protocol (Section 3.1.1) provides support, along with data from early evaluation of erdafitinib as treatment for advanced solid tumors discussed in this section, for the expansion of the DDI substudy population to those with advanced solid tumors. CCI

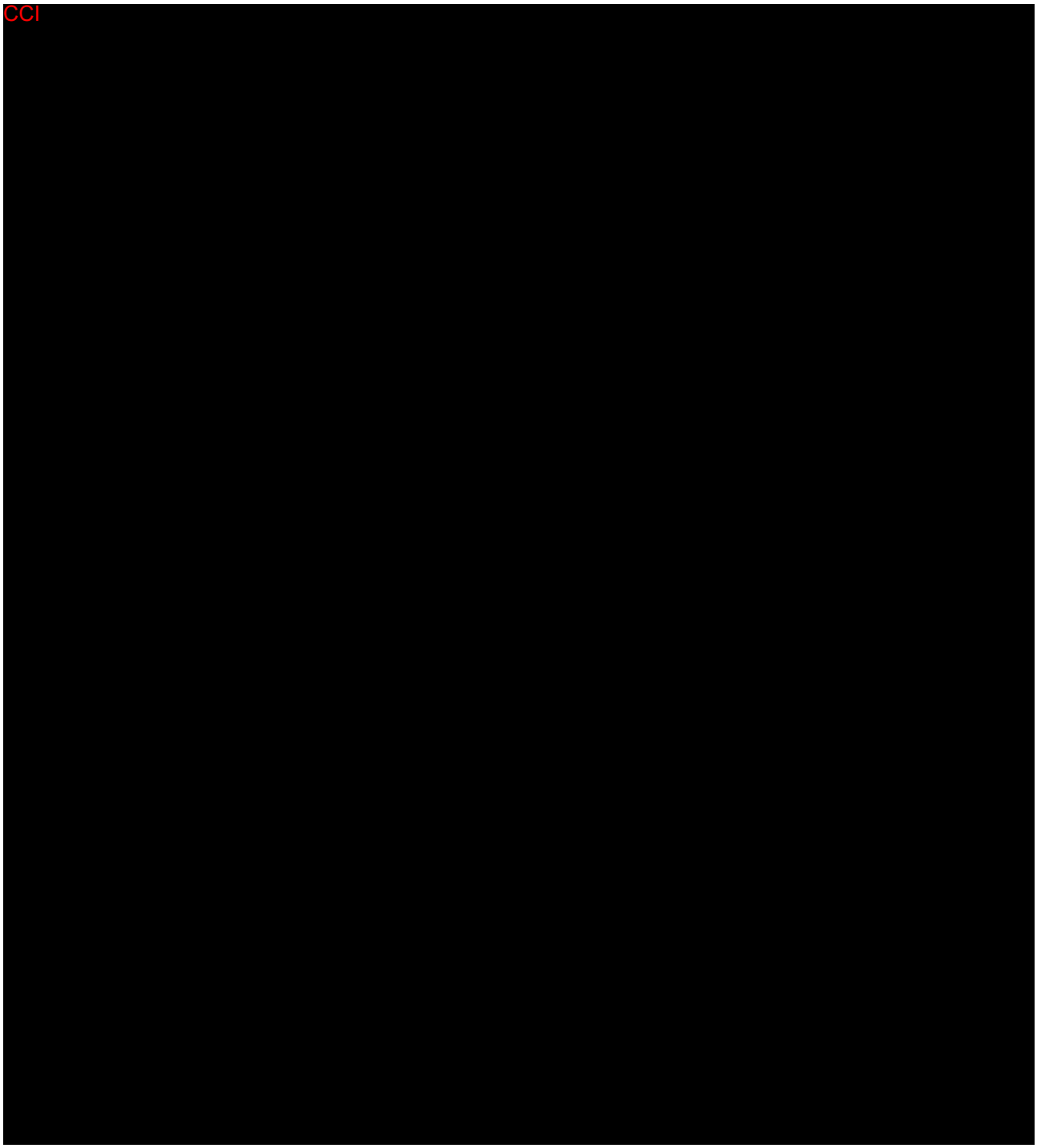
[redacted]

Erdafitinib is a treatment for cancer patients, a population that frequently requires concomitant medications. Time-dependent inhibition of CYP3A-mediated metabolism by erdafitinib can lead to a decreased rate of elimination of concomitantly administered drugs resulting in an increased systemic exposure and possible toxicity. Also, induction of CYP3A-mediated metabolism by erdafitinib can lead to an increased rate of elimination of concomitantly administered drugs resulting in a decreased systemic exposure and possible loss of efficacy. An increased systemic exposure is also possible if in vivo inhibition of OCT2-mediated drug transport by erdafitinib is significant. Currently, there is no existing data on the in vivo effect of erdafitinib on CYP3A enzyme and OCT2 transporter.

The rationale for the use of erdafitinib in FGFR-eligible subjects with metastatic or surgically unresectable urothelial cancer (one of the tumor types in the DDI substudy), as well as background

detail for the earlier Phase 2 dose selection of erdafitinib, is provided in the Main Protocol (Section 3).

CCI



1.3. Study Purpose

As previously mentioned, the purpose of this DDI substudy is to evaluate the potential inhibition or induction effects of erdafitinib on the CYP3A-mediated metabolism of the probe drug midazolam and the potential inhibition effect on the OCT2-mediated transport of the probe drug metformin. In addition, this substudy will ensure characterization of the maximal erdafitinib-

mediated effect on CYP3A and OCT2. The DDI test will be conducted after erdafitinib reaches steady-state exposure. This substudy is designed to fulfill the FDA post-marketing requirement for evaluation of the DDI of repeated doses of erdafitinib with a sensitive CYP3A substrate and the post-marketing commitment for evaluation of the DDI of repeated doses of erdafitinib with a OCT2 probe substrate. The study results will characterize the extent of CYP3A inhibition and/or induction and OCT2 inhibition in vivo by erdafitinib that will guide the update to erdafitinib labeling and will help provide recommendations for administration of co-medications that are substrates for CYP3A4 or OCT2.

1.4. Study Design Rationale

Study Design Rationale

The rationale for the conduct of the DDI assessment after erdafitinib reaches steady-state and the explanation for administration of midazolam and metformin as single doses to the same group of subjects is described in this section.

To ensure characterization of the maximal erdafitinib-mediated effect of CYP3A and OCT2, the DDI test will be conducted after erdafitinib reaches steady-state. Due to the potential tolerability issue of administering multiple doses of erdafitinib to healthy subjects, the study will be conducted in FGFR-eligible subjects, who will be administered single doses of midazolam and metformin before initiating continuous daily dosing of erdafitinib. Once erdafitinib reaches steady-state after approximately 2 weeks, subjects will receive an additional single dose of midazolam and metformin concomitantly with erdafitinib.

In order to more efficiently characterize the potential for in vivo drug interactions in cancer subjects, midazolam and metformin will be administered as single doses to the same group of subjects. Considering the non-overlapping metabolism and disposition pathway of midazolam and metformin, there is no theoretical basis for an interaction between these 2 drugs. To avoid the chance of an unexpected interaction, midazolam and metformin will be dosed on 2 consecutive days. Compared with the administration of individual probe drugs in separate studies, administration of multiple probe drugs in the same group of subjects offers the advantage of reduced study complexity and duration, an important consideration when having to conduct the DDI substudy in cancer subjects with genetic alterations.

