Janssen Research & Development *

Clinical Protocol

A Phase 2 Study of Erdafitinib in Subjects with Advanced Solid Tumors and FGFR Gene Alterations

Protocol 42756493CAN2002; Phase 2
Amendment 6

JNJ-42756493 (erdafitinib)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (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

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	22 February 2023
Amendment 5	10 November 2022
Amendment 4	29 August 2022
Amendment 3	12 Aug 2021
Amendment 2	19 Aug 2020
Stand-alone National Disaster Appendix	08 Jun 2020
Amendment 1	15 Aug 2019
Original Protocol	25 Jun 2019

Amendment 6 (22 February 2023)

Overall Rationale for the Amendment: To modify the end of study definition and introduce a long-term extension phase for continued treatment with erdafitinib, with limitation of data collection, after study completion.

The changes made to Clinical Protocol 42756493CAN2002 as part of Protocol Amendment 6 are listed below, including the rationale for each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.14 Appendix 14: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall Design, Intervention Groups and Duration; 1.3 Schedule of Activities: For Adults (≥18 years of age [footnote a]); 1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age [footnote b]) 4.1 Overall Design; 4.3 Justification for Dose; 5.5 Study Completion (ie, End of Data Collection Timepoint) and End of Study 5.5.1 Study Completion (i.e. End of Data Collection Timepoint) Definition; 5.5.2 End of Study Definition – Overall Study; 6.1 Study Drug Administered; 6.7 Study Drug After Study Completion. 8.1.2 Treatment Phase; 8.1.3 End-of-Treatment Visit; 8.1.4 Follow-Up Phase; 9.4.3.2 Final Analysis;	Study completion is defined as the end of data collection timepoint, ie, the date at which the clinical cutoff for the primary analysis has been achieved. For subjects <18 years of age, the end of data collection is defined as the timepoint when the most recently enrolled pediatric subject still participating in the study has 6 months of follow-up or the last follow-up visit of the last pediatric subject, whichever occurs first. The end of study is defined as the time when the last subject receives the last dose of study drug on the study. The title of Section 5.5, End of Study Definition, was revised to Study Completion (ie, End of Data Collection Timepoint) and End of Study. The title of Section 5.5.1, End of Study Definition Per Cohort, was revised to Study Completion (i.e. End of Data Collection Timepoint) Definition. In the applicable sections, it was clarified that the subject follow-up and data collection will end once the end of data collection timepoint has been achieved (removed "for a cohort"). Subjects in the treatment phase who continue to derive benefit from study treatment will be allowed to receive study treatment in the LTE Phase and only serious adverse events will be reported in the company safety repository.	To revise the end of study definition, study completion definition (ie, end of data collection timepoint definition), and to modify data collection during continued treatment with erdafitinib after the study data collection timepoint. To clarify monitoring of only serious adverse events for subjects continuing study treatment (ie, in the LTE Phase).

Section Number and Name	Description of Change	Brief Rationale
10.3.1 Regulatory and Ethical Considerations (Long-term Extension and Post-trial Access)		
1.2 Schema (Figure 1); 1.3 Schedule of Activities: For Adults (≥18 Years of Age); 1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age); 5.5.1 Study Completion (i.e. End of Data Collection Timepoint) Definition; 6.7 Study Drug After Study Completion; 8.1.3 End-of-Treatment Visit; 10.3.1 Regulatory and Ethical Considerations (Long-Term Extension and Post-trial Access); 10.13 Appendix 13 Long-term Extension Phase	Added Appendix 13 for the Long-term Extension (LTE) Phase. In the applicable sections, added reference to Appendix 13 for details on the LTE phase.	Additional instruction for continued treatment with erdafitinib after the end of the data collection timepoint (termed the LTE Phase with Amendment 6) was provided.
1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)	Timepoints removed and added that the PRO measurements are discontinued with Amendment 6.	PRO measurements after this timepoint are no longer necessary.
8.2 Efficacy Assessments	Removed with Amendment 6, the IRC central read for confirmation of progression.	IRC confirmation of progression of disease is no longer required.
1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age); 3. Objectives and Endpoints; 9.4.8 Other Analyses	Removed acceptability and palatability of erdafitinib as an exploratory objective and Palatability VAS as an assessment. Removed Section 9.4.8 (Other Analyses) and Appendix 10.13 (Pediatric Cohort Medicine Palatability Testing).	Palatability VAS assessment is no longer required for children included in the study.
Throughout the protocol	Minor corrections, formatting or spelling changes were made.	Minor errors, formatting or spelling errors were noted

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2 Study of Erdafitinib in Subjects with Advanced Solid Tumors and FGFR Gene Alterations

Erdafitinib (JNJ-42756493) is a selective and potent pan fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor with demonstrated clinical activity in subjects with solid tumors identified to have alterations in the FGFR pathway.

OBJECTIVES

Primary Objective (Broad Panel Cohort and Core Panel Cohort)

- To evaluate the efficacy of erdafitinib in terms of overall response rate (ORR) as assessed by the Independent Review Committee (IRC) in subjects with advanced solid tumors with target FGFR mutations and any gene fusions (Broad Panel Cohort), or in a pre-specified subgroup of subjects with a selected panel of FGFR markers (Core Panel Cohort), or in both cohorts.

Primary Objective (Pediatric Cohort)

- To evaluate the efficacy of erdafitinib in terms of ORR as assessed by the IRC in pediatric subjects with advanced solid tumors with FGFR mutations, any gene fusions or FGFR internal tandem duplication (Pediatric Cohort), including adolescent subjects with target FGFR mutations and any gene fusions

Secondary Objectives

- To evaluate the efficacy of erdafitinib, in terms of ORR, as assessed by the investigator
- To evaluate the efficacy of erdafitinib in terms of duration of response (DOR)
- To evaluate other measures of efficacy including disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS)
- To evaluate erdafitinib pharmacokinetics (PK)
- To evaluate safety and tolerability of erdafitinib
- To evaluate health-related quality of life (HRQoL)

Cholangiocarcinoma Expansion Cohort

- To evaluate the efficacy and safety of erdafitinib in subjects with cholangiocarcinoma with target FGFR mutations and any gene fusions

OVERALL DESIGN

This is a Phase 2, open-label study of the efficacy and safety of erdafitinib in subjects ≥6 years of age with advanced solid tumors (other than urothelial tumors) and FGFR gene alterations. Subjects ≥12 years of age with target FGFR mutations or any FGFR gene fusions will be enrolled into the Broad Panel Cohort. Target FGFR mutations include select mutations based on predicted likelihood for pathogenicity with preclinical sensitivity to erdafitinib, or those with clinical or correlative evidence supporting inclusion. A subgroup of subjects in the Broad Panel Cohort with a select panel of pre-specified FGFR markers will be identified as the Core Panel Cohort (for analysis only). While the Broad Panel Cohort consists of target FGFR mutations and any fusions, the Core Panel Cohort consists of a select subset of FGFR mutations or fusions with known observed clinical activity in previous studies and/or with a high level of recurrence. Subjects with any other

FGFR mutations that are not captured in the Broad Panel Cohort will be included in the study as the Exploratory Cohort. A separate Cholangiocarcinoma Expansion Cohort will enroll subjects with target FGFR mutations or any FGFR gene fusion once the Broad Panel Cohort has reached the cap of approximately 30 subjects for cholangiocarcinoma. A Pediatric Cohort will enroll all subjects ≥6 to <18 years of age with locally advanced or metastatic solid tumors harboring FGFR alterations who have either progressed following prior therapies and who have no acceptable standard therapies, or who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. Adolescent subjects enrolled in the Broad Panel Cohort (≥12 to <18 years) will be analyzed as part of the Broad Panel Cohort and the Pediatric Cohort.

The Screening Phase will start with the Molecular Eligibility Screening Period. Subjects with study-eligible FGFR alterations may be identified by central next-generation sequencing (NGS) from tissue sample, or based on locally performed and commercial testing from tissue or blood (NGS tests, direct digital counting methods, or the Qiagen *therascreen*® FGFR reverse transcription polymerase chain reaction [RT-PCR] test). Starting with Amendment 4, only local reports will be used for molecular screening. The Full-study Screening Period will occur after the completion of prior treatment and documentation of disease progression for subjects who meet the molecular screening criteria. The Treatment Phase will continue until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or the end of data collection timepoint has been achieved. 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 study completion, whichever comes first.

Study completion and end of study are distinct timepoints. Study completion is defined as the end of data collection timepoint, ie, the date at which the clinical cutoff for the primary analysis has been achieved. For subjects <18 years of age, the end of data collection is defined as the timepoint when the most recently enrolled pediatric subject still participating in the study has 6 months of follow-up or the last follow up visit of the last pediatric subject, whichever occurs first. End of study is defined as the time when the last subject receives the last dose of study drug on the study.

Upon initiation of the LTE Phase, participation in the Follow-Up Phase will end and study data collection will conclude in the clinical database; and only serious adverse events will be reported to the company safety repository.

NUMBER OF SUBJECTS

Approximately 280 subjects ≥12 years of age with FGFR genetic alterations will be enrolled in the Broad Panel Cohort (approximately 240 subjects) and the Exploratory Cohort (approximately 40 subjects). An additional approximately 30 subjects will be enrolled in the Cholangiocarcinoma Expansion Cohort. The Pediatric Cohort (approximately 26 subjects) consisting of children or adolescent subjects ≥6 to <18 years of age with locally advanced or metastatic solid tumors will enroll 20 children or adolescent subjects who have progressed following prior therapies and who have no acceptable standard therapies, and approximately 6 additional children or adolescent subjects who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. Adolescent subjects enrolled in the Broad Panel Cohort (≥12 to <18 years) will be analyzed as part the Broad Panel Cohort and the Pediatric Cohort.

INTERVENTION GROUPS AND DURATION

Subjects will take erdafitinib orally once daily for 21 days on a 21-day cycle until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or the end of data collection timepoint has been achieved. Adults (aged 18 years and older for dosing purposes) and adolescent subjects aged ≥15 to <18 years will start with an erdafitinib dose of 8 mg with possible up-titration to 9 mg based on Cycle 1 Day 14 serum phosphate levels. Adolescent subjects aged ≥12 to <15 years will start with an erdafitinib dose of 5 mg with possible up-titration to 6 mg or further to 8 mg based on Cycle 1 Day 14 and Cycle 2 Day 7 serum phosphate levels. Children aged ≥6 to <12 years will start with

an erdafitinib dose of 3 mg with possible up-titration to 4 mg or further to 5 mg based on Cycle 1 Day 14 and Cycle 2 Day 7 serum phosphate levels.

EVALUATIONS

Assessment of response will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) or Response Assessment in Neuro-Oncology (RANO) by the IRC and investigators. Pharmacokinetic assessments (plasma concentrations of erdafitinib and alpha-1-acid glycoproteins, total protein, and fraction unbound, if required, using venous blood samples), biomarker assessments (molecular screening to determine eligibility for the study; and possibly exploratory deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein analyses using archival or fresh biopsy tissue and blood (circulating tumor [ct]DNA) for exploratory research), patients' health-related QoL assessments, and safety assessments (including adverse event [AE] reports and results of vital sign measurements, electrocardiograms [ECGs], physical examinations, clinical laboratory tests, performance status assessment, and ophthalmologic examinations) will be conducted as described on the Schedule of Activities. Additional safety assessments for children and adolescent subjects include radiographic (growth plate assessment and bone age) imaging, dual-energy X-ray absorptiometry (DEXA) scan for bone densitometry, and clinical laboratory tests for thyroid stimulation hormone (TSH), total triiodothyronine (T3), and free thyroxine (T4) and insulin-like growth factor 1 (IGF-1), and will be conducted as described on the Schedule of Activities.

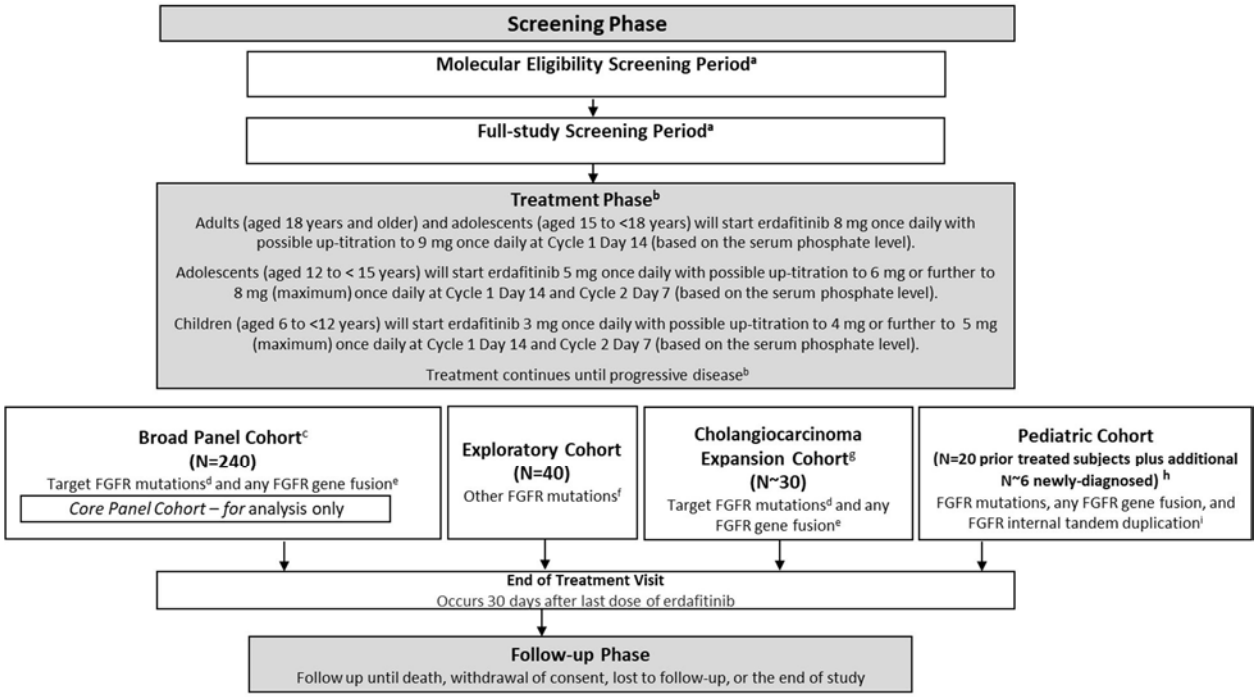
STATISTICAL METHODS

For the Broad Panel Cohort, the primary endpoint is ORR based on RECIST v1.1. or RANO as assessed by the IRC and will be calculated with a 95% 2-sided exact confidence interval (CI). The primary endpoint will be analyzed using data from the Treated Population (defined as all subjects [FGFR+] who receive at least 1 dose of study drug) in the Broad Panel Cohort and the Core Panel Cohort. An error-spending function approach will be used to split the significance level for the Broad Panel Cohort and the Core Panel Cohort. The secondary endpoints include ORR by investigator assessment, DOR, DCR, CBR, PFS, OS, PK exposure parameters, incidence and severity of AEs, and PROs. The ORR assessed by the investigator will be analyzed in the same way as the ORR assessed by the IRC. The distributions of DOR, PFS and OS will be summarized using Kaplan-Meier estimates and the estimated median will also be reported along with a 95% CI. The PRO assessments will be analyzed with descriptive summaries (ie, mean, standard deviation including change from baseline) at each assessment time point. The Pediatric Cohort will have the same primary and secondary endpoints as the Broad Panel Cohort; subjects in the Pediatric Cohort will be evaluated separately from the Broad Panel Cohort. The Cholangiocarcinoma Expansion Cohort will also be evaluated separately from the Broad Panel Cohort.

Three interim futility analyses are planned when 30%, 50%, and 70% of the subjects in the Broad Panel Cohort (ie, approximately 60, 100, and 140 subjects) have been treated and are considered response-evaluable by investigator assessment, irrespective of the tumor histologies and the distribution among the tumor histologies. The interim analyses for futility will be based on the ORR assessed by investigator using a Bayesian hierarchical model (BHM), implemented in FACTS v6.2 Enrichment Design – Dichotomous. In addition, an interim efficacy analysis will be conducted for the Broad Panel Cohort at the same time as the second interim futility analysis.

1.2. Schema

Figure 1: Schematic Overview of the Study



Note: The LTE phase is not included in the schematic (see Appendix 13).

[a] See Section 8.1.1 for information regarding consent during the screening periods. During the Molecular Eligibility Screening Period, either the central or local screening approach may be followed as described in Section 8.1.1.1. Starting with Amendment 4, only local reports will be used for molecular screening.
[b] See Section 6.1 for detailed information regarding titration of erdafitinib based on serum phosphate levels. Treatment is continued until progressive disease, intolerable toxicity, consent withdrawal, or investigator decision to stop treatment. See Section 8.2.2 for continuation of treatment after progressive disease. Note that children and adolescent subjects remain under the titration and dosing schedule under which they were enrolled.
[c] Up to 30 subjects in each tumor histology will be enrolled in the Broad Panel Cohort with the possibility of increasing the number of subjects in a specific tumor histology upon decision by the sponsor's Data Review Committee. The rationale for biomarker selection is described in Section 4.2.1.
[d] Subjects with target FGFR mutations are eligible for enrollment in the Broad Panel Cohort. The List of Target FGFR Mutations (over 30 validated FGFR mutations) is provided in Section 10.11.
[e] Subjects with any FGFR gene fusion are eligible for enrollment in the Broad Panel Cohort. FGFR gene fusions must have an intact FGFR kinase domain. FGFR gene identifiers for reference are provided in Section 5.1, Criterion 2.
[f] Subjects with FGFR mutations that do not meet the Broad Panel Cohort criteria (ie, not on the List of Target FGFR Mutations) are eligible for enrollment in the Exploratory Cohort.
[g] A separate Cholangiocarcinoma Expansion Cohort will enroll subjects with target FGFR mutations or any FGFR gene fusion once the Broad Panel Cohort has reached the cap of approximately 30 subjects for cholangiocarcinoma.
[h] The Pediatric Cohort will enroll 20 children and adolescent subjects who have progressed following prior therapies and who have no acceptable standard therapies, and approximately 6 additional children and adolescent subjects who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. Adolescent subjects enrolled in the Broad Panel Cohort (≥12 to <18 years) will be analyzed as part of the Broad Panel Cohort and the Pediatric Cohort; therefore 240 subjects in the Broad Panel Cohort can include subjects from Pediatric Cohort.
[i] Subjects with FGFR mutations (exclusive of valine gatekeeper and resistance alterations), any FGFR gene fusion, or FGFR internal tandem duplication are eligible for enrollment in the Pediatric Cohort (see Section 5.1, Criterion 2).

1.3. Schedule of Activities: For Adults (≥18 Years of Age)

(For the Long-term Extension Phase Schedule of Activities, please refer to Appendix 13)

Schedule of Activities: For Adults (≥18 Years of Age)

Parameter		Screening Phase			Treatment Phase[g] (21-day cycles)			End of Treatment Visit[g]	Follow-Up Phase[g]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3		Cycle 4+		
					Day 1	Day 14	Day 1		
Visit Window	NOTES	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[a]	every 12 weeks± 7 days
Screening/Administrative: Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.3. Check clinical status again before first dose of study drug. The End-of-Treatment Visit should occur before the start of any subsequent therapy, if such therapy starts within 30 days after last dose on study.									
Informed Consent (molecular and full study)	A Molecular Eligibility Testing ICF is used to allow for assessment of archived tumor tissue (central eligibility testing) or for the review of historical reports from tissue or blood samples (local review of historical report) prior to entering the Full-study Screening Period. A separate Full-study ICF must be signed by all subjects before any study-related activity (eg, fresh biopsy)[b]	X	X						
Inclusion/exclusion criteria, medical history, and smoking history	Histological documentation of specific tumor histology. Record demographic information.		X						
Local FGFR results for molecular eligibility[c]	Subjects may enroll based on local results (ie, historical report). See Section 5.1 and Section 8.1.1.1 for full details on local testing requirements. • Subjects with local FGFR tissue or blood results must submit test report to sponsor for central verification. • Tumor tissue must be submitted.* See '**Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostics Development**'. Where central confirmation of local FGFR testing results is performed, the results of central confirmation do not affect the subject's eligibility for the study. * If tissue is not available, please contact the sponsor prior to proceeding with full-study screening.	X							
Central Molecular Eligibility Testing from Tissue[c]	Starting with Amendment 4, only local reports will be used for molecular screening. For subjects who are eligible for central molecular testing (see Screening Phase Section 8.1.1.1), tumor tissue (archival or fresh biopsy) must be submitted to the central lab for molecular eligibility screening. See '**Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostics Development**'. If a fresh biopsy sample is collected, the subject must sign the Full-study ICF prior to collection.	X (If fresh biopsy, done during full study screening period)							

Schedule of Activities: For Adults (≥18 Years of Age)

Parameter		Screening Phase			Treatment Phase[g] (21-day cycles)			End of Treatment Visit[g]	Follow-Up Phase[g]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3		Cycle 4+		
					Day 1	Day 14	Day 1		
Visit Window	NOTES	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[a]	every 12 weeks± 7 days
Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostics Development	Tumor tissue must be submitted.* Samples will be used for any or all of the following purposes: molecular screening for study eligibility (Central Screening); biomarker research; diagnostic development; central confirmation of local FGFR testing results (if applicable). Starting with Amendment 4, only local reports will be used for molecular screening. * If tissue is not available, please contact the sponsor prior to proceeding with full-study screening.	X							
Study Drug Administration									
Erdafitinib	Start with 8 mg with possible increase to 9 mg based on C1D14 phosphate value (see guidelines in Section 6.1)				Once Daily			X[a]	
Study Drug Diary	Subjects will record study drug administration in dosing diaries.				Once Daily				
Safety Assessments									
History of seizure and physical examination	During Screening Phase, complete physical examination including neurological examination, height, and weight. During Treatment Phase, limited physical examination of affected organs, neurological examination including record of seizure activity (subjects with primary CNS tumors, CNS metastases or other subjects at the investigator's discretion, only) and weight; record new abnormalities as AE. If examination occurs more than 7 days prior to the first dose of study drug, it must be repeated on C1D1 prior to dosing.		X		X		X	X	
Vital signs	Check temperature, heart rate, systolic and diastolic blood pressure; record all clinically significant abnormalities as AE.		X		X		X	X	
ECOG performance status				X	X		X		
Urine or serum β-hCG pregnancy test	Females of childbearing potential only. Screening test within 7 days prior to the first dose, or at C1D1 prior to the first dose.			-7 days	Day 1 of every cycle from Cycle 2			X	
12-lead ECG	Record postdose ECGs (see Section 8.3.3 for exact timing). May be performed more often as clinically indicated. Please conduct ECGs preferably at the same time each day at each visit (at which an ECG is conducted).		X		C2D1		C4D1		
Ophthalmologic exam	To be performed by an ophthalmologist, for exact assessments see Section 8.3.5.		X						
Amsler Grid Test	To be performed by treating physician or nurse (as directed by specific site instructions).		X		C2D1 C3D1		X	X	

Schedule of Activities: For Adults (≥18 Years of Age)

Parameter		Screening Phase			Treatment Phase[g] (21-day cycles)			End of Treatment Visit[g]	Follow-Up Phase[g]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3		Cycle 4+		
					Day 1	Day 14	Day 1		
Visit Window	NOTES	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[a]	every 12 weeks± 7 days
Clinical Laboratory Assessments: Results (except parathyroid hormone) must be available prior to dosing at C1D1 and subjects should continue to meet eligibility requirements per the Inclusion/Exclusion criteria. Results of previous testing should be available for comparison as clinically necessary.									
Hematology	May be performed within 3 days prior to D1 of each cycle (Section 10.2)			X	X	X	X	X	
Chemistry	May be performed within 3 days prior to D1 of each cycle (Section 10.2)			X	X	X	X	X	
Parathyroid hormone (PTH)	May be performed within 3 days prior to D1 of each cycle (Section 10.2)			X	X	X	X (every 3rd cycle after C6)	X	
Efficacy Assessments									
Radiological assessment and/or skin photography, as applicable	Identical methodology [CT, or MRI if site of disease not evaluable by CT] should be used for disease assessment at baseline and throughout the study whenever possible. Additional assessments may be performed, if clinically indicated. Skin lesions that cannot be measured radiographically may be assessed using skin photography (Please refer to Imaging Acquisition Guidelines).		X[d]		Every 6 weeks (2 cycles) for 12 months (±7 days) from C1D1, then every 12 weeks (4 cycles) thereafter (±7 days). Note: After Week 48, the next radiological assessment will be performed at Week 60. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 8.1.2). Imaging during continuation of treatment after disease progression is detailed in Section 8.2.2.				
Investigator RECIST or RANO Assessment	RECIST 1.1 will be applied by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status. The RANO criteria will be used to assess response for subjects with primary CNS tumors.				X				
Patient-reported Outcome Assessments (Conducted in the order shown below)									
PGIS	PRO measures to be completed preferably before any other study procedures. Predose at C1D1.[e] During the Treatment Phase, PRO measures stop at Cycle 49 (Cycle 49 is the last assessment).				X (See notes)	C1D14	X	X (See notes)	
PGIC	PRO measures to be completed preferably before any other study procedures.[e] During the Treatment Phase, PRO measures stop at Cycle 49 (Cycle 49 is the last assessment).				C2D1 (See notes)			X (See notes)	

Schedule of Activities: For Adults (≥18 Years of Age)