Overview of Probe Drugs

Midazolam

Midazolam is a short-acting benzodiazepine commonly used as an anxiolytic and sedative/hypnotic before procedures. Midazolam is commercially available as solution for oral administration. Time to onset of effect is most frequently reported as 10 to 20 minutes. Midazolam is extensively metabolized by CYP3A to 1'-hydroxymidazolam in the liver and intestine and is widely used as a sensitive CYP3A probe drug for evaluating the effect of an inhibitor or inducer on CYP3A activity in vivo. Following a single oral dose, peak midazolam concentrations are achieved at 0.5 to 1 hour. The C_{max} values are reported to average 10 and 24 ng/mL following a single oral dose of 2 and 5 mg, respectively. The elimination half-life values of midazolam have been reported to range from 2.1 to 3.7 hours. The extent of plasma protein binding of midazolam is moderately high and concentration-independent. In adults, midazolam is approximately 97% bound to plasma protein, principally to albumin. Midazolam is a Biopharmaceutics Classification System Class 1 Drug with high solubility and high permeability. Comparable bioavailability and oral absorption are expected for the different formulations of this drug. For more detailed information, refer to the package insert for oral midazolam (as available on the local market).

Metformin

Metformin is a biguanide antihyperglycemic agent that improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption, and increasing insulin-mediated glucose uptake. Metformin is commercially available as tablet for oral administration. Metformin is transported by the organic cation transporters OCT1 and OCT2. The uptake of metformin in the liver, which is the primary target of metformin, is mediated primarily by OCT1. Studies in healthy volunteers suggest that human multidrug and toxin extrusion 1 (MATE1) and MATE2-K also contribute to the renal excretion of metformin.

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

1.5. Background

In the US, erdafitinib (BALVERSA™) was approved on 12 April 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations and has progressed during or following at least 1 line of prior platinum containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum containing chemotherapy. The label also notes that patients are selected for therapy based on an FDA-approved companion diagnostic, ie, the QIAGEN *therascreen*® FGFR RGQ RT PCR Kit that was also approved by the Agency on 12 April 2019. Detailed information regarding erdafitinib, as well as the role of FGFR and FGFR alterations in solid tumors is provided in this section

1.6. Dose Selection Rationale for Probe Drugs

Midazolam

Oral doses used for midazolam in DDI studies in human subjects range from 2 to 10 mg. A 2 mg oral dose of midazolam given in combination with ketoconazole, a strong CYP3A inhibitor, has been reported to be safe and tolerated in healthy subjects, despite increases in midazolam AUC and C_{max} of approximately 16- and 5-fold, respectively. CCI

[redacted]

Metformin

Oral doses used for metformin in DDI studies in human subjects range from 250 to 2,000 mg. In a DDI study, co-administration of a 1,000 mg single oral dose of metformin with vandetanib in subjects wild-type for OCT2 has been reported to be safe and tolerated in healthy subjects, with a 74% increase in AUC_{inf} and a 50% increase in C_{max}. This magnitude of increase in metformin systemic exposure is consistent with the reported impact on metformin exposure known prototypical OCT2 inhibitors (such as cimetidine). CCI

[redacted]

CCI

[redacted]

CCI [redacted]

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the DDI substudy are provided below.

Objectives	Endpoints
Primary	
• To evaluate the effects of repeated dosing of erdafitinib on the single-dose pharmacokinetics (PK) of midazolam (sensitive CYP3A4 substrate) and metformin (sensitive OCT2 substrate) in FGFR-eligible subjects with an unresectable, locally advanced, or metastatic solid tumor malignancy	• The endpoints are PK parameters for midazolam and its metabolite (1-OH-midazolam), and for metformin (in the absence or presence of erdafitinib) including but not limited to C_{max}, t_{max}, AUC_{last}, and AUC_{∞}.

CCI [redacted]

The safety objective of the main study is applicable to subjects enrolled in the DDI substudy (Main Protocol Section 2.1). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, clinical laboratory tests, and Eastern Cooperative Oncology Group (ECOG) performance status at specified time points as described in the protocol.

3. STUDY DESIGN

This is a multicenter, open-label, single-sequence substudy designed to evaluate the effect of repeated doses of erdafitinib on a single-dose of midazolam and metformin given on consecutive days in subjects with advanced solid tumors, including those with metastatic or surgically unresectable urothelial cancer, that harbor target FGFR mutations or FGFR gene fusions.

The study comprises a Screening Phase (both molecular screening and full-study screening, Section 4), a Treatment Phase, an LTE Phase, and an End of Treatment Visit. The beginning of the Treatment Phase up to Day 15 is designated the DDI Treatment Phase. See DDI Table 28 for the Time and Events Schedule for those enrolled under the DDI substudy. See DDI Table 29 for the Time and Events Schedule for subjects in the LTE Phase.

Upon meeting the eligibility criteria and enrollment, subjects will receive pretreatment with single doses of midazolam (Day -2) and metformin (Day -1). Treatment with 8 mg erdafitinib daily begins on Day 1, while single doses of midazolam (Day 13) and metformin (Day 14) will be administered after erdafitinib has reached steady state. Pharmacokinetic samples are collected around the times of the first (Days -2, -1, and 1) and second (Day 13, 14, and 15) administration of probe drugs. The conduct of the DDI Treatment Phase including the collection of PK samples is discussed further in Section 9.2.

Upon completion of the DDI Treatment Phase on Day 15, erdafitinib treatment will continue until disease progression, or until any of the other conditions listed in Section 10.2 are met such as unacceptable toxicity and refusal of further treatment. On Day 15, erdafitinib may be uptitrated to 9 mg erdafitinib daily based on Day 14 serum phosphate levels as described in Section 6. Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, and ophthalmologic examinations conducted as described in the Time and Events Schedule. Further detail regarding safety evaluations is provided in Section 9.3). Radiological assessments are done for the purpose of identification of disease progression (Section 9.5).CCI

Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 11.

The DDI portion of this study will be reported separately from the Main Study, as well as the safety data and biomarker data for subjects who are enrolled under the DDI substudy.

Following approval of Protocol Amendment 9, once the end of study data collection timepoint has been achieved, subjects who continue to benefit from study treatment, as determined by their investigator, may continue to receive access to study treatment as described in DDI Section 9.1.5.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for subjects enrolled in the DDI substudy are provided in the following 2 subsections. If there is a question about the eligibility criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. (Do NOT use the inclusion and exclusion criteria in the main study.)

4.1. Inclusion Criterion for the DDI Substudy

Potential subjects must meet all of the inclusion criteria to be eligible to participate in the study:

1. 18 years of age or older.

2. Criterion modified per Amendment 8

   2.1 Histologic demonstration of an unresectable, locally advanced, or metastatic solid tumor malignancy.

3. Criterion modified per Amendment 8

   3.1 Subject must have had documented disease progression after having received at least one prior line of systemic therapy in the advanced, unresectable, or metastatic setting. Subject does not have standard of care options that have shown meaningful clinical benefit for the relevant underlying histology and line of therapy or the subject is unable to tolerate the therapy. Documented progression of disease is defined as any progression that requires a change in treatment, prior to full study screening.

4. Criterion modified per Amendment 8

   4.1 Subjects with target FGFR mutations (The List of Target FGFR Mutations is provided in DDI Table 31) or * FGFR gene fusions are eligible for enrollment in the substudy, as determined by local** screening.

   * FGFR gene fusions:
   - Have a report suggesting the presence of an intact FGFR kinase domain
     - FGFR fusion with a 3-prime partner (FGFR gene is listed first, eg, FGFR-GENE or FGFR3-TACC3):
       - The FGFR portion of the fusion must involve exon 17 or greater (≥17)
     - FGFR fusion with a 5-prime partner (Partner gene is listed first and FGFR gene is second, eg, GENE-FGFR or KLK2-FGFR2):
       - The FGFR portion of the fusion must involve less than or equal to exon 11 (≤11)
   - Have a named FGFR fusion partner gene (rearrangements, eg, FGFR-FGFR, are not eligible)

   FGFR gene identifiers, canonical transcript identifiers, and kinase domain positions are provided below for reference.