Parameter		Screening Phase			Treatment Phase[g] (21-day cycles)			End of Treatment Visit[g]	Follow-Up Phase[g]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3		Cycle 4+		
Visit Window	NOTES	N/A	-30 days	-14 days	Day 1	Day 14	Day 1	30 (+7) days after last dose[a]	every 12 weeks± 7 days
EORTC-QLQ-C30	PRO measures to be completed preferably before any other study procedures. Predose at C1D1. The follow-up visit may be conducted by telephone. This assessment is performed during the Follow-up Phase for the first 3 visits or until the start of subsequent anticancer therapy.[e] During the Treatment Phase, PRO measures stop at Cycle 49 (Cycle 49 is the last assessment).				C1: -3 days to D1 C2, C3: -2 to +2 days X (See notes)	+2 days C1D14	-2 to +2 days X	X (See notes)	X (See notes)
EQ-5D-5L	PRO measures to be completed preferably before any other study procedures. Predose at C1D1. The follow-up visit may be conducted by telephone. This assessment is performed during the Follow-up Phase for the first 3 visits or until the start of subsequent anticancer therapy.[e] During the Treatment Phase, PRO measures stop at Cycle 49 (Cycle 49 is the last assessment).				X (See notes)	C1D14	X	X (See notes)	X (See notes)
PK and Biomarker Assessments									
Blood (plasma) for ctDNA	Collect sample predose				C1D1 (predose)		C4D1 C7D1	X	
Fresh tumor biopsy for biomarker research[c] (Paired biopsies)	Starting with Amendment 5, the biomarker exploratory objective was revised to remove paired biopsies.								
PK Blood Sample	At C1D14, if morning visit, collect predose sample. If afternoon visit, collect postdose sample. At C2D1, collect predose sample and 2-4-hour postdose sample. Record dosing and PK collection times. See Section 8.5 for exact timing.				C2D1[f] (See note)	C1D14 (See note)			
Protein Binding Blood Sample	At C2D1, collect a sample 2-4 hours postdose. Record dosing and protein binding sample collection times. See Section 8.5.				C2D1 (See note)				
CYP2C9 Blood Sample	This sample is collected at C1D14 at any time, or any day after C1D14.					C1D14 (See note)			
Optional "Other Assessment"									
CSF PK sample in CNS tumor only (when conducted					CSF PK sample collected any time after Cycle 1 during the Treatment Phase				

Schedule of Activities: For Adults (≥18 Years of Age)

Parameter		Screening Phase			Treatment Phase[g] (21-day cycles)			End of Treatment Visit[g]	Follow-Up Phase[g]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3		Cycle 4+		
Visit Window	NOTES	N/A	-30 days	-14 days	Day 1	Day 14	Day 1	30 (+7) days after last dose[a]	every 12 weeks± 7 days
as part of routine CSF procedure)									
Plasma PK Sample at time of CSF Evaluation					Plasma PK sample collected at the same time as the CSF Evaluation during the Treatment Phase				
Ongoing Subject Review									
Concomitant medications	Concomitant therapies must be recorded at the time of full-study screening, during the study, and up to 30 days after the last dose of study drug.		X					X	
Adverse events	Collected from the day the Full-study ICF is signed until 30 days after last dose of study drug. If study drug is discontinued due to drug-related AE, AE should be monitored until it resolves to baseline, stabilizes, or is deemed irreversible, subject dies, or subsequent therapy is started, whichever occurs first.		X					X	X
Survival status	May be assessed via telephone call. Survival status will be monitored until death, withdrawal of consent, lost to follow up, or end of study, whichever occurs first							X	X
Subsequent anticancer therapy	May be assessed via telephone call. Start of subsequent anticancer therapy will be monitored until death, withdrawal of consent, lost to follow up, or end of study, whichever occurs first							X	X
Medical Resource Utilization	Collected throughout the study (See Section 8.9)		Continuous (Section 8.9)					X	

Abbreviations: AE=adverse event; β-hCG=beta-human chorionic gonadotropin; C=cycle; CNS=central nervous system; CSF=cerebrospinal fluid; CT= computed tomography; ctDNA=circulating tumor DNA; CXDX=Cycle X Day X; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EQ-5D-5L=European Quality of Life – 5 Dimensions-5 Levels; FGFR=fibroblast growth factor receptor; ICF=informed consent form; MRI= magnetic resonance imaging; NGS=next-generation sequencing; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Symptom Severity; PK=pharmacokinetic; PRO=patient reported outcome; PTH=Parathyroid hormone; RANO=Response Assessment in Neuro-Oncology; RECIST=Response Evaluation Criteria in Solid Tumors

a. The End of Treatment Visit is conducted 30 (+7) days after last dose of study drug or prior to starting any subsequent cancer treatment. Once the end of data collection timepoint has been achieved, follow-up of subjects will end, and data collection will conclude. Only serious adverse events will be reported in the company safety repository (See Appendix 13). Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment (see Section 6.7); during this period, only serious adverse events will be reported into the company safety repository.
b. See Section 8.1.1 for detailed instruction regarding the consent process. For subjects signing a Full-study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 30-day window starts with the first planned study procedure other than the tissue biopsy and informed consent; however, AEs will need to be collected from the time the Full-study ICF is signed.
c. 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. Biopsy of the brain, lung/mediastinum, pancreas, or for endoscopic procedures extending beyond the esophagus, stomach, or bowel is not permitted; please contact sponsor prior to conducting biopsy.
d. CT/MRI performed as part of routine standard of care but prior to the ICF being signed, will be accepted provided the subject enrolls within 30 days of assessment.
e. PRO measures may be conducted using Interview Mode, if necessary.
f. If indicated by the emerging safety findings or if the scheduled PK samples are not collected due to treatment interruption, blood samples may be collected at a later site visit (on C2D14, C3D1, or C3D14).
g. Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Section 10.12.

1.4. Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

(For the Long-term Extension Phase Schedule of Activities, please refer to Appendix 13)

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3			Cycle 4+		
					Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days
Screening/Administrative: Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.3. Check clinical status again before first dose of study drug. The End-of-Treatment Visit should occur before the start of any subsequent therapy, if such therapy starts within 30 days after last dose on study.										
Informed Consent (molecular and full study)	A Molecular Eligibility Testing ICF is used to allow for assessment of archived tumor tissue (central eligibility testing) or for the review of historical reports from tissue or blood samples (local review of historical report) prior to entering the Full-study Screening Period. A separate Full-study ICF must be signed by the subject or by the subject's legal representative before any study-related activity (eg, fresh biopsy)[c]	X	X							
Inclusion/exclusion criteria, medical history, and smoking history	Histological documentation of specific tumor histology. Record demographic information.		X							
Local FGFR results for molecular eligibility[d]	Subjects may enroll based on local results (ie, historical report). See Section 5.1 and Section 8.1.1.1 for full details on local testing requirements. • Subjects with local FGFR tissue or blood results must submit test report to sponsor for central verification. Tumor tissue must be submitted.* See '**Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostics Development**'. Where central confirmation of local FGFR testing results is performed, the results of central confirmation do not affect the subject's eligibility for the study. * If tissue is not available, please contact the sponsor prior to proceeding with full-study screening.	X								
Central Molecular Eligibility Testing from Tissue[d]	Starting with Amendment 4, only local reports will be used for molecular screening. For subjects who are eligible for central molecular testing (see Screening Phase Section 8.1.1.1), tumor tissue (archival or fresh biopsy) must be submitted to the central lab for molecular eligibility screening. If a fresh biopsy sample is collected, the subject or the subject's legal representative must sign the Full-study ICF. See '**Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostics Development**'.	X (If fresh biopsy, done during full study screening period)								

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3			Cycle 4+		
					Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days
Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostics Development	Tumor tissue must be submitted.* Samples will be used for any or all of the following purposes: molecular screening for study eligibility (Central Screening); biomarker research; diagnostic development; central confirmation of local FGFR testing results (if applicable). Starting with Amendment 4, only local reports will be used for molecular screening. * If tissue is not available, please contact the sponsor prior to proceeding with full-study screening.	X								
Study Drug Administration										
Erdafitinib	For adolescents ≥15 to <18 years: Start with 8 mg, possible increase to 9 mg based on C1D14 phosphate value. For adolescents ≥12 to <15 years: Start with 5 mg, possible increase to 6 mg or further to 8 mg (maximum) based on C1D14 and C2D7 phosphate value. For subjects ≥6 to <12 years: Start with 3 mg, possible increase to 4 mg or further to 5 mg (maximum) based on C1D14 and C2D7 phosphate value. See guidelines in Section 6.1 for full details of dosing. Note that children and adolescents remain under the titration and dosing schedule under which they were enrolled				Once Daily				X[b]	
Study Drug Diary	Subjects or their parent/guardian will record study drug administration in dosing diaries.				Once Daily					
Safety Assessments										
Medical history and physical examination	During Screening Phase, complete physical examination including neurological and hip examination, height, and weight. Screening for risk factors for musculo-skeletal diseases, eg SCFE should be conducted at screening. During Treatment Phase, limited physical examination of affected organs, neurological examination including seizure activity (subjects with primary CNS tumors, CNS metastases or other subjects at the investigator's discretion, only) and weight; record new abnormalities as AE. Weight with corresponding percentiles should be documented. If examination occurs more than 7 days prior to the first dose of study drug, it must be repeated on C1D1 prior to dosing. Measure height using a stadiometer. Height with corresponding percentiles should be documented.		X		X	C2D7	X	X	X	
Tanner Staging	Tanner Staging is discontinued at 18 years of age.				X			X		
Vital signs	Check temperature, heart rate, systolic and diastolic blood pressure; record all clinically significant abnormalities as AE.		X		X	C2D7	X	X	X	

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3			Cycle 4+		
					Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days
Performance status	Performance status using the Lansky Score (≥6 to <16 years of age) or the Karnofsky Score (≥16 to <18 years of age)			X	X			X		
Urine or serum β-hCG pregnancy test	Females of childbearing potential only. Screening test within 7 days prior to the first dose, or at C1D1 prior to the first dose.			-7 days	Day 1 of every cycle from Cycle 2				X	
12-lead ECG	Record postdose ECGs (see Section 8.3.3 for exact timing). May be performed more often as clinically indicated. Please conduct ECGs preferably at the same time each day at each visit (at which an ECG is conducted).		X		C2D1			C4D1		
Ophthalmologic exam	To be performed by an ophthalmologist, for exact assessments see Section 8.3.5.		X							
Amsler Grid Test	To be performed by treating physician or nurse (as directed by specific site instructions).		X		C2D1 C3D1			X	X	
Radiographic (growth plate assessment) imaging	Plain anteroposterior (AP) radiograph of the (left or right) tibia prior to C1D1. - If closed growth plate, no further radiographs required. - If open growth plate, repeat plain AP radiographs of the same growth plate every 3 months for 6 months, and thereafter, every 6 months. If there is evidence of growth plate changes, see Section 8.3.7 for instruction regarding follow up.		X		Every 3 months (from C1D1) for 6 months, and, thereafter, every 6 months (±7 days) (ONLY for children and adolescents with open growth plates. See notes)					
Radiographic (bone age) imaging	Plain posteroanterior (PA) radiograph of the nondominant hand and wrist prior to C1D1.		X		Every 3 months (from C1D1) for 6 months, and, thereafter, every 6 months (±7 days)					
Radiographic imaging of the hip	AP and frog leg lateral of both hips. If closed growth plate, no further radiographs required. Note: Additional imaging may be performed if clinically indicated (groin, hip, thigh or knee pain, and/or difficulty with ambulation). If X-ray imaging is inconclusive and symptoms persist, a MRI should be performed. If there is evidence of growth plate changes, see Section 8.3.7 for instruction regarding follow up.		X		Every 24 weeks (from C1D1) (±7 days) See Note					
DEXA Scan	Bone densitometry should be conducted as shown.		X		At 6 months, at 12 months, and, thereafter, every 12 months (from C1D1) as clinically indicated (±14 days)					

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3			Cycle 4+		
					Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days
Clinical Laboratory Assessments: Clinical laboratory test results (except parathyroid hormone) must be available prior to dosing at C1D1 and subjects should continue to meet eligibility requirements per the Inclusion/Exclusion criteria. Results of previous testing should be available for comparison as clinically necessary.										
Hematology	May be performed within 3 days prior to D1 of each cycle (Section 10.2)			X	X	C2D7	X	X	X	
Chemistry	May be performed within 3 days prior to D1 of each cycle (Section 10.2)			X	X	C2D7	X	X	X	
Parathyroid hormone (PTH)	May be performed within 3 days prior to D1 of each cycle (Section 10.2)			X	X	C2D7	X	X (every 3rd cycle after C6)	X	
Thyroid stimulating hormone (TSH), T3, T4				X	C1D1 C3D1			odd numbered cycles	X	
Insulin-like growth factor 1 (IGF-1)				X	At time of DEXA scan					
Efficacy Assessments										
Radiological assessment and/or skin photography, as applicable	Identical methodology [CT, or MRI if site of disease not evaluable by CT] should be used for disease assessment at baseline and throughout the study whenever possible. Additional assessments may be performed, if clinically indicated. Skin lesions that cannot be measured radiographically may be assessed using skin photography. For subjects with low-grade gliomas where a lower frequency of imaging is sufficient, a 24-week frequency (±7 days) may be adopted after a minimum of 12 months with the sponsor's approval. If a response (partial response or complete response) is observed, an additional scan for confirmation is required 4-8 weeks (±7-day window) after the first scan showing the response.		X[e]		Every 12 weeks (4 cycles) (±7 days). See notation regarding low-grade gliomas. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 8.1.2). Imaging during continuation of treatment after disease progression is detailed in Section 8.2.2.					
Investigator RECIST or RANO Assessment	RECIST 1.1 will be applied by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status. The RANO criteria will be used to assess response for subjects with primary CNS tumors.				X					

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
					Cycles 1, 2, and 3			Cycle 4+		
		Molecular Eligibility Screening Period	Full-study Screening Period		Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days
Patient-reported Outcome Assessments (Conducted in the order shown below)										
PGIS	PRO measures to be completed preferably before any other study procedures. Predose at C1D1.[f] During the Treatment Phase, PRO measures stop at Cycle 49 (Cycle 49 is the last assessment).	PRO measurements discontinued with Amendment 6								
PGIC	PRO measures to be completed preferably before any other study procedures.[f]									
Peds FACT-Br Child/Adolescent version	PRO measures to be completed preferably before any other study procedures. Predose at C1D1. The follow-up visit may be conducted by telephone. This assessment is performed during the Follow-up Phase for the first 3 visits or until the start of subsequent anticancer therapy.[f]									
EQ-5D-5L	PRO measures to be completed preferably before any other study procedures. Predose at C1D1. The follow-up visit may be conducted by telephone. This assessment is performed during the Follow-up Phase for the first 3 visits or until the start of subsequent anticancer therapy.[f]									
Peds FACT-Br Parent of Child/Adolescent version	PRO measures to be completed preferably before any other study procedures. Predose at C1D1. The follow-up visit may be conducted by telephone. This assessment is performed during the Follow-up Phase for the first 3 visits or until the start of subsequent anticancer therapy.[f]									
PK and Biomarker Assessments[i]										
Blood (plasma) for ctDNA	Collect sample predose				C1D1 (predose)			C4D1 C7D1	X	
PK Blood Sample	At C1D14 and C2D14, if morning visit, collect predose sample. If afternoon visit, collect postdose sample. At C2D1, collect predose sample and 2-4-hour postdose sample. Record dosing and PK collection times. See Section 8.5 for exact timing. At C3D1, collect predose sample and 1h, 2h, 4h, 6h, 12h postdose. The 12-hour postdose sample can alternatively be collected at 24h postdose.				C2D1 C3D1[g] (See note)		C1D14 C2D14 (See note)	C4D1 predose		

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
		Molecular Eligibility Screening Period	Full-study Screening Period		Cycles 1, 2, and 3			Cycle 4+		
					Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days
Protein Binding Blood Sample	At C3D1, collect a sample 2 hours postdose. Record dosing and protein binding sample collection times. See Section 8.5.				C3D1 (See note)					
CYP2C9 Blood Sample	This sample is collected at C1D14 at any time, or any day after C1D14.					C1D14 (See note)				
Optional "Other Assessment"										
CSF PK sample in CNS tumor only (when conducted as part of routine CSF procedure)					CSF PK sample collected any time after Cycle 1 during the Treatment Phase					
Plasma PK Sample at time of CSF Evaluation					Plasma PK sample collected at the same time as the CSF Evaluation during the Treatment Phase					
Ongoing Subject Review										
Concomitant medications	Concomitant therapies must be recorded at the time of full-study screening, during the study, and up to 30 days after the last dose of study		X						X	
Adverse events	Collected from the day the Full-study ICF is signed until 30 days after last dose of study drug. If study drug is discontinued due to drug-related AE, AE should be monitored until it resolves to baseline, stabilizes, or is deemed irreversible, subject dies, or subsequent therapy is started, whichever occurs first.		X						X	X
Survival status	May be assessed via telephone call. Survival status will be monitored until death, withdrawal of consent, lost to follow up, or end of study, whichever occurs first								X	X
Subsequent anticancer therapy	May be assessed via telephone call. Start of subsequent anticancer therapy will be monitored until death, withdrawal of consent, lost to follow up, or end of study, whichever occurs first								X	X
Medical Resource Utilization	Collected throughout the study (See Section 8.9)				Continuous (Section 8.9)				X	

Abbreviations: AE=adverse event; β-hCG=beta-human chorionic gonadotropin; C=cycle; CNS=central nervous system; CSF=cerebrospinal fluid; CT= computed tomography; ctDNA=circulating tumor DNA; CXDX=Cycle X Day X; D=day; DEXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life – 5 Dimensions-5 Levels; FGFR=fibroblast growth factor receptor; ICF=informed consent form; IGF-1=Insulin-like growth factor 1; MRI= magnetic resonance imaging; NGS=next-generation sequencing; Peds FACT-Br = Pediatric Functional Assessment Of Cancer Therapy – Brain; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Symptom Severity; PK=pharmacokinetic; PRO=patient reported outcome; PTH=Parathyroid hormone; RANO=Response Assessment in Neuro-Oncology; RECIST=Response Evaluation Criteria in Solid Tumors; TSH=thyroid stimulation hormone, T3=total triiodothyronine, T4=free thyroxine.

Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)

Parameter		Screening Phase			Treatment Phase[h] (21-day cycles)				End of Treatment Visit[h]	Follow-Up Phase[h]
					Cycles 1, 2, and 3			Cycle 4+		
		Molecular Eligibility Screening Period	Full-study Screening Period		Day 1	Day 7	Day 14	Day 1		
Visit Window	NOTES[a]	N/A	-30 days	-14 days	C1: -3 days to D1 C2, C3: -2 to +2 days	C2 only +2 days	+2 days	-2 to +2 days	30 (+7) days after last dose[b]	every 12 weeks ±7 days

[a]Adolescent subjects who become 18 years of age during the study will continue the assessments on the Adolescent Schedule of Activities with the exception of Tanner staging that will no longer be performed once subjects turn age 18 years of age. However, they will sign the adult ICF at 18 years of age (or the age of majority in their respective country/territory).

[b]The End of Treatment Visit is conducted 30 (+7) days after last dose of study drug or prior to starting any subsequent cancer treatment. Once the end of data collection timepoint has been achieved, follow-up of subjects will end, and data collection will conclude. Only serious adverse events will be reported in the company safety repository (See Appendix 13). Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment (see Section 6.7); during this period, only serious adverse events will be reported into the company safety repository.

[c]See Section 8.1.1 for detailed instruction regarding the consent process. For subjects signing a Full-study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 30-day window starts with the first planned study procedure other than the tissue biopsy and informed consent; however, AEs will need to be collected from the time the Full-study ICF is signed.

[d] 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. Biopsy of the brain, lung/mediastinum, pancreas, or for endoscopic procedures extending beyond the esophagus, stomach, or bowel is not permitted; please contact sponsor prior to conducting biopsy.

[e]CT/MRI performed as part of routine standard of care but prior to the ICF being signed, will be accepted provided the subject enrolls within 30 days of assessment.

[f]PRO measures may be conducted using Interview Mode, if necessary.

[g]If indicated by the emerging safety findings or if the scheduled PK samples are not collected due to treatment interruption, blood samples may be collected at a later site visit (on C3D14).

[h]Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Section 10.12.

[i]In the event an investigator perceives any risk from any blood collection, the investigator can contact the sponsor to evaluate the possibility to delay sampling or reducing the number of blood tubes necessary.

2. INTRODUCTION

Erdafitinib (JNJ-42756493) is a selective and potent pan fibroblast growth factor receptor (FGFR) 1-4 inhibitor with demonstrated clinical activity in subjects with solid tumors identified to have alterations in the FGFR pathway. In the United States (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. This Phase 2, open-label study will evaluate the safety and efficacy of erdafitinib in subjects with advanced solid tumors (other than urothelial tumors), and FGFR gene alterations.

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.

2.1. Study Rationale

FGFR gene alterations (mutations and fusions) are proposed to be oncogenic drivers in many solid tumors. Review of literature and genetic databases reveal multiple solid tumor histologies with FGFR mutations and fusions that may be plausible targets for treatment with erdafitinib. FGFR alteration frequency and observed alterations (mutations versus fusions) vary across tumor types, eg, FGFR mutations are more common in urothelial carcinoma while FGFR fusions are more frequently observed in glioblastoma. The common result of FGFR alterations across tumor types is activated FGFR signaling, providing rationale that patients with FGFR alterations may benefit from erdafitinib treatment. The antitumor effect of erdafitinib was observed in subjects with urothelial cancer with select FGFR alterations in both Phase 1 and Phase 2 studies, and clinical activity has also been observed in subjects with cholangiocarcinoma (Chen 2018). This study targets the underlying altered biology of FGFR-driven tumors irrespective of the solid tumor histology subtype.

Patients with solid tumors with a significant frequency of FGFR alterations (Table 1) have a dismal prognosis in advanced disease and limited efficacy with standard of care options in the recurrent, metastatic setting; especially for second-line therapy or beyond. Glioblastoma multiforme (GBM) is a solid tumor with a high frequency of FGFR alterations (~21%). Approved second-line GBM therapies include bevacizumab (US) or lomustine (European Union [EU]) with a median progression-free survival (PFS) of 4 months and a median survival of 9 months (Friedman 2009). Squamous cell carcinomas of the head and neck (ie, HNSCC) have an FGFR alteration frequency of 9%, and HNSCC patients with recurrent or metastatic disease on second-line therapy have a median survival between 7 to 8 months and a median PFS of 2.1 months with programmed death-ligand 1 (PD-L1) therapies (Ferris 2016). Cholangiocarcinoma is a low prevalence tumor type with a notable frequency of FGFR alterations (11%) for which there are no approved second-line therapies. Patients with solid tumors in which FGFR alterations are most frequently observed (Table 1) have poor outcomes and limited therapeutic options; thus, there remains a high unmet need for additional treatments in the metastatic setting. In general, for pediatric subjects, no standard of care has been established for relapsed and or refractory disease in these tumor types,

which represents an unmet medical need. Taken together, the common underlying biology of FGFR-altered tumors in conjunction with the high unmet need for additional therapeutic options for patients with these tumors provide a strong rationale for targeting the FGFR-positive population across solid tumors with erdafitinib.

2.2. 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.

2.2.1. Erdafitinib

Erdafitinib is an oral pan-FGFR tyrosine kinase inhibitor shown to have in vivo antitumor activity in mouse xenograft models of FGFR-driven gastric, bladder, and non-small cell lung cancer (NSCLC) tumor models, and in patient-derived xenografts from squamous NSCLC, gastric, breast, and hepatocellular tumors.

In humans, erdafitinib exhibited a dose-related increase in the maximum plasma drug concentration (C_{max}) and area under the curve (AUC) and time-independent pharmacokinetics (PK) within the dose range of 0.5 mg to 12 mg, both after single and multiple daily dosing. Median time to maximum concentration observed 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.

An in vitro metabolism study in human liver microsomes and hepatocytes showed major involvement of cytochrome P 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 AUC following multiple daily dosing.

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. For all subjects with relapsed/refractory urothelial cancer, the overall response rate (ORR) across dose levels was 40.0% (12/30 subjects). At the 9 mg dose level, ORR was 70.0% (7/10 subjects) for response-evaluable subjects with urothelial cancer who harbored selected FGFR aberrations. The most frequently reported adverse events (AEs) were hyperphosphatemia (65%), dry mouth (46%), asthenia (45%), stomatitis (39%), constipation (37%), and decreased appetite (34%).

In a Phase 2a Study (Study 42756493LUC2001, based on preliminary data from the cholangiocarcinoma cohort with a clinical cut-off date of 25 March 2019), the antitumor effect of erdafitinib was observed among subjects with any FGFR alterations (ORR, 46.7% [7/15 subjects]; median duration of response [DOR], 7.1 months; disease control rate [DCR], 80.0% [12/15 subjects]; median PFS, 5.6 months [13/15 subjects]) and an even greater antitumor response was observed among the 9 evaluable subjects with FGFR2 or FGFR 3 fusions (ORR, 66.7% [6/9 subjects]; median DOR, 7.3 months; DCR, 100.0% [9/9 subjects]; median PFS, 12.7 months [7/9 subjects with events]). In addition, for the 6 subjects with FGFR2 and FGFR 3 mutations, the ORR was 16.7% (1/6 subjects) and the DCR was 50.0% (3/6 subjects).

In a global Phase 2 study (Study 42756493BLC2001, n=210), the antitumor effect of erdafitinib was demonstrated in subjects with locally advanced or metastatic urothelial cancer who also had select FGFR alterations. The confirmed ORR for chemo-relapsed/refractory subjects who were treated in the erdafitinib 8-mg daily regimen with pharmacodynamically guided up-titration to 9-mg daily (N=87) was 40.2% based on investigator assessment and 32.2% by Independent Review Committee (IRC) assessment. The most frequently reported AEs were hyperphosphatemia (77%), stomatitis (58%), diarrhea (51%), and dry mouth (46%). For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Investigator's Brochure.

A subprotocol of the NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) Trial APEC1621B[a] is currently enrolling pediatric subjects ≥1 and ≤21 years of age with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses, and central nervous system (CNS) tumors) harboring specified activating mutations of the FGFR1/2/3/4 pathway for treatment with erdafitinib. The primary endpoint is ORR. Subjects will remain on treatment until progression of disease or drug-related toxicity requiring discontinuation of treatment; otherwise, a subject may remain on erdafitinib for 2 years. The study began 30 November 2017 and approximately 20 subjects are expected to be enrolled. As of CCI, no new safety signals from the CCI subjects enrolled (C subjects aged between ≥1 and <12 years of age and C subjects aged between ≥12 and <21 years of age) were reported from this ongoing study.