Gene	Ensembl ID	RefSeqID mRNA	Kinase Domain AA Position[1]	Kinase Domain Exons[1]
FGFR1	ENST00000447712	NM_023110.3	478 → 754	Exons 11-17
FGFR2	ENST00000358487	NM_000141.5	481 → 757	Exons 11-17
FGFR3	ENST00000440486	NM_000142.4	478 → 754	Exons 11-17
FGFR4	ENST00000292408	NM_002011.5	467 → 743	Exons 11-17

Pfam= Protein Families (database)

[l]Kinase domains defined by Pfam annotations from NCBI Entrez Gene. Exons of the RefSeq transcript are inclusive of the kinase domain. Exon boundaries defining the kinase domain are equivalent to NM_015850.

**Locally performed or commercial testing results from tissue or blood with NGS tests, direct digital counting methods, or the Qiagen *therascreen*® FGFR RT-PCR test performed in Clinical Laboratory Improvement Amendments (CLIA)-certified or regional equivalent laboratories.

Mutations in this study are defined as protein-coding single nucleotide variant (SNV) and insertions or deletions (indels).

5. ECOG performance status score 0, 1, or 2 (Attachment 1).

6. Criterion modified per Amendment 8

6.1 Adequate bone marrow, liver, and renal function as described below:

- Bone marrow function (without the support of cytokines and/or erythropoiesis-stimulating agent [ESA] in preceding 2 weeks):
  - Absolute neutrophil count (ANC) ≥1000/mm^3
  - Platelet count >75,000/mm^3
  - Hemoglobin ≥8.0 g/dL (without transfusion or demonstrate stability, ie, no significant decline in hemoglobin, for 2 weeks after transfusion).
- Liver function:
  - Total bilirubin ≤1.5 x institutional upper limit of normal (ULN), unless know to have Gilbert's disease, OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN.
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x institutional ULN or ≤5x institutional ULN for subjects with liver metastases (ALT and AST both ≤1.5xULN and alkaline phosphatase ≤2.5xULN).
  - Albumin ≥2.0 g/dL
- Renal function: Creatinine clearance ≥60 mL/min either directly measured via 24-hour urine collection or calculated using Cockcroft-Gault. (Attachment 2)

7. Criterion modified per Amendment 8

7.1 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

a. For women of childbearing potential (defined as: fertile, following menarche and until becoming postmenopausal unless permanently sterile):

- Highly effective method of contraception (failure rate of <1% per year when used consistently and correctly).
- Permanent sterilization methods (for the purposes of this study) include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- Examples of highly effective contraceptives include:

  - user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation; vasectomized partner; sexual abstinence: true abstinence when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.)
  - user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

- agrees to remain on a highly effective method of contraception during the study and for at least 3 months after the last dose of study drug
- agrees to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after the last dose of study drug
- not breastfeeding and not planning to become pregnant during the study and for at least 3 months after the last dose of study drug
- advised on egg preservation prior to entering the study

b. For men who are sexually active with women of childbearing potential:

- agrees to use a condom with spermicidal foam/gel/film/cream/suppository
- agrees to not donate sperm during the study and for at least 3 months after the last dose of study drug
- not planning to father a child during the study or within 3 months after the last dose of study drug
- advised on sperm banking prior to entering the study

8. Negative pregnancy test (urine or serum beta human chorionic gonadotropin [β-hCG]) at Screening (ie, screening test within 7 days before treatment) for women of child-bearing potential who are sexually active.

9. Subject (or his/her legally acceptable representative) must sign the informed consent documents indicating that they understand the purpose of procedures required for the DDI substudy and continuation of treatment until disease progression and are willing to participate in the study.

DDI Table 31: List of Target Fibroblast Growth Factor Receptor (FGFR) Mutations

Gene	Variant
FGFR1	K656E
FGFR1	R189C
FGFR1	S125L
FGFR1	P150S

Gene	Variant
FGFR2	C390YS
FGFR2	E565G
FGFR2	E565Q
FGFR2	S252L
FGFR2	C382F
FGFR2	P253L
FGFR2	R251Q
FGFR2	A389T
FGFR2	S252P
FGFR2	R210Q
FGFR2	S252T
FGFR2	R203H
FGFR2	S252A
FGFR2	S351C
FGFR2	Y340C
FGFR2	G338R
FGFR2	S354C
FGFR2	L617F
FGFR2	W290R
FGFR2	L550F
FGFR2	M535I
FGFR2	Y308C
FGFR2	E777*
FGFR2	K641R
FGFR2	T370R
FGFR2	W72C
FGFR2	K526E
FGFR2	D304N
FGFR2	K659M
FGFR2	S267P
FGFR2	E731K
FGFR2	M537I
FGFR2	F276C
FGFR2	I547V
FGFR2	E565A
FGFR2	V395D
FGFR2	W290C
FGFR2	R678G
FGFR2	E777K
FGFR2	C382R
FGFR2	S372C
FGFR2	A315T
FGFR2	D101Y
FGFR2	Y375C
FGFR2	E219K
FGFR2	L770*
FGFR2	L770V
FGFR2	K659N

Gene	Variant
FGFR3	M528I
FGFR3	K650T
FGFR3	S371G
FGFR3	K650N
FGFR3	G380E
FGFR3	E627D
FGFR3	Y373N
FGFR3	Y373H
FGFR3	D641N
FGFR3	S249Y
FGFR3	A391V
FGFR3	S249F
FGFR3	S371R
FGFR3	R248H
FGFR3	G370S
FGFR3	R669Q
FGFR3	P250R
FGFR3	Y278C
FGFR3	L324V
FGFR3	S84L
FGFR3	R750C
FGFR3	S433C
FGFR3	K650Q
FGFR3	S371C
FGFR3	S249C
FGFR3	G370C
FGFR3	R248C
FGFR3	Y373C

Gene	Variant
FGFR4	Y367C

Note: Numbering may differ depending on which reference sequence was used.

4.2. Exclusion Criterion for the DDI Substudy

Potential subjects who meet any of the following criteria will be excluded from participation in the study:

1. Treatment with any other investigational agent in another clinical study within 30 days prior to randomization.
2. Persistent phosphate level >ULN during screening (within 14 days of treatment and prior to Cycle 1 Day 1) despite medical management.
3. History of uncontrolled cardiovascular disease including:

   any of the following in the preceding 3 months: unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure (Main Protocol, Attachment 3), cerebrovascular accident, or transient ischemic attack.
   a. QTc prolongation as confirmed by ECG assessment at screening (Fridericia; QTc >480 milliseconds).
   b. Pulmonary embolism or other venous thromboembolism within the preceding 2 months
4. Any reason that in the view of investigator would substantially impair the ability of the subject to comply with study procedures and increase the risk to the subject.
5. Females who are pregnant, breast-feeding, or planning to become pregnant within 3 months after the last dose of study drug and males who plan to father a child while enrolled in this study or within 5 months after the last dose of study drug.
6. Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, or Grade 1 neuropathy).
7. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.
8. Major surgery within 4 weeks before enrollment.
9. Known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection (subjects with history of hepatitis C infection but negative hepatitis C virus polymerase chain reaction (PCR) test and subjects with hepatitis B with positive hepatitis B surface antibody are allowed.) For known active AIDS (human immunodeficiency virus (HIV) infection), unless the subject has been on a stable anti-retroviral therapy regimen for the last 6 months or more, has had no opportunistic infections in the last 6 months, and has CD4 count >350.
10. Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients (see current version of the Investigator's Brochure).
11. Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade.

12. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

    a. skin cancer treated within the last 24 months that is considered completely cured

    b. adequately treated lobular carcinoma in situ (LCIS) and ductal CIS

    c. history of localized breast cancer and receiving antihormonal agents, or history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy

13. Medications known to induce or inhibit CYP3A or CYP2C9, or inhibit OCT2 must be discontinued or substituted 1 week prior to the first intake of the probe drugs, or must be temporarily interrupted during the course of the DDI substudy (see tables in DDI Section 8).

14. Known allergies, hypersensitivity, or intolerance to any of the probe drugs or excipients.

15. Use of midazolam and metformin from 2 weeks before the first intake of probe drugs (for DDI purpose on Day -2 or Day -1), and until the last PK sample is collected on Study Day 15 (last 24-hour PK sampling).

16. Known contraindication to the use of metformin and/or midazolam, based on the local prescribing information.

17. Criterion modified per Amendment 8

    The known* presence of FGFR gatekeeper and resistance alterations. Mutations in the following positions: FGFR1 V561; FGFR2 V564; FGFR3 V555; FGFR4 V550; FGFR1 N546; FGFR2 N549; FGFR3 N540; and FGFR4 N535.

    *Observation of a gatekeeper/resistance alteration in the local or central report. If the local test does not screen for all four FGFRs, eg FGFR4, the local report remains evaluable for molecular screening.

    Subjects with known germ-line mutations will not be eligible.

18. Criterion modified per Amendment 8

    For NSCLC subjects only - pathogenic somatic mutations in EGFR* or BRAF V600E, or any gene fusions in the following genes: ALK, ROS1, or NTRK.

    *Assessment of these genes may be performed per institutional standard and do not have to be assessed via NGS.

Subjects will be allowed to be rescreened only once for eligibility (both molecular and main-study eligibility) after consultation with the sponsor's medical monitor, if the investigator has a valid reason to rescreen (eg, resolution of conditions previously meeting the exclusion criteria, availability of a different tumor tissue for FGFR testing, molecular test internal quality control failure).

5. TREATMENT ALLOCATION AND BLINDING

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

6.1. Administration of Study Drug

The Time and Events Schedule (DDI Table 28) provides detailed dosing information for administration of erdafitinib, midazolam, and metformin. Midazolam and metformin will only be administered at the study site during the DDI portion of the substudy. Erdafitinib will be administered on an outpatient basis, except at Cycle 1 on Days 1, 13, 14, and 15.

During the LTE Phase, dispensation of erdafitinib will occur every 1 to 6 months in accordance with local practice. Subjects will be supplied with 1 to 6 months of erdafitinib at each visit. Subjects can be withdrawn if an alternative access to erdafitinib is available, or marketing authorization is obtained in accordance with local regulations.

Midazolam 2.5 mg will be administrated orally as a syrup, solution, or suspension dosage form (including pre-filled oral syringes). Metformin will be administered orally as a single tablet of 1,000-mg strength. Erdafitinib 8 mg will be administered orally once daily, with the possibility of up-titration to 9 mg once daily based on Day 14 serum phosphate levels as described further in this section).

Instructions regarding the administration of erdafitinib, midazolam, and metformin are outlined below:

- Study drug administration should be at approximately the same time in the morning from Day -2 to Day 14. Subjects should not take erdafitinib on the morning of study visits designated for PK sampling until the appropriate time during the site visit. Specifically, subjects will be contacted by telephone and reminded NOT to take their morning dose of erdafitinib at home but rather will be instructed to bring erdafitinib to the study site.
- Day -2 and Day -1: midazolam (Day -2) and metformin (Day -1) will be administered orally after an overnight fast of at least 8 hours. Subjects will continue to fast from food and drink (except water) for another 4 hours after dosing. The study drugs are to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact and subjects should not attempt to dissolve them in water, tablets must not be broken or chewed. Subjects should avoid consuming grapefruit or Seville oranges due to CYP450 3A4/5 inhibition.
- Erdafitinib self-administered at home (Cycle 1: Day 2 to Day 12, Day 16, and daily thereafter) may be taken with or without food during the morning hours. Erdafitinib administration will take place at the site on Cycle 1 Days 1, 13, 14, and 15.
- Cycle 1 Day 13 and Day 14: erdafitinib (daily), midazolam (Cycle 1 Day 13), metformin (Cycle 1 Day 14) will be administered orally after an overnight fast of at least 8 hours, one after the other, ie, first erdafitinib and then midazolam (Cycle 1 Day 13) and metformin (Cycle 1 Day 14) within 2 minutes with a glass of water. Subjects will continue to fast from food and drink (except water) for another 4 hours after dosing.

- In the case of severe sedation by oral midazolam, the benzodiazepine antagonist flumazenil may be used via intravenous route per local standard of care.

Erdafitinib treatment will continue until disease progression, or until any of the other conditions listed in Section 10.2 are met such as unacceptable toxicity and refusal of further treatment.

If a dose is missed, then it can be taken up to 6 hours after the scheduled time; the subject may return to the normal schedule the following day. If more than 6 hours have passed since the missed dose, the dose should be skipped and the subject should continue treatment at the scheduled time the following day. If vomiting occurred with drug administration, no replacement dose will be taken and any such event that occurs up to 4 hours following dose administration must be recorded on the electronic case report form (eCRF).

The study drug will be dispensed at the first visit of each cycle. All study drug doses dispensed must be captured in the source documents, and the eCRF. Unused study drug in the issued bottles and empty bottles must be returned to the site at each study visit. Study drug must be returned to the site when a subject discontinues study treatment. Returned tablets may not be re-issued in this study or outside the study (follow study drug accountability guidelines in the Site Investigational Product Manual). During the LTE Phase, the study drug dispensation will be performed at the investigator's discretion.

The exposure of erdafitinib is predicted to increase by 50% in subjects with the CYP2C9 *3/*3 genotype, estimated to be 0.4% to 3% of the population among various ethnic groups. Therefore, monitor for increased adverse reactions in subjects who are known or suspected to have CYP2C9*3/*3 genotype. Dose titration is guided by serum phosphate levels in all subjects irrespective of genotype; therefore, the implications of higher exposures of erdafitinib including safety may be addressed.

6.2. Dose Uptitration Guidelines

See Main Protocol Section 6.2.

6.3. Dose Modifications and Dose Delays (Management of Toxicities)

Guidance for dose modification and management of toxicities including eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity are found in the Main Protocol (Section 6.3).

7. TREATMENT COMPLIANCE

See Main Protocol Section 7.

8. PROHIBITIONS AND RESTRICTIONS

During the DDI portion of the substudy, potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the DDI substudy to be eligible for participation:

- Subjects should discontinue prohibited medications listed in DDI Table 32 and DDI Table 33.

- Subjects should not consume grapefruit, grapefruit juice, or Seville oranges (or products containing grapefruit or Seville oranges) from 72 hours before the first intake of the probe drugs (Study Day -2 onwards) until after the last PK sample is collected on Study Day 15 (Cycle 1 Day 15). This restriction is also in place after completion of the 14-day DDI Treatment Phase during continued treatment with erdafitinib.
- Subjects may not consume food or beverages containing alcohol on Day -3 to Day 1, and on Day 12 to Day 15. Alcohol intake should not be more than 1 drink per day on a daily basis on Days -5, -4, -3, and on Days 10, 11 and 12. Note that 1 drink is equivalent to 5 ounces of wine, 12 ounces of beer, or 1 ounce of hard liquor.
- Subjects should not use midazolam and metformin from 2 weeks before the first intake of probe drugs and until after the last PK sample is collected on Study Day 15 (Cycle 1 Day 15), as it will interfere with the DDI evaluation.