2.2.2. The Role of Fibroblast Growth Factor Receptor

The FGFRs 1 to 4 are a family of highly conserved, widely distributed transmembrane tyrosine kinase receptors (Parker 2014). Binding of fibroblast growth factor to FGFR results in receptor dimerization and phosphorylation of the kinase domain, with activation of subsequent downstream signaling pathways regulating key cellular processes, including differentiation, proliferation, survival, migration, and angiogenesis (Dienstmann 2014).

[a] The National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) APEC1621B study, Phase 2 Subprotocol of JNJ-42756493 (Erdafitinib) in Patients with Tumors Harboring FGFR1/2/3/4 Alterations; this is the sponsor's collaborative study with NCI and the Children's Oncology Group (COG).

Deregulation of FGFR signaling has been implicated in many forms of human malignancies (Babina 2017, Dienstmann 2014, Touat 2015). FGFR signaling can be aberrantly activated in tumor cells in several ways including amplification, gene fusion, or mutation. Mutations occurring in the extracellular or transmembrane domains of the receptor result in ligand-independent dimerization and constitutive activity. FGFR gene fusions induce aberrant activation via substitution of the C-terminal regulatory domain of FGFR with protein-protein interaction modules of the fusion partner, leading to ligand-independent dimerization and activation of FGFR (Katoh 2019). FGFR alterations have been associated with neoplastic progression and tumor vascularization in multiple cancer types, including breast, lung, prostate, endometrial, gastric, and urothelial carcinoma (Parker 2014, Katoh 2019). Therefore, targeting FGFRs with a small molecule kinase inhibitor is a logical development strategy.

2.2.3. Fibroblast Growth Factor Receptor Alterations in Solid Tumors

FGFR alterations in adult and pediatric solid tumors are discussed in the following subsections. Further detail regarding tumor histologies selected for central screening and the inclusion of any FGFR mutation or fusion positive tumor histology based on local testing is provided in Section 8.1.1.1. Starting with Amendment 4, only local reports will be used for molecular screening.

Adult Solid Tumors

FGFR alterations including gene amplification, mutation, and fusion are observed across many types of cancer, with FGFR amplification being the most commonly observed event (Katoh 2019). Although FGFR gene amplifications are frequent, clinical activity with FGFR kinase inhibitors like erdafitinib has been most clearly observed in patients with FGFR mutations and gene fusions.

FGFR mutations and fusions have been reported in breast cancer, urothelial cancer, NSCLC, cholangiocarcinoma, gynecological cancers, and other tumor histologies.

For some tumor histologies, the predominant FGFR alteration (ie, fusion vs. mutation) may be tissue specific. For example, FGFR fusions are more prevalent (than mutations) in glioblastoma and cholangiocarcinoma, while FGFR mutations are more prevalent (than fusions) in urothelial and endometrial cancers (Katoh 2019, Knowles 2015, Babina 2017).

Target FGFR mutations and FGFR fusions, FGFR mutations and fusions predicted to likely be pathogenic based on genomic features, as defined in Study CAN2002 (see Section 4.2.1), are found across multiple tumor histologies. Table 1 lists approximate frequencies of total (unfiltered), and target FGFR mutations and gene fusions based on filtering of alterations identified in the TCGA (The Cancer Genome Atlas) and GENIE (the AACR Project Genomics Evidence Neoplasia Information Exchange) genomic databases. For pancreatic cancer, although no target FGFR alterations were observed in TCGA and GENIE databases, clinical experience supports the presence of target FGFR alterations (ie, FGFR fusions) in this histology.

Table 1: Frequency of FGFR Mutations and Fusions in Advanced Cancer

	GENIE Database Estimates	
Tumor Type	**N**	**RAGNAR Eligible FGFR variants %[1]**
Cholangiocarcinoma	1111	7.65
Head and Neck Squamous Cell Carcinoma	1076	2.51
Low Grade Glioma	1157	2.33
High Grade Glioma	1986	2.06
Cervix	522	1.92
Endometrial Carcinoma	3240	1.82
Lung Squamous Cell Carcinoma	1134	1.68
Cancer of Unknown Primary	2669	1.09
Colorectal Adenocarcinoma	7451	0.47
Invasive Breast Carcinoma[2]	8367	0.45
Cervical Adenocarcinoma	241	0.41
Stomach Adenocarcinoma	746	0.40
Salivary Carcinoma	597	0.34
Lung Adenocarcinoma	8127	0.25
Soft Tissue[3]	3778	0.16
Pancreas	3805	0.16
Renal Cell Carcinoma	1591	0.13

1. AACR-GENIE database accessed June 2021
2. In CAN2002 ER/PR positive only
3. Soft Tissue cancers (in AACR-GENIE database) including: Dendritic Cell Sarcoma, Epitheloid Fibrosarcoma, Liposarcoma, Myxoma, Rhabdomyosarcoma

Pediatric Solid Tumors

FGFR alterations have also been observed in pediatric cancers.

The screening protocol for the NCI-COG Pediatric MATCH study identified 422 pediatric patients (aged 1 to 21 years) with treatment-refractory or recurrent cancers between 24 July 2017 and 31 December 2018: 71% solid tumors, 24% CNS tumors, and 5% lymphomas/histiocytoses (Parsons 2019). The percentage of subjects with actionable mutations was similar between younger (35%, <12 years of age) and older (25%, ≥12 years of age) subjects and 5 subjects were reported with FGFR1 alterations.

While the incidence and prevalence of specific types of solid tumors differs between adult and pediatric subjects, FGFR alterations are observed in both populations which may be candidates for targeted treatment with erdafitinib. Observed differences between adult and pediatric cancers

indicate that the pediatric FGFR-altered subject population may be better served with customized, broader FGFR molecular eligibility criteria.

The list of Broad Panel Cohort eligible FGFR mutations was defined based on genomic datasets derived predominantly from adult subjects. Broad Panel Cohort eligible FGFR mutations are observed in the pediatric population (Table 2). However, a significant number of pediatric tumors have mutations not included on the Broad Panel Cohort list. This list was determined by assessing the FGFR alteration landscape of the 8 most common pediatric tumors (Table 2). Although 9 of 185 FGFR mutations observed in the pediatric population are present in the Broad Panel Cohort (Figure 2), the bulk of pediatric mutations are not represented.

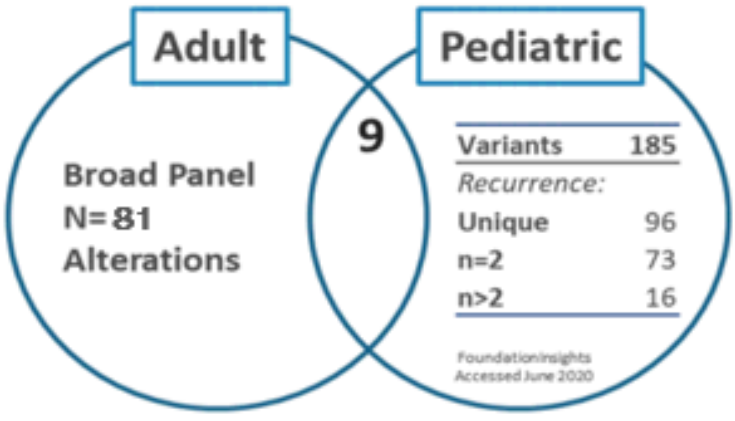
Table 2: FGFR Mutations and Fusions Observed in Common Pediatric Tumors

Abbreviation	Histology	Patients	FGFR+ %	Broad Panel Cohort Representation (%)
GBM	Glioblastoma multiforme	267	33	8
LGG	Low Grade Glioma	1179	20	10
PA	Pilocytic Astrocytomas	241	14	9
RMS	Rhabdomyosarcomas	321	13	8
WLM	Wilms' tumor	127	6	1
NBL	Neuroblastoma	394	5	1
EWS	Ewing Sarcoma	268	3	
MDB	Medulloblastoma	199	1	

FGFR=fibroblast growth factor receptor
FoundationInsights database accessed June 2020.
Note that the FoundationInsights database may underrepresent fusions due to limitation of DNA-based profiling.

Figure 2 shows the overlap of the pediatric landscape of FGFR mutations in 8 common pediatric tumors with the list of Broad Panel Cohort eligible alterations derived from adult data. Notably, compared with the >8,000 mutations observed across adult tumors, the most common pediatric tumors exhibited 185 distinct FGFR mutations.

Figure 2: Overlap of Pediatric Alterations with Broad Panel Cohort Markers

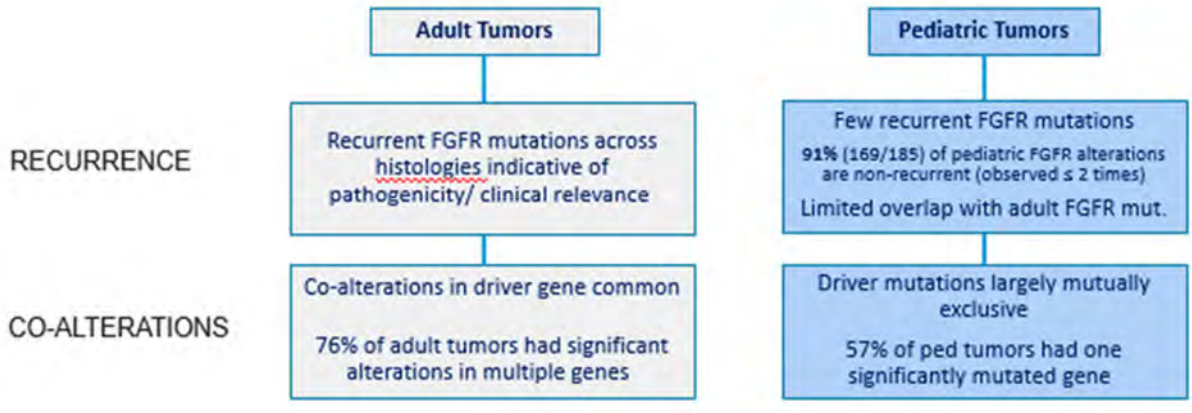


FGFR alteration frequencies for 8 of the most frequently observed pediatric tumors were assessed utilizing the FoundationInsights database. The table below lists the percent of pediatric subjects with FGFR mutations and fusions and the proportion of subjects eligible for the Broad Panel Cohort.

Additional considerations supportive of a custom cohort for pediatric tumors are the smaller landscape of FGFR alterations in pediatric tumors, the lower overall mutation burden in pediatric tumors compared to adults, and that driver alterations are largely mutually exclusive in the pediatric population. Gröbner et al (Gröbner 2018), analyzed the landscape of genomic alterations across childhood cancers compared with adults. As anticipated, the burden of somatic alterations was higher in the adult population compared to pediatric patient tumors, with mutation frequencies 14 times lower in the pediatric cancers. Significantly mutated genes were largely mutually exclusive across pediatric cancer types, highlighting the relevance of single-driver alterations in pediatric cancers versus the adult population where co-alterations are more frequent. Notably, FGFR1 was reported as one of 77 significantly mutated genes in pediatric cancers. In contrast, FGFR1 alterations are relatively rare in the adult population where FGFR2 and FGFR3 alterations are more common.

Recurrence of alterations, within or across tumor types, was a key factor in determining likely pathogenicity in the Broad Panel Cohort based on adult genomic data. Recurrent FGFR mutations are relatively rare in the pediatric population. Assessment of the 8 most common pediatric tumors using the FoundationInsights database revealed that 91% of 185 FGFR alterations identified were observed in ≤2 instances (Figure 3). Additionally, the Gröbner study (Gröbner 2018) reported 47% of pediatric tumors had at least one significant mutation with 57% of those tumors having only one significantly mutated gene; as opposed to the adult population where 93% of cancers had at least one significantly mutated gene alteration and 76% had alterations in multiple significantly mutated genes.

Figure 3: Key molecular differences between adult and pediatric cancers



Mut = mutation

These data indicate that a customized approach is warranted to best serve the pediatric FGFR-altered subject population. Therefore, the molecular eligibility criteria selected for the Pediatric Cohort differ from those of the Broad Panel Cohort (see Section 5.1).

2.3. Benefit-Risk Assessment

FGFR alterations have been shown to be associated with oncogenic potential in several tumor histologies and have been observed across many tumor histologies. The patients with advanced life-threatening disease and FGFR alterations who will be enrolled in this study will have already failed at least one prior line of systemic therapy and have limited available treatment options. For this group, there is unmet medical need due to the absence of available treatments at this stage of their disease. Erdafitinib inhibits FGFR signaling in FGFR-driven tumors. In clinical studies, erdafitinib treatment resulted in durable anti-tumor response. Corresponding DOR, PFS, and OS endpoints predict clinical benefit for patients with locally advanced or metastatic urothelial cancer who have FGFR alterations and have relapsed after platinum-based chemotherapy. The potential risks of erdafitinib for adults include central serous retinopathy and hyperphosphatemia. In addition to the risk for adults, risks for adolescents and children include the possibility of bone growth abnormalities based on pre-clinical findings in rats and dogs (cartilage dysplasia) attributed to the pharmacology of erdafitinib. In this study, to monitor bone growth in adolescents and children (subjects younger than 18 years), radiographic imaging and bone densitometry will be conducted as indicated on the Schedule of Activities for Children and Adolescents. Subjects <6 years of age are not included in the study because an age-appropriate formulation of erdafitinib is not currently available. The safety profile of erdafitinib was acceptable in the urothelial cancer population; the profile was characterized by mostly mild to moderate eye, skin and nail disorders. The events in the urothelial population were manageable with available medical measures, temporary treatment interruption, or eventual dose reduction.

Taking into account the measures utilized to minimize risk to subjects in this study (eg, guidance regarding blood volume in adolescents in Section 4.2.4, guidance for specific erdafitinib toxicities in Section 6.6.1, prohibited medications in Section 6.5.2, precautions for concomitant medications in Section 6.5.3, and monitoring of results of safety assessments in Section 8.3), the potential risks identified in association with erdafitinib are justified by the anticipated benefits that may be afforded to patients with advanced solid tumors with FGFR gene alterations for whom there are no available treatments, including subjects ≥6 years of age. More detailed information about the known and expected benefits and risks of erdafitinib may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective (Broad Panel Cohort and Core Panel Cohort)	
To evaluate the efficacy of erdafitinib in terms of ORR as assessed by the Independent Review Committee (IRC) in subjects with advanced solid tumors with target FGFR mutations and any gene fusions (Broad Panel Cohort), or in a pre-specified subgroup of subjects with a selected panel of FGFR markers (Core Panel Cohort), or in both cohorts.	The proportion of subjects who achieve a complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (RECIST v1.1.) or Response Assessment in Neuro-Oncology (RANO) as assessed by IRC
Primary Objective (Pediatric Cohort)	
To evaluate the efficacy of erdafitinib in terms of ORR as assessed by the IRC in pediatric subjects with advanced solid tumors with FGFR mutations, any gene fusions, or FGFR internal tandem duplication (Pediatric Cohort), including adolescent subjects with target FGFR mutations and any gene fusions	The proportion of subjects who achieve a CR or PR based on RECIST v1.1 or RANO as assessed by IRC
Secondary Objectives	
To evaluate the efficacy of erdafitinib, in terms of the ORR, as assessed by investigator	The proportion of subjects who achieve a CR or PR based on RECIST v1.1 or RANO as assessed by investigator
To evaluate the efficacy of erdafitinib in terms of DOR	DOR: the duration 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, whichever comes first. Data from subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment
To evaluate other measures of efficacy including DCR, clinical benefit rate (CBR), PFS, and overall survival (OS)	• DCR: the proportion of subjects with CR, PR or stable disease (SD) • CBR: the proportion of subjects with CR, PR or durable SD (defined as a duration of at least 4 months) • PFS: 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 • OS: 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
To evaluate erdafitinib PK	PK exposure parameters. This endpoint includes pediatrics.
To evaluate safety and tolerability of erdafitinib	Incidence and severity of AEs
To evaluate Health-Related Quality of Life (HRQoL)	Change from baseline in patient-reported health status and physical functioning scales of the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC-QLQ-C30; for subjects ≥18 years of age) or Pediatric Functional Assessment Of Cancer Therapy-Brain (Peds FACT-Br for subjects <18 years of age), Patient Global Impression of Symptom Severity (PGIS), Patient Global Impression of Change (PGIC), and European Quality of Life – 5 Dimensions-5 Levels (EQ-5D-5L).

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of erdafitinib in subjects with advanced solid tumors in the Exploratory Cohort in terms of ORR	• The proportion of subjects who achieve a CR or PR based on RECIST v1.1 or RANO as assessed by the investigator • DOR, DCR, CBR, PFS, OS
Identify FGFR mutations and tumor histologies sensitive to erdafitinib from the Exploratory Cohort	FGFR mutations and tumor histologies with clinical response to erdafitinib which are not represented in the Broad Panel Cohort.
To explore PK exposure-response relationships	Quantitative relationship between PK exposure parameters, pharmacodynamic (PD) parameters (serum phosphate), and safety/efficacy parameters
To assess tumor-specific biomarkers (DNA, RNA, protein) in archival tumor samples, and possibly blood that potentially predict tumor response or resistance to erdafitinib	Analysis of co-occurring genomic alterations from archival tumor samples
To evaluate the relationship between CYP2C9 polymorphism and PK of erdafitinib	Effect of CYP2C9 polymorphism on the PK of erdafitinib
To assess the distribution of erdafitinib in the cerebrospinal fluid (CSF) (when available)	Erdafitinib concentration in CSF, ie, the CSF-to-plasma concentration ratios
To collect Medical Resource Utilization data that may be used in future economic models	Evaluation of all the health states generated by the EQ-5D-5L utility and visual analog scale (VAS).

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

Hypothesis

The primary hypothesis of this study is that treatment with erdafitinib orally once daily will improve ORR with a target rate of 35% over a null rate of 15% in subjects with advanced solid tumors that harbor target FGFR alterations in the Broad Panel Cohort, the Core Panel Cohort, or both cohorts. Comparable response from erdafitinib treatment is expected in the pediatric and adult study populations, ie, a 35% of ORR with a null hypothesis of 15% for ORR.

3.1. Cholangiocarcinoma Expansion Cohort

Objectives	Endpoints
To evaluate the efficacy and safety of erdafitinib in subjects with cholangiocarcinoma with target FGFR mutations and any gene fusions	Key efficacy endpoints will be evaluated including ORR assessed by IRC/investigator, DOR, PFS, and OS Incidence and severity of AEs

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label study of the efficacy and safety of erdafitinib in subjects with advanced solid tumors (other than urothelial tumors) and FGFR gene alterations. A diagram of the study design is provided in Section 1.2, Schema (Figure 1).

Approximately 280 subjects ≥12 years of age with FGFR genetic alterations will be enrolled in the Broad Panel Cohort (approximately 240 subjects for 200 response-evaluable subjects) and the Exploratory Cohort (approximately 40 subjects). An additional, approximately 30 subjects will be enrolled in the Cholangiocarcinoma Expansion Cohort. A separate Pediatric Cohort (≥6 to <18 years) will enroll 20 children or adolescent subjects who have progressed following prior therapies and who have no acceptable standard therapies, and approximately 6 additional children or adolescent subjects who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. Adolescent subjects enrolled in the Broad Panel Cohort (≥12 to <18 years) will be analyzed as part the Broad Panel Cohort and the Pediatric Cohort.

Subjects will be instructed to take erdafitinib orally at approximately the same time each day, with or without food, until disease progression, intolerable toxicity, withdrawal of consent decision by the investigator to discontinue treatment, or the end of data collection timepoint has been achieved. Instructions for subjects who have difficulties swallowing the tablets are provided in Section 6.1. Adults (aged 18 years and older) and adolescent subjects aged ≥15 to <18 years will start with a dose of 8 mg, once daily for 21 days on a continuous 21-day cycle. The dose will be up-titrated to 9 mg once daily based on Cycle 1 Day 14 serum phosphate levels. Adolescent subjects aged ≥12 to <15 years will start with an erdafitinib dose of 5 mg with possible up-titration to 6 mg or further to 8 mg based on Cycle 1 Day 14 and Cycle 2 Day 7 serum phosphate levels. Children ≥6 to <12 years of age will start with an erdafitinib dose of 3 mg with possible up-titration to 4 mg or further to 5 mg based on Cycle 1 Day 14 and Cycle 2 Day 7 serum phosphate levels. See Section 4.3 for dose justification.

The Screening Phase will start with the Molecular Eligibility Screening Period during which samples are screened for FGFR alterations by the central or local laboratory, or the presence of an FGFR alteration is identified by an existing local report (that must be reviewed by the sponsor).

- Subjects from all solid tumor histologies (except bladder) with an eligible FGFR mutation or fusion identified via local testing results (as outlined in Section 8.1.1) are considered molecularly eligible for the study.

- Subjects with advanced solid tumors may receive central molecular screening if they have received at least 1 line of systemic therapy and are anticipated to fulfill study eligibility criteria within 6 months. Central molecular screening will be selective to the following tumor histologies (see Figure 6): high-grade gliomas (eg, glioblastoma) and low-grade gliomas; squamous cell head and neck cancers; soft tissue sarcoma; cholangiocarcinoma; endometrial, cervical, and ovarian cancers; squamous NSCLC; renal cell cancer; esophageal and gastric cancers; hormone-sensitive breast cancer (estrogen positive [ER]/progesterone positive [PR]); hepatocellular carcinoma, pancreatic cancer, salivary gland tumors, colorectal cancer, and thymic cancer/thymoma. Central screening for any tumor type will be allowed for children and adolescent subjects or if a local report is deemed insufficient. For enrollment in each tumor histology, the sample size is capped at approximately 30 subjects. The tumor histology list for this cap, including a group of Other, is pre-defined in **Table 16**.

- Starting with Amendment 4, only local reports will be used for molecular screening.

The Full-study Screening Period will occur after the completion of prior treatment and documentation of disease progression for subjects who meet the molecular screening criteria. There must be no intervening therapy between documented disease progression and enrollment in this study.

The Treatment Phase will continue until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or the end of data collection timepoint has been achieved. Treatment with erdafitinib may continue beyond the initial demonstration of disease progression (according to criteria in Section 8.2.2.). 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 study ends (ie, the end of data collection timepoint has been achieved), whichever comes first.

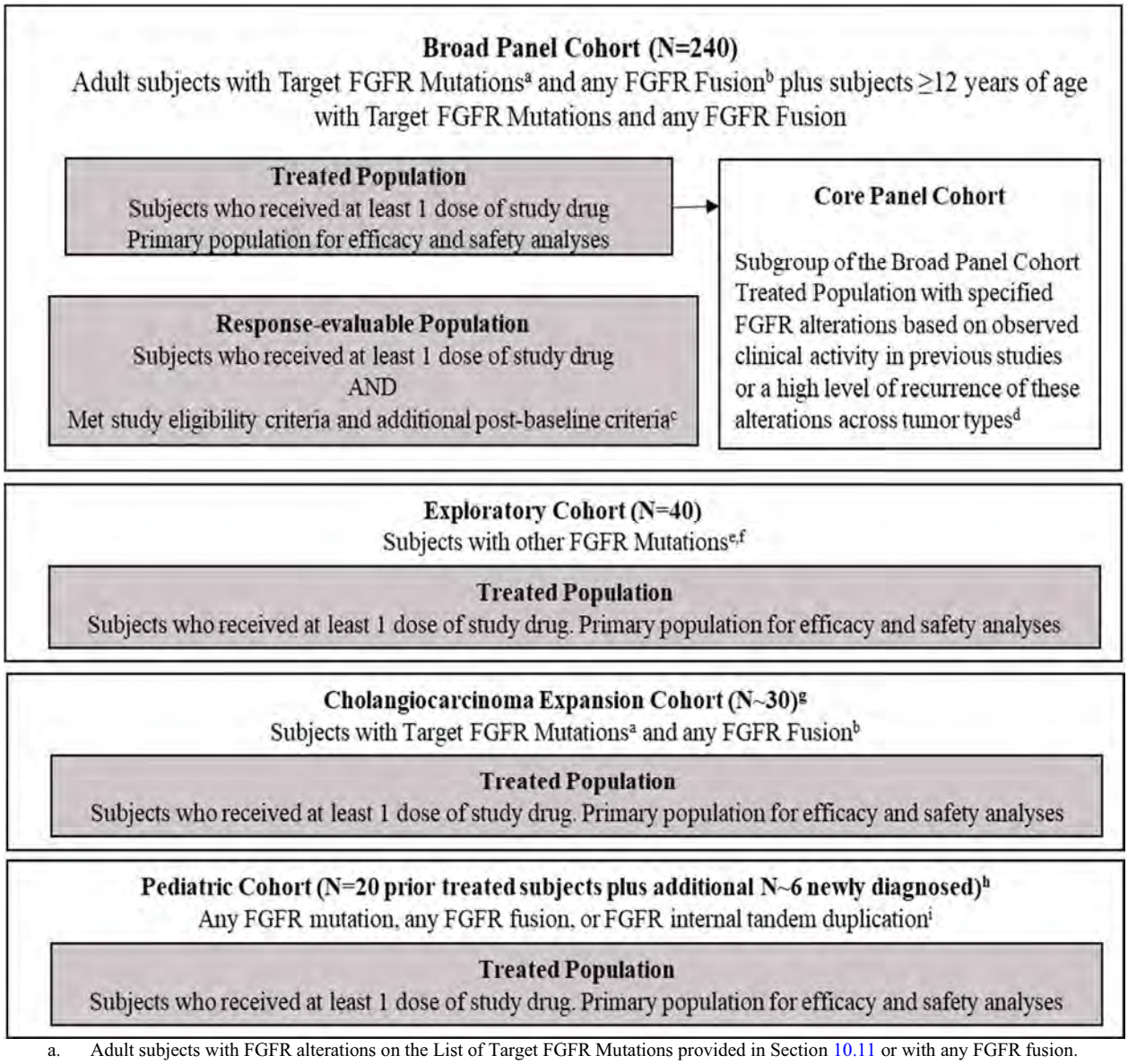
Once the end of data collection timepoint has been achieved, follow-up of subjects will end, and data collection will conclude. Only serious adverse events will be reported in the company safety repository. Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment either on this study, with only data collection of serious adverse events in the company safety repository via LTE phase or a post-trial access program, when permitted by local regulations.