Moderate to strong CYP3A4 inducers and inhibitors (DDI Table 32) and moderate CYP2C9 inducers and inhibitors and OCT2 inhibitors (DDI Table 33) are prohibited one week before the start of dosing (on Day -2) until the end of the DDI Treatment Phase (Cycle 1 Day 15).

After completion of the DDI portion of the study, subjects will follow the instruction regarding concomitant therapy in the Main Protocol (Section 8).

DDI Table 32: Prohibited Concomitant Medications: Moderate to Strong CYP3A4 Inducers and Inhibitors

Moderate to Strong CYP3A4 Inducers

Moderate CYP3A4 Inducers: 50% to 80% decrease in area under the curve (AUC)	
Bosentan	Efavirenz
Etravirine	Modafinil
Nafcillin	Lersivirine
Talviraline	Tipranavir
Lopinavir	
Strong CYP3A Inducers: ≥80% decrease in AUC.	
Avasimibe	Carbamazepine
Barbiturates eg, phenobarbital	Phenytoin
Rifabutin	Rifampin
St. John's wort	Mitotane
Enzalutamide	Apalutamide

Moderate to Strong CYP3A Inhibitors

Moderate CYP3A4 Inhibitors	
Netupitant	Darunavir
Atazanavir/ritonavir	Darunavir/ritonavir
Amprenavir	Diltiazem
Atazanavir	Verapamil
Grapefruit juice	Imatinib
Aprepitant	Crizotinib
Casopitant	Tofisopam
Cimetidine	Lomitapide
Nilotinib	
Strong CYP3A4 Inhibitors: ≥5-fold increase in AUC or >80% decrease in CL	
Boceprevir	Conivaptan
Clarithromycin	Indinavir
Lopinavir	Itraconazole
Mibefradil	Ketoconazole
Nefazodone	Ritonavir
Posaconazole	Nelfinavir
Saquinavir	Erythromycin
Telaprevir	Troleandomycin
Telithromycin	Fluconazole
Voriconazole	

DDI Table 33: Prohibited Concomitant Medications: Moderate CYP2C9 Inducers and Inhibitors and OCT2 Inhibitors and Substrates

Moderate CYP2C9 Inhibitors and Inducers

Moderate CYP2C9 Inhibitors	
Fluconazole	Amiodarone
Miconazole	Piperine
Oxandrolone	Ataciguat
Tienilic acid	Azapropazone
Bucolome	Sulfaphenazole
Benzbromarone	

Moderate CYP2C9 Inducers	
Carbamazepine	Rifampin
Enzalutamide	Aprepitant

OCT2 Inhibitors

Abacavir	Gefitinib
Amantadine	Imatinib
Amitriptyline	Irinotecan
Amsacrine	Nilotinib
Bosutinib	Ondansetron
Cimetidine	Pentamidine
Clopidogrel	Phenoxybenzamine
Clonidine	Prazosin
Dasatinib	Propafenone
Doxazosin	Quetiapine
Erlotinib	Quinidine
Rabeprazole	Verapamil
Repaglinide	Zidovudine
Sunitinib	

OCT2 Substrates (Transporters)

6-beta-hydroxycortisol	Oxyplatin
Amantadine	Oxybutynin
Carboplatin	Phenformin
Cisplatin	Picoplatin
Histamine	Pramsorafenib
Lamivudine	Tropisetron
Linagliptin	Trospium
Metformin	Varenicline
Umeclidinium	

University of Washington's Drug Interaction Database:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#4
These references may not be exhaustive and up-to-date at any given time. Please consult the product information of ongoing and new concomitant medications for the most accurate information.

9. STUDY EVALUATIONS

9.1. Study Procedures

The Time and Events Schedule in the DDI substudy summarizes the frequency and timing of efficacy, safety, pharmacokinetic, and biomarker assessments for this study. See DDI Table 29 for the Time and Events Schedule for LTE phase.

For subjects who will have the optional fresh tissue biopsy at baseline (done after the most recent progression prior to enrollment), every effort should be made to conduct another biopsy at C1D15 and disease progression.

The total blood volume is (approximately 44 mL at screening, 316 mL for Cycles 1 to 3, 24 mL for each subsequent cycle [except for Cycle 5 that is approximately 44 mL], and 37 mL at the end of treatment visit) is considered within the normal range allowed for this subject population over this time frame. For adult subjects, the amount of blood collected is less than the American Red Cross standard blood donation of 500 mL over 60 days[a] and is aligned with World Health Organization blood donation guidelines.[b]

9.1.1. Molecular and DDI Substudy Screening

Subjects considered for this substudy will undergo assessment of molecular eligibility after consent is obtained using the molecular eligibility informed consent form (ICF). Consent for molecular eligibility screening (but not full study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance. Subjects must meet appropriate molecular eligibility criteria, as determined by available test results (from tissue or blood) using next-generation sequencing (NGS), direct digital counting methods, or the Qiagen Therascreen® FGFR RGQ RT-PCR kit. After meeting molecular eligibility, potential subjects will provide consent using the DDI Substudy ICF and will be assessed using the Inclusion and Exclusion Criteria in Section 4.

Archival tumor tissue for concordance testing of FGFR alterations from local testing will be sent to the central laboratory for alterations detected by the Qiagen Therascreen® FGFR RGQ RT-PCR kit if available.

[a] American Red Cross. Available at: http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics. Accessed 29 March 2019.

[b] World Health Organization. Blood donor selection. Guidelines on assessing donor suitability for blood donation. https://www.who.int/bloodsafety/publications/bts_guideline1/en/ Accessed 13 May 2019.

9.1.2. Pretreatment with Probe Drugs

Qualified subjects will be pretreated with the probe drugs on 2 consecutive days (midazolam 2.5 mg on Day -2 and metformin 1,000 mg on Day -1) before administration of erdafitinib under fasting conditions (ie, no food should be eaten at least 8 hr before dosing and 4 hr after dosing). A full PK profile will be collected before dosing and over 24 hours after dosing with midazolam and metformin in order to obtain baseline PK data for these probe drugs.

9.1.3. Treatment Phase (DDI Treatment Phase Through Day 15)

The DDI Treatment Phase begins after the 24-hour PK sample for metformin (administered on Day -1) is collected on Cycle 1 Day 1. During this phase, erdafitinib 8 mg will be taken once daily beginning on Day 1. This first dose will be administered at the study site in the morning after the 24-hour PK sample for metformin is collected. From Days 2 to 12, erdafitinib will be self-administered at home with or without food at approximately the same time each day in the morning. Subjects will record the date and time of each erdafitinib dose on Days 2 to 12 on a diary card. Compliance with the erdafitinib assigned dose and dose administration time will be confirmed by study personnel during study visits (ie, via subject diaries). If a subject cannot read or write for any reason, it is acceptable for the subject to have diary card information completed by an independent witness.

During the DDI Treatment Phase, midazolam and metformin are administered again on Day 13 and Day 14, respectively. On Day 13, subjects will NOT take their morning dose of erdafitinib at home but will bring erdafitinib to the study site. Study personnel must contact the subject the day before Day 12 by telephone to remind the subject of this requirement. A predose PK sample for midazolam will be collected before administration of a single oral dose of 8 mg erdafitinib followed by a single oral dose of 2.5 mg midazolam (taken within 2 minutes of each other with a glass of water) under fasting conditions. A full PK profile for midazolam will then be collected over the following 24 hours.