Subjects will be assessed for disease response by the IRC and by the investigator according to RECIST 1.1 or RANO guidelines. Pharmacokinetic assessments (plasma concentrations of erdafitinib and alpha 1-acid glycoproteins, total protein, and fraction unbound, if required, using venous blood samples), biomarker assessments (molecular screening to determine eligibility for the study; and possibly exploratory DNA, RNA, and protein analyses using archival or fresh biopsy tissue and blood [ctDNA] for exploratory research), patients' health-related QoL assessments, and safety assessments (including AE reports and results of vital sign measurements, electrocardiograms, physical examinations, clinical laboratory tests, Eastern Cooperative Oncology Group [ECOG] performance status, and ophthalmologic examinations) will be conducted as described on the Schedule of Activities. Additional safety assessments for children and adolescent subjects include radiographic (growth plate assessment and bone age) imaging, dual-energy X-ray absorptiometry (DEXA) scan for bone densitometry, and clinical laboratory tests for thyroid stimulating hormone (TSH, T3, and T4) and insulin-like growth factor 1 (IGF-1) (Section 8.3).

Statistical analyses will be primarily based on the Broad Panel Cohort of subjects with target FGFR mutations and any gene fusion (described in Section 4.2.1). In addition, statistical analyses will be performed in a subset of subjects from the Broad Panel Cohort whose tumors have select FGFR alterations (listed in Section 9.3.1), this analysis subset is designated the Core Panel Cohort. No formal hypotheses will be tested in the Exploratory Cohort. Subjects in the Pediatric Cohort will be evaluated separately from the Broad Panel Cohort (Figure 4).

The Cholangiocarcinoma Expansion Cohort will also be evaluated separately from the Broad Panel Cohort.

Figure 4: Study CAN2002: Analysis Cohorts and Populations



a. Adult subjects with FGFR alterations on the List of Target FGFR Mutations provided in Section 10.11 or with any FGFR fusion.
b. Adult subjects with any FGFR gene fusion are eligible for enrollment in the Broad Panel Cohort. FGFR gene fusions must have an intact FGFR kinase domain. FGFR gene identifiers for reference are provided in Section 5.1, Criterion 2.
c. The Response-evaluable Population is composed of subjects who received at least 1 dose of study drug; met eligibility criteria for the study; and had a baseline and at least 1 adequate post-treatment radiological disease evaluation, had clinical signs or symptoms of disease progression, or died prior to the first posttreatment disease evaluation (these subjects will be considered non-responders). Adequate disease assessment is defined as having enough evidence to indicate that disease progression has or has not occurred.
d. The Core Panel Cohort is a subgroup of the Broad Panel Cohort Treated Population composed of subjects with a specified subset of core FGFR alterations listed in Section 9.3.1. This is an analysis cohort only.
e. Subjects with FGFR mutations not on the List of Target FGFR Mutations will be included in the Exploratory Cohort.
f. The Exploratory Cohort is closed for enrollment as of 11 May 2020.
g. A separate Cholangiocarcinoma Expansion Cohort will enroll subjects with target FGFR mutations or any FGFR gene fusion once the Broad Panel Cohort has reached the cap of approximately 30 subjects for cholangiocarcinoma
h. The Pediatric Cohort will enroll 20 children or adolescent subjects who have progressed following prior therapies and who have no acceptable standard therapies, and approximately 6 additional children or adolescent subjects who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. Adolescent subjects enrolled in the Broad Panel Cohort will be analyzed as part the Broad Panel Cohort and the Pediatric Cohort.
i. FGFR gene amplifications or copy number variation (CNV) are not eligible. See Section 5.1 for molecular eligibility criteria definitions.

A Data Review Committee (DRC) will be commissioned for this study. Refer to Committees Structure in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations for details.

4.2. Scientific Rationale for Study Design

4.2.1. Cohort Design

This study will enroll subjects into 4 cohorts (the Broad Panel Cohort, the Exploratory Cohort, the Cholangiocarcinoma Expansion Cohort, and the Pediatric Cohort). The histology agnostic Broad Panel Cohort will enroll subjects ≥12 years of age with target FGFR mutations or any FGFR gene fusion. The Exploratory Cohort will enroll subjects with FGFR mutations not captured in the Broad Panel Cohort. A separate Cholangiocarcinoma Expansion Cohort will enroll subjects with target FGFR mutations or any FGFR gene fusion once the Broad Panel Cohort has reached the cap of approximately 30 subjects for cholangiocarcinoma. The definition of target FGFR mutations and rationale for the cohort design are outlined below. The Pediatric Cohort will enroll subjects ≥6 to <18 years of age with FGFR mutations, any FGFR gene fusion, or FGFR internal tandem duplication. Adolescent subjects enrolled in the Broad Panel Cohort (≥12 to <18 years) will be analyzed as part of the Broad Panel Cohort and the Pediatric Cohort.

Over 8,000 unique mutations in FGFR1-4 have been reported in the GENIE (the AACR Project Genomics Evidence Neoplasia Information Exchange) and FoundationInsights™ genomic databases as of February and May 2019, respectively. It is possible that many of these mutations represent passenger events and may not be drivers of disease. To identify FGFR mutations with oncogenic driver potential and sensitivity to erdafitinib, genomic filtering and in-vitro sensitivity assays were applied to FGFR mutations in the GENIE and FoundationInsights databases.

The GENIE database represents ~46,000 patients across 48 cancers, and the FoundationInsights database contains genomic data from ~231,000 patients from 64 cancers. The >8,000 unique mutations in FGFR1-4 were collected and annotated for pathogenicity based on the following criteria:

- Presence of the variant in 1 of 2 oncology variant knowledge databases, which annotate the oncogenic effect of somatic molecular alterations (OncoKB 2019, Chakravarty 2017, Cancer Hotspots 2019, Chang 2018)
- Annotation of the variant in Foundation Insights genomic database indicating known or likely pathogenicity
- Variant recurrently detected in the GENIE genomic database (GENIE 2019)
- Variant recurrently detected in the FoundationInsights genomic database (FoundationInsights 2019)
- Variant identified in multiple tumor types across genomic datasets
- Variant is not in a position of a canonical gatekeeper mutation (FGFR1_V561, FGFR2_V564, FGFR2_N549; FGFR3_V555, FGFR4_V550)

The resulting list of FGFR mutations were subsequently tested in transient transfection assays for in-vitro sensitivity to erdafitinib, determined by inhibition of extracellular-signal-regulated kinase (ERK) phosphorylation. FGFR mutations meeting the above criteria and with in-vitro sensitivity to erdafitinib were designated as target FGFR mutations. The list of Target FGFR Mutations also includes additional mutations with clinical or correlative evidence supporting inclusion. The List of Target FGFR Mutations is provided in Section 10.11.

The frequency of target FGFR alterations in Table 1 includes filtering for likely pathogenic FGFR gene fusions based on assessment of fusion characteristics and recurrence. Molecular eligibility for this study has been extended to subjects with any FGFR gene fusion (FGFR gene fusions must have an intact FGFR kinase domain. FGFR gene identifiers for reference are provided in Section 5.1 Criterion 2). This extension of molecular ability is based on clinical experience in cholangiocarcinoma and other tumor types where clinical responses to erdafitinib were observed in patients with novel gene fusions.

A subgroup of subjects in the Broad Panel Cohort with a defined panel of pre-specified FGFR markers will be identified as the Core Panel Cohort (see Section 9.3.1). The Core Panel Cohort will be used only for statistical analysis purposes and will not affect enrollment. FGFR markers for the Core Panel Cohort were selected based on observed clinical activity in previous studies or a high level of recurrence of these alterations across tumor histologies.

The selection process described above, while aiming to increase the likelihood of evaluating erdafitinib activity in FGFR-driven tumors, is not expected to capture all FGFR mutations with oncogenic driver potential or sensitivity to erdafitinib. Therefore, the Exploratory Cohort has been included to capture and assess driver mutation potential and sensitivity in FGFR mutations not eligible for the Broad Panel Cohort.

Subjects from all solid tumor histologies (except bladder) with an FGFR mutation or fusion identified via local testing results (as outlined in Section 8.1.1.1) are considered molecularly eligible for the study, pending review and approval by the sponsor. However central molecular screening will be selective to specified tumor histologies. Based on the predicted frequency of target FGFR alterations, prevalence of tumor histology, and predictive modeling of distribution; the tumor histologies that were selected for central molecular screening in this study are provided in Figure 6.

4.2.2. Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of erdafitinib and may help to identify population subgroups that respond differently to erdafitinib. The goal of the biomarker analyses is to further understand the mechanism of action and potential erdafitinib-clinical response relationships. Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.3. Patient-reported Outcomes Research

Patient-reported outcome data complement data collected by other methods to support the clinical data and cost-effectiveness modeling as well as contributing to enhanced communication of value to patients, clinicians, regulators, and payers. The patient-reported outcome (PRO) endpoints of interest include domain scales from the EORTC-QLQ-C30 (for subjects ≥18 years of age) or Peds FACT-Br (for subjects <18 years of age), PGIS, PGIC, and EQ-5D-5L (utility value and visual analog scale). PRO assessments are necessary to quantify patient benefit early in the development on an investigational drug. Collecting PRO assessments at this time will support further development in future studies. PRO data will be collected as outlined in the Schedule of Activities to understand how the endpoints change over time.

4.2.4. Study-Specific Ethical Design Considerations

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 (or their legally acceptable representative) who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the informed consent/assent form (ICF), the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies; children ≥6 to <12 years of age, adolescents 12 years of age and above and adults will be enrolled in this study. Minors who reach the age of majority (per local regulations) during study will need to (re)sign an ICF. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

In view of the positive results for the subjects with urothelial cancer and select FGFR alterations in these studies and the prognosis for the subject population being considered for the study, a positive risk-benefit profile is anticipated. It should be noted that in the Phase 1 study, different histologies harboring FGFR amplifications, mutations or translocations did not behave uniformly to erdafitinib treatment. Instead the response was higher in certain tumor histologies such as urothelial cancer or cholangiocarcinoma compared to other tumor histologies included in the study. Subjects will be closely monitored throughout the study, as discussed throughout this protocol, for

both safety and clinical benefit.

The potential risks of erdafitinib to adults, as well as children and adolescents, include central serous retinopathy and hyperphosphatemia. Pre-clinical findings of cartilage dysplasia could be indicative of possible bone growth abnormalities in children and adolescents. The safety profile of erdafitinib, based on the urothelial population, was characterized by mild to moderate eye, skin and nail disorders; these events were manageable with available medical measures, temporary treatment interruption, or eventual dose reduction.

The total blood volume (approximately 230 mL for adults and 275 mL for adolescents over 6 cycles, including the screening and end of study visits [approximately 15 mL is collected at each additional cycle]) that will be collected is considered within the normal range allowed for this subject population over this time frame, including the adolescent subjects. For adult subjects, the amount of blood collected is less than the American Red Cross standard blood donation of 500 mL over 60 days (American Red Cross 2019). For children and adolescents, generally no more than 1 percent of the total blood volume may be collected at any one draw or over a 24-hour period, and no more than 3 percent of the total blood volume may be collected over a 30-day period (Veal 2014, Howie 2011, EMA 2019). Thus, an adolescent weighing 40 kg would have a total blood volume of 3.2 liters and a limit of approximately 30 mL at any 1 blood draw and 90 mL over 30 days. In this study, the total blood volume collected from an adolescent subject weighing 40 kg exceeds the 30 mL limit at Cycle 1 Day 1 visit only, due to the collection of a 20 mL blood sample for circulating tumor DNA. All subsequent study visits do not collect blood volumes in excess of 30 mL. This difference from the maximum limit increases as body weight decreases. The investigator should evaluate the risk versus the potential benefit of enrolling an adolescent subject with lower body weights into this study.

4.2.5. Participant Input Into Design

The results of the study may be made available to all participants through a plain language summary; a technical summary of results on registries such as clinicaltrials.gov, clinicaltrialsregister.eu or other national registries at the conclusion of the study according to local standards/restrictions.

4.3. Justification for Dose

Adult Dose Justification

In adults, erdafitinib will be provided as a tablet for oral administration and subjects will be instructed to take an 8-mg starting dose orally once daily on a continuous 21-day cycle, until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or the end of data collection timepoint has been achieved. Treatment will be up-titrated to 9 mg, maintained at 8 mg, or withheld; based on the phosphate level measured on Cycle 1 Day 14 and the observed toxicity to that day, as described in detail in Section 6.1.

The 8-mg starting dose was selected based on PD biomarker (serum phosphate), clinical activity, and safety data as summarized below.

Clinical Activity

Data from the completed Phase 1 Study EDI1001 indicates that an increase in phosphate level of at least 35% over the baseline level may be associated with anti-tumor response. Therefore, a PD objective of a 50% increase in phosphate level over baseline is considered clinically meaningful. Given the median phosphate level of 3.6 mg/dL at baseline in the Phase 1 study, and the phosphate level of 3.3 mg/dL at baseline in the Phase 2 Study BLC2001 (Interim Analysis 1 data), an increase of at least 50% for the majority of subjects would correspond to an absolute phosphate level of around 5.5 mg/dL (which is also 35% over the upper limit of normal for phosphate). Subjects achieving a phosphate level of less than 5.5 mg/dL during the first dosing cycle period would be considered to have had inadequate PD effect and would be candidates for dose escalation or up-titration to the 9-mg once daily dose to achieve an optimal PD effect (ie, phosphate level above 5.5 mg/dL).