On Day 14, subjects will NOT take their morning dose of erdafitinib at home but will bring erdafitinib to the study site. Study personnel must remind the subject of this requirement while in the clinic on Day 13 or by telephone. A predose PK sample taken for erdafitinib and a 24-hour postdose PK sample for midazolam will be collected before administration of a single oral dose of 8 mg erdafitinib followed by a single oral dose of 1,000 mg metformin (taken within 2 minutes of each other with a glass of water) under fasting conditions. A full PK profile for metformin will then be collected over the following 24 hours.

On Day 15, subjects will NOT take their morning dose of erdafitinib at home but will bring erdafitinib to the study site. Study personnel must inform the subject of this requirement while in the clinic on Day 14 or by telephone. The 24-hour postdose PK sample for metformin will be collected prior to the erdafitinib dose on Day 15.

The full PK profile of midazolam and metformin on Day 13 and Day 14, respectively, in the presence of erdafitinib at steady-state, will be compared with the baseline full PK profiles (prior to erdafitinib dosing) to assess the extent of effects of erdafitinib daily dosing on CYP3A and

OCT2 activities. A detailed overview of the dosing regimen for erdafitinib and the probe drugs, and the PK sampling timepoints for erdafitinib and the probe drugs are provided in the Time and Events Schedule in the DDI Substudy.

9.1.4. Continued Treatment with Erdafitinib

Upon completion of the DDI Treatment Phase, erdafitinib will be continued until disease progression or unacceptable toxicity, or until another condition for treatment discontinuation is met (Section 10.2). A treatment cycle with erdafitinib will consist of 4 weeks (28 days). Radiological assessments will be conducted every 3 months for the first 6 months and thereafter per standard of care for assessment of response (and disease progression) by the investigator.

9.1.5. Long-Term Extension Phase

Following approval of Protocol Amendment 9, once the end of study data collection timepoint has been achieved, subjects who continue to benefit from study treatment, as determined by their investigator, may continue to receive access to study treatment on this study, in the LTE Phase or any other post-trial access program, when permitted by local regulations. Provision of erdafitinib through the study may continue until the subject can commercially access study treatment within the local healthcare system, until the investigator decides it is in the best interest of the subject that study treatment be discontinued, or until 2 years after local marketing authorization is obtained for the studied indication, whichever comes first.

There are no protocol-required assessments during the LTE Phase; radiological and safety assessments including laboratory assessments will be performed based on the investigator's discretion (DDI Table 29). Data for subjects in the LTE Phase will not be added to the clinical database. All SAEs and associated concomitant therapies will be reported through the Company Safety Repository.

9.2. Pharmacokinetic Evaluations

9.2.1. Pharmacokinetic Evaluations

Serial venous blood samples (2 mL/time point/analyte) will be collected for measurement of plasma concentrations of midazolam and its metabolite, 1-OH-midazolam, and metformin, at timepoints specified in DDI Table 28 and processed, handled, and identified according to the Laboratory Manual. An indwelling intravenous cannula may be used for blood sample collection. If a mandarin (obturator) is used, blood loss due to discard is not expected.

The exact dates and times of dosing, and exact dates and times of blood sampling must be recorded on the laboratory requisition form and appropriate eCRF in the clinical database. If vomiting of probe drugs (midazolam, metformin) or study drug (erdafitinib) occurs within 4 hours of dosing, the time of vomiting should also be recorded on the eCRF.

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9.2.2. Analytical Procedures

Midazolam and metformin plasma samples will be analyzed to determine the concentrations of midazolam, and 1-OH-midazolam, and metformin, using validated, specific, and sensitive Liquid Chromatography-Tandem Mass Spectrometry methods by, or under the supervision of, the sponsor's Bioanalytical Laboratory Department of Bioanalysis.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

9.2.3. Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the sponsor in accordance with the current Clinical Pharmacokinetics Guideline. Additional PK parameters and details of the PK analysis, including data handling rules and software used to perform PK analysis will be provided in the Clinical Pharmacology Analysis Plan. Based on the individual plasma concentration-time data based on sampling schedule per DDI Table 28 (not including erdafitinib timepoints), using the actual sampling times, the following PK parameters will be derived:

- Erdafitinib:
  - Predose concentration of erdafitinib on Cycle 1 Day 14
- Midazolam and its metabolite 1-OH-midazolam, and metformin:
  - C_{max}, t_{max}, AUC_{last}, AUC_{∞}, λz, $_{t1/2term}$
  - CL/F (only for parent compounds midazolam and metformin)
  - Ratio $C_{max,\ metabolite/parent}$, Ratio $AUC_{last,\ metabolite/parent}$, Ratio $AUC_{\infty,\ metabolite/parent}$ (metabolite/parent = 1-OH-midazolam/midazolam) – for midazolam only
  - Ratio $C_{max,\ test/reference}$, Ratio $AUC_{last,\ test/reference}$, Ratio $AUC_{\infty,\ test/reference}$ (test/reference = probe drug in presence of erdafitinib/probe drug alone)

9.2.4. Sample Collection and Handling

The actual dates and times of PK sample collection must be recorded on the laboratory requisition form and appropriate eCRF in the clinical database. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, US Pharmacopeia (or equivalent), and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to DDI Table 28 for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

9.2.5. Criteria for PK Evaluability

At least 15 subjects will be enrolled in this DDI substudy. Due to the potential for subjects not to meet the PK evaluability criteria or other criteria relevant to PK (ie, co-medication exclusion criteria), additional subjects may be enrolled to ensure that the required number of PK-evaluable subjects is met.

The minimum criteria for PK evaluability are as follows:

- Subjects took planned dose (2.5 mg) of midazolam on Day -2 and Day 13. Two interpretable PK profiles were obtained following the administration of midazolam and midazolam plus erdafitinib at a dose of 8 mg.
- Subjects took planned dose (1,000 mg) of metformin on Day -1 and on Day 14. Two interpretable PK profiles were obtained following the administration of metformin and metformin plus erdafitinib at a dose of 8 mg.
- Subjects did not vomit within 4 hours after receiving either dose of the probe drugs (midazolam, metformin) and no reported vomiting with erdafitinib dosing while at home for 5 consecutive doses before co-administration of the probe drugs on Day 13 and Day 14.
- Subjects received the next 5 consecutive doses of erdafitinib at a dose of 8 mg prior to co-administration of the probe drugs on Day 13 and Day 14.
- Additionally, the DDI PK data for a specific subject may be considered non-evaluable as per scientific judgment by the sponsor even if the above criteria are fulfilled. For such a case, the reason will be documented.

The final assessment of PK evaluability will be determined by the sponsor based on the available PK data and other relevant data. The DDI Treatment Phase will be completed after the collection of the 24-hour metformin PK sample on Day 15.

9.3. Safety Evaluations

There are no protocol-required assessments during the LTE Phase; safety assessments including laboratory assessments will be performed based on the investigator's discretion (DDI Table 29). Data for subjects in the LTE Phase will not be added to the clinical database. All SAEs and associated concomitant therapies will be reported through the Company Safety Repository.

9.3.1. Physical Examinations

A full physical examination, including height and weight, will be performed at screening. Subjects should have a repeated physical examination at Cycle 1 Day 1 before dosing if the previous physical examination during screening occurred more than 14 days previously. Targeted physical examinations, including involved organs of the disease state, will be performed at subsequent visits as listed in the Time and Events Schedule for the DDI Substudy. Height and weight measurements are not required after screening. The investigator must review physical examination results and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

9.3.2. Vital Signs

Vital signs will be assessed per the Time and Events Schedule in the DDI Substudy. Blood pressure (systolic and diastolic), heart rate, and temperature will be assessed. The investigator must review vital signs results and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

9.3.3. Electrocardiograms

Twelve-lead electrocardiograms will be performed as specified in the Time and Events Schedule for the DDI Substudy. Additional ECGs may be performed as clinically indicated. During treatment, ECGs should be performed before study drug is taken for the day. The subject should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs. The 12-lead ECG recorder device used should have been recently serviced and calibrated per institutional standard. The following intervals should be measured: PR, QRS, QT, RR. QTcF (Fridericia) will be used for assessment of QTc interval. It is recommended that all ECGs be performed at approximately the same time each day to minimize circadian variation in QT interval. The investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings).