In Study BLC2001, analysis of clinical response for all subjects in the 8-mg daily regimen shows that while responses were achieved both above and below 5.5 mg/dL, the ORR and DCR were higher (43.1% vs. 34.6% for ORR; 86.1% vs. 65.4% for DCR), and DOR and PFS were longer (6.01 vs. 4.44 months for DOR; 5.59 vs. 3.81 months for PFS) in subjects with a serum phosphate level ≥5.5 mg/dL compared to those with a level <5.5 mg/dL (BLC2001). Of note, all 3 CRs occurred in subjects with serum phosphate ≥5.5 mg/dL. Median OS for subjects with serum phosphate ≥5.5 mg/dL was not reached with a lower bound of the 95% confidence interval (CI) at 11.3 months, while median OS was 7.49 months for subjects with serum phosphate less than 5.5 mg/dL (BLC2001).

Based on an exploratory analysis of response for subjects in the 8-mg daily regimen in Study BLC2001, when a higher phosphate level of 7 mg/dL was used as the new threshold, a larger separation of clinical response was observed between subjects with serum phosphate ≥7 mg/dL and <7 mg/dL (45.5 vs. 31.6% for ORR; 90.9% vs. 75% for DCR).

Hence, the clinical goal is to maximize the number of subjects reaching the new target phosphate level of 7 mg/dL in order to attain maximum and sustained target inhibition.

Clinical Safety

The 8-mg daily regimen from the ongoing Study BLC2001 was well tolerated and without significant treatment interruptions (approximately 10% to 15% anticipated early interruptions). Up-titration from the 8-mg daily regimen to the 9-mg daily regimen on Cycle 1 Day 14 in subjects with both serum phosphate level below 5.5 mg/dL (ie, suboptimal PD effect) and without significant drug-related toxicity (ie, Grade ≥2 toxicity or Grade ≥1 central serous retinopathy or retinal pigment epithelial detachments) is likely to have a good overall tolerability profile and increases the likelihood of improved efficacy.

Moreover, the observed safety of the 9-mg daily regimen in the completed Phase 1 Study EDI1001 did not raise concerns about prolonged hyperphosphatemia, and no soft-tissue calcification or electrolyte disturbance or endocrine abnormalities were reported. Similarly, in the ongoing Phase 2 study, no such abnormalities were observed. Therefore, a more aggressive approach to up-titration may be adopted, allowing up-titration in subjects whose Day 14 phosphate is below 7 mg/dL (instead of below 5.5 mg/dL) without concurrent temporary use of phosphate binder treatment, or

whose serum phosphate is between 7 and 9 mg/dL with concurrent temporary use of phosphate binder treatment (see Section 6.1).

In conclusion, the pharmacodynamically-guided dose up-titration scheme from 8-mg daily regimen to 9-mg daily regimen based on the target phosphate level of 7 mg/dL on Cycle 1 Day 14 is expected to increase clinical activity without significantly increasing dose interruptions or toxicity. The appropriateness of this proposed dosing regimen is also supported by modeling and simulations and is currently being tested in Phase 3 study BLC3001 and subsequent erdafitinib studies, ie, the proposed up-titration scheme is predicted to achieve serum phosphate target level of 7 to 9 mg/dL in more subjects compared to the reference up-titration scheme using target phosphate level of 5.5 mg/dL, while not increasing the number of unforeseen dose interruptions and dose adaptations.

Children and Adolescent Dose Justification

For adolescents aged ≥15 years to <18 years, the adult regimen of 8 mg once daily with up-titration to 9 mg once daily on Cycle 1 Day 14 will be used. For adolescents aged ≥12 years to <15 years (ie, until the day before they turn 15 years of age), the 5-mg daily starting dose with possible up-titration to 6 mg daily or further up-titration to 8 mg (maximum) daily will be used. For children aged ≥6 to <12 years (ie, until the day before they turn 12 years of age), the 3 mg daily starting dose with possible up-titration to 4 mg daily or further up-titration to 5 mg (maximum) daily will be used. The up-titration decision for adolescents 12 to <15 of age and children ≥6 to <12 years of age will be based on the phosphate level measured on Cycle 1 Day 14 and Cycle 2 Day 7 and the observed toxicity to that day, as described in detail in Section 6.1. Specifically, the up-titration scheme is an age group dependent 2-step approach. No subjects will be allowed to up-titrate directly from the starting dose of 3 mg and 5 mg to the maximum daily dose of 5 mg and 8 mg for children aged ≥6 to <12 years and adolescents ≥12 to <15 years of age, respectively. The adolescent (≥12 to <15 years of age) and children (≥6 to <12 years of age) dose selections are

primarily driven by the baseline serum phosphate level and age effect on phosphate. The weight effect on pharmacokinetics is minimal relative to the age effect on phosphate. No new safety signals were observed following a review of data by the DRC from the first 2 adolescent subjects (12 and 13 years of age) enrolled in the Broad Panel Cohort.

It has previously been shown that serum phosphate is a biomarker for erdafitinib's safety and efficacy based on the BLC2001 Study. In addition, it is known that serum phosphate is highly correlated with age. Based on erdafitinib studies, adults have an average serum phosphate baseline level of 3.1 mg/dL for men and 3.5 mg/dL for women. However, among adolescents across the age range of 11 to 15 years, it has been reported that the median serum phosphate level is 4.9 mg/dL and 4.5 mg/dL in boys and girls, respectively and for children across the age range of 6 to 10 years 5.0 mg/dL (Adeli 2015). The serum phosphate level shows a trend of higher values among children and younger adolescents and a gradual decrease to the adult value among older adolescents.

Using the established PK-PD model, assuming similarity in the PK-PD relationship between adults, adolescents and children, higher phosphate baseline distribution in adolescents and children compared to adults and similar target phosphate threshold (7-9 mg/dL) between adults, adolescents and children; simulations were conducted across the different age groups (≥6 to <12, ≥12 to <15, and ≥15 to <18) to predict the percentage of subjects reaching the target phosphate range and safety phosphate threshold (>9 mg/dL). The appropriate dosing regimen of children and adolescents was selected for different age groups based on i) maximizing the proportions within the target phosphate range, ii) minimizing the proportions above the target phosphate range, and iii) minimizing the proportions with treatment interruptions as predicted by the PK-PD model, as well as clinical considerations.

Among adolescents aged ≥15 to <18 years of age following the adult regimen, at week 6, which corresponds to the median time to response and time of peak serum phosphate level, the percentage of subjects within the target phosphate range was predicted to be 30.2%, compared to 21.6% in adults. The percentage of subjects ≥15 to <18 years of age above the safety threshold was predicted to be 11.7% compared to 6.9% in adults, and 20.4% of subjects were predicted to have their dose interrupted within the first 6 weeks compared to 13% in adults. These predictions suggest that among this older group of adolescents, following the same dosing regimen as adults is likely to be acceptable from both safety and efficacy perspectives.

Among adolescents aged ≥12 to <15 years of age, the adult regimen leads, on average, to 20.4% subjects above the target phosphate range, which is more than the 13.8% pre-specified 2-fold increase compared with the adult reference and was not deemed acceptable. A lower starting dose of 5 mg with up-titration to 6 mg and a starting dose of 6 mg with up-titration to 8 mg led to an acceptable proportion of subjects with phosphate levels above 9 mg/dL, while retaining a good proportion of subjects within the target phosphate range. The dosing algorithm was further refined to allow for 2 possible up-titrations. This would allow younger adolescents to potentially benefit from a wider spread of doses, between 5 and 8 mg. Up-titrations at Day 7 and 14 and up-titrations at Day 14 and 28 were tested. The proportion of adolescents within and above the target phosphate

range after refinement led to 39.5% of subjects within the target range, while maintaining the proportion below 13.8% for the 2-week up-titration (14.8% for the 1-week up-titration and 12.0% for the 2-week up-titration). The proportion of subjects whose dose was interrupted was predicted 27.8% and 24.7% for the 1- and 2-week scenario, respectively. As the 2-week interval allows PK and PD to reach steady-state and leads to satisfactory efficacy and safety proportions, a 5-6-8 mg dose regimen with up-titrations at Day 14 and Day 28 was selected as the recommended dose for adolescents ≥12 to <15 years old. Note that the predicted proportion of up-titrated subjects is around 96% at Day 14 and 85% at Day 28 for the selected scenario with starting dose of 5 mg and 2-week up-titration to 6 and 8 mg.

Given the results in young adolescents, simulations for children ≥6 to <12 years focused on 2 up-titrations either 1 week or 2 weeks apart. The regimen that was deemed to best match the adult reference was a starting dose of 3 mg with 4 and 5 mg up-titrations at 2-weekly intervals, ie, at Day 14 and Day 28 with 42.8% of subjects within the target range while maintaining the proportion above the target range at 9.9%. The proportion of subjects whose dose was interrupted was predicted to be 22.3%. Note that the predicted proportion of subjects up-titrated is around 96% at Day 14 and 87% at Day 28.

The table below shows an overview of proposed pediatric dosing regimens maximizing the proportion of children and adolescent subjects within the target range, while keeping the proportion of children and adolescent subjects that require interruptions due to phosphate levels >9 mg/dL, less than or equal to 12%.

Age group	**Proposed erdafitinib dose regimen**
Adults (reference)	8 mg with potential up-titration to 9 mg on Day 14
Adolescents ≥15 to <18 years	8 mg with potential up-titration to 9 mg on Day 14 (same as adult dose)
Adolescents ≥12 to <15 years	5 mg with potential up-titration to 6 mg on Day 14 and 8 mg on Day 28
Children ≥6 to <12 years	3 mg with potential up-titration to 4 mg on Day 14 and 5 mg on Day 28

As it is unknown whether the sensitivity to erdafitinib as well as the phosphate thresholds observed in adults directly translate to children and adolescents, the simulation results need to be interpreted with caution. However, if elevated phosphate levels are observed in children or adolescents during the study, the phosphate elevation management guideline as described in Table 3 (Erdafitinib Dose Modification Rules Based on Toxicity Severity) and Table 8 (Guidelines for Management of Serum Phosphate Elevation) will be followed. In addition, this protocol mandates additional PK sampling and serum phosphate testing on blood samples collected on Cycle 1 Day 14 and Cycle 2 Day 14 for children and adolescents. Emerging PK and phosphate data, as well as efficacy and safety data, will be analyzed after a minimum of 5 children and adolescent subjects become evaluable for response, and used for PK-PD analysis to evaluate the need for modification of the dosing regimen in adolescents.

5. STUDY POPULATION

Screening for molecular eligibility is performed prior to the Full-study Screening Period. See information on the consent process for molecular screening in Section 8.1.1. Full study screening for molecularly eligible subjects will be performed within 30 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Criterion modified per Amendment 3

   1.1 ≥6 years of age.

2. Criterion modified per Amendment 1

   2.1 Criterion modified per Amendment 2

   2.2 Criterion modified per Amendment 3

   2.3 Histologic demonstration of an unresectable, locally advanced, or metastatic solid tumor malignancy bearing an FGFR mutation or fusion, as determined by local* or central laboratory screening (Section 8.1.1.1).

   * 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.

   Molecular Criteria for Broad Panel Cohort and Cholangiocarcinoma Expansion Cohort:

   - Subjects with target FGFR mutations or any** FGFR gene fusions are eligible for enrollment in the Broad Panel Cohort (The List of Target FGFR Mutations is provided in Section 10.11).
   - Subjects with other FGFR mutations*** not captured in the Broad Panel Cohort are eligible for enrollment in the Exploratory Cohort.

   Molecular Criteria for Pediatric Cohort:

   - Subjects with any FGFR mutation*** (exclusive of FGFR valine gatekeeper and resistance alterations defined in the Exclusion Criteria) or any** FGFR gene fusions,

or FGFR internal tandem duplication**** are eligible for enrollment in the Pediatric Cohort

**FGFR Fusion Specifications:

- 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 (self-fusions or rearrangements, eg FGFR-FGFR, are not eligible) (Broad Panel Cohort only)

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)
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.

*** Mutations in this study are defined as protein-coding single nucleotide variant (SNV) and insertions or deletions (indels). Copy number gains or gene-level amplifications are not eligible. FGFR mutations annotated as germline in local reports, or subjects presenting with a hereditary condition/disorder associated with a germline FGFR mutation are not eligible for enrollment in the absence of a qualifying FGFR mutation or fusion. Note, testing for germline mutations is not required for this study.

**** For Pediatric Cohort Only: Intragenic duplication of the FGFR kinase domain (FGFR-FGFR) if one breakpoint is located within intron 8 through exon 11 and the other breakpoint is in intron 17 through intron 18 (including 3' UTR). Copy number gains or gene-level amplifications are not eligible.

3 Measurable disease according to RECIST v1.1 or RANO for primary brain tumors.

4. Criterion modified per Amendment 2

4.1 Criterion modified per Amendment 3

4.2 Subject must have received at least one prior line of systemic therapy in the advanced, unresectable, or metastatic setting; or is a child or adolescent subject with a newly-diagnosed solid tumor and no acceptable standard therapies.

5. 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.

6. Criterion modified per Amendment 4

6.1 Documented