9.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected for all subjects as indicated in the Time and Events Schedule for the DDI substudy. More frequent clinical laboratory tests may be performed, as indicated by the overall clinical condition of the subject and for abnormalities that warrant more frequent monitoring. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

Laboratory test results completed on Day -3 should be reviewed prior to enrollment (except PTH), and subjects should continue to meet eligibility requirements per the inclusion/exclusion criteria.

The following tests will be performed by the local laboratory:

Hematology Panel

-hemoglobin
-platelet count
-white blood cell count
-absolute neutrophil count

Comprehensive Metabolic Panel

-alanine aminotransferase (ALT)
-aspartate aminotransferase (AST)
-total bilirubin
-creatinine
-sodium
-magnesium
-calcium
- potassium
- albumin
- bicarbonate (if feasible)
- alkaline phosphatase

Parathyroid Hormone

Phosphate

9.3.5. Ophthalmologic Examination

All subjects should have an ophthalmologic examination performed at Screening by an ophthalmologist, which should include assessment of visual acuity, fundoscopy (examination of both central and peripheral zones should be performed), slit lamp biomicroscopy, and Optical Coherence Tomography (OCT). The Amsler grid test will also be administered by the treating physician or nurse at Screening. A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment, or at regular intervals as deemed necessary by the screening ophthalmologist.

When central serous retinopathy (CSR)/retinal pigment epithelial detachment (RPED) is suspected, or fundoscopic retinal abnormalities are observed, as well as each time ocular adverse events lead to the subject being referred to an ophthalmologist, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected Retinal Vein Occlusion (RVO). In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered.

All images of the OCT scans for enrolled subjects must be stored in the subject's records.

Amsler Grid Testing

Amsler grid (Attachment 5) testing will be administered to all subjects at Screening and during the treatment phase according to the Time and Events Schedule for the DDI substudy. Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days. However, if the subject has an abnormal Amsler grid test and otherwise normal ophthalmologic exam at baseline (during Screening), then a repeat ophthalmologic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler grid test at Screening, or the subject has developed new clinical symptoms.

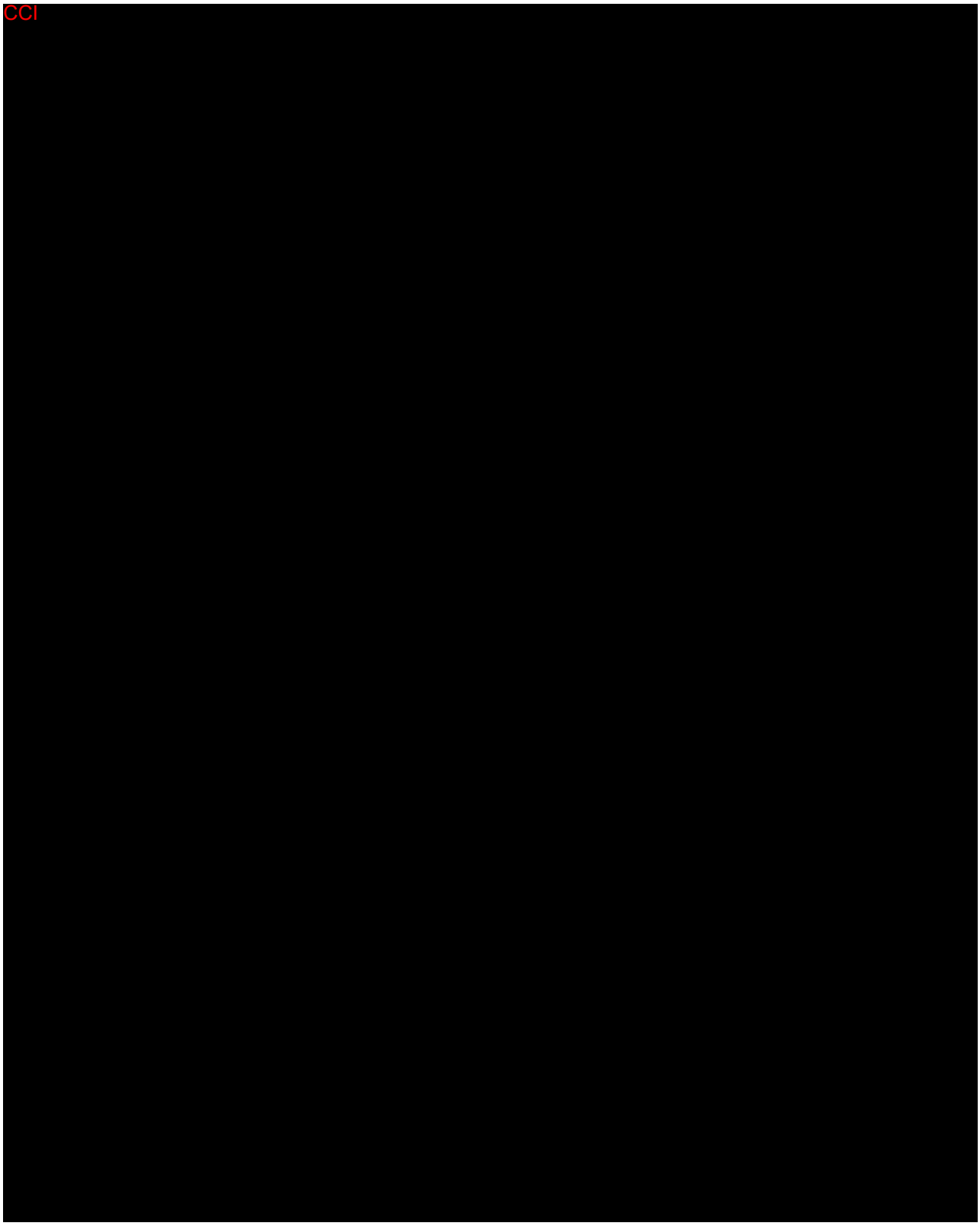
9.3.6. Pregnancy Testing: Urine or Serum β-hCG

Urine or serum samples will be obtained for β-hCG pregnancy testing in female subjects of child bearing potential at time points indicated in the Time and Events Schedule for the DDI substudy. Pregnancy tests will be performed to establish the absence of pregnancy at any time during the subject's participation in the study.

9.3.7. ECOG Performance Status

Eastern Cooperative Oncology Group performance status grade will be determined as part of screening evaluations. The scoring information is provided in Main Protocol, Attachment 1.

CCI



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[redacted]

9.5. Radiologic Assessment for Identification of Disease Progression

Radiologic assessments will be performed according to the Time and Events Schedule for the DDI Substudy for the purpose of determining disease progression. More frequent radiological assessments are allowed, if clinically indicated/desirable. If symptomatic deterioration (on the basis of global deterioration of health status) occurs without documentation of radiographic progression, the clinical findings used to make this determination must be specified in the eCRF and documented in the source documents. During the DDI Substudy, assessment of responses for solid tumors will be performed according to standard of care per the principal investigator's judgement.

During the LTE Phase, please refer to the Time and Events Schedule (DDI Table 29).

10. SUBJECT COMPLETION/WITHDRAWAL FOR THE DDI SUBSTUDY

10.1. Completion

A subject will be considered to have completed the DDI portion after completing the assessments on Cycle 2 Day 1.

For subjects who continue to derive benefit from study treatment following the end of study data collection timepoint, please refer to LTE Phase Section 9.1.5.

10.2. Discontinuation of Study Treatment

A subject's study treatment will be discontinued for any of the following reasons:

- Concurrent medical conditions or unmanageable disease-related events for which the investigator believes that it is in the best interest of the subject to stop treatment
- The subject becomes pregnant
- Disease progression
- Unacceptable toxicity (Exception: If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as

appropriate, along with appropriate clinical follow-up as designated by the investigator (please see Main Protocol Section 16.2.3 for details.)

- The subject refuses further treatment with the study drug
- The sponsor terminates the study
- Investigator decision approved by the sponsor

If a subject discontinues treatment, an End-of-Treatment visit should be conducted within 30 days of the subject's last dose of study drug. Subjects who re-consent to LTE Phase will not be required to complete EoT visit. The primary reason for treatment discontinuation will be clearly documented in the subject's medical record and recorded in the eCRF. Once a subject discontinues treatment with the study drug, the subject will not be permitted to be retreated.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

A subject may be replaced if the subject withdraws prior to study drug administration or prior to the first disease assessment for reasons other than toxicity or disease progression.

11. STATISTICAL METHODS

Treated subjects in the DDI portion of the substudy who completed Cycle 2 Day 1 will be included in the analysis. Safety analyses will be based on the Safety Analysis Set, defined as all subjects who received at least 1 dose of study drug, and will be based on actual treatment received, unless otherwise specified. The same safety analysis methods described in the main study SAP will be used.

11.1. Sample Size Determination

Approximately 22 subjects will be enrolled to account for a potential greater intra-subject variability for this DDI substudy that will be conducted in FGFR-eligible cancer patients. The sample size calculation is based on statistical estimation enabling the study to provide an estimate with reasonable precision on the magnitude of the interaction. If the number of subjects evaluable for PK in the DDI Treatment Phase up to Study Day 15 (Cycle 1 Day 15) drops below 15, additional subjects may be enrolled.

Previous DDI studies with the same probe drugs conducted by the sponsor indicated that the intra-subject coefficient of variation (CV) for probe drugs ranged from 16% to 21% for C_{max} and 11% to 18% for AUC (DDI Table 34).

DDI Table 34: Intra-subject Coefficient of Variation for the Probe Drugs and Their Metabolites From Previous Drug-Drug Interaction Studies and Publications

JNJ Study Number	Compound	Intra-Subject CV	
		C_{max}	AUC
54179060CLL1017	midazolam 2 mg	16% - 20%	17% - 18%
ESKETINTRD1010	midazolam 6 mg	17%	11%
28431754DIA1028	metformin 2,000 mg	21%	17%
Intra-subject CV Range		16% - 21%	11% - 18%

AUC=area under the curve; C_{max}=maximum plasma concentration; CV= coefficient of variation

Assuming an intra-subject CV of 21% among the probe drugs for AUC and C_{max}, a sample size of 15 subjects would be sufficient for the point estimate of the geometric mean ratio of AUC and C_{max} of the probe drugs with and without erdafitinib, to fall within 88% and 114% of the true value with 90% confidence.

11.2. Pharmacokinetic Analyses

Descriptive statistics will be provided for the plasma concentrations of erdafitinib, and for the probe drugs, metformin and midazolam (and its metabolite 1-OH-midazolam). Statistical analysis will be performed for the PK parameters of each of the following analytes:

- The probe drugs: metformin and midazolam (and its metabolite 1-OH-midazolam).

The test / reference treatments are defined as follows:

Study Day 13 (midazolam [2.5 mg] + erdafitinib [8 mg] / Study Day -2 (midazolam [2.5 mg])

Study Day 14 (metformin [1,000 mg] + erdafitinib [8 mg] / Study Day -1 (metformin [1,000 mg])

The primary PK parameters of interest for statistical analysis are C_{max}, AUC_{last}, and $AUC\infty$ of the parent compounds of the probe drugs. For each analyte, all subjects who have the primary PK parameters of interest from both prior to treatment and the DDI Treatment Phase will be included in the statistical analysis.

Linear mixed effects models will be applied to log-transformed PK parameter data with treatment as fixed-effect and subject as random-effect. The least square means and intra-subject coefficients of variation will be derived from the model. The geometric mean ratios and the 90% confidence interval of the PK parameters of each drug probes with and without co-administration of erdafitinib will then be constructed through back-transformed results based on the model.

12. ADVERSE EVENT REPORTING

Instruction regarding adverse event reporting is provided in the Main Protocol (Section 12); however, attribution definitions (ie, assessment of causality) and the severity criteria have been updated for the DDI Substudy.

During the LTE Phase, all SAEs and associated concomitant therapies will be reported through the Company Safety Repository.

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all adverse events.

Related

There is a reasonable causal relationship between study intervention administration and the adverse event.

Not Related

There is not a reasonable causal relationship between study intervention administration and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

Severity Criteria

Adverse event severity is a clinical determination of the intensity of an adverse event. The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE, Version 5.0. Any adverse event or serious adverse event not listed in the NCI-CTCAE, Version 5.0 will be graded according to the investigator clinical judgment by using the standard grades as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).[a]

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

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.[a]

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to adverse event.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

Any adverse event will be graded as per the above. Should an adverse event become fatal or have a fatal outcome, the original grade is not changed but "fatal" shall be reported as an outcome.

Only in the following cases a Grade 5 event is to be reported:

- Death NOS: only for deaths due to unknown reason (pending follow-up information; if further information becomes available this should be adapted as adequate)

- Sudden death: a sudden (defined as instantaneous or within 1 hour of the onset of symptoms) cessation of life that cannot be attributed to a CTCAE term.

13. PRODUCT QUALITY COMPLAINT HANDLING

See Main Protocol Section 13.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

The erdafitinib study drug supplied for this study is formulated as 3-, 4-, and 5-mg tablets for oral use. Refer to the Investigator's Brochure for a list of excipients.

Description of the probe drugs is supplied in the Study Investigational Product Procedures Manual.

14.2. Packaging

The study drug and probe drugs for oral use in this study will be packaged in child-resistant bottles.

14.3. Labeling

Study drug and probe drug labels will contain information to meet the applicable regulatory requirements. No medication can be relabeled without prior approval from the sponsor.

[a] Self-care ADL refers to bathing; dressing and undressing; feeding self; using the toilet; taking medications; and not bedridden.

14.4. Preparation, Handling, and Storage

Refer to the study pharmacy manual (Investigational Product Binder)/study Investigational Product Preparation Instructions and Investigational Product Procedures Manual for additional guidance on study drug and probe drug preparation, handling, and storage.

14.5. Drug Accountability

See the Main Protocol (Section 14.5) for instruction regarding drug accountability.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Protocol
- Investigator's Brochure
- Electronic CRFs and electronic data capture (eDC) manual
- Site Investigational Product Manual
- Laboratory manual
- Kits for PK, pharmacodynamics/biomarker, and tissue sample assessments
- Subject diary card and information booklet
- Investigator binder to store all documents concerning the study. This is a confidential binder and only personnel involved in the study should have access to it.
- Amsler Grid tests

16. ETHICAL ASPECTS

See Main Protocol Section 16.

17. ADMINISTRATIVE REQUIREMENTS

See Main Protocol Section 17.

INVESTIGATOR AGREEMENT

JNJ-42756493

Clinical Protocol 42756493BLC2001 – Amendment 9

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 191

Status: Approved, Date: 4 October 2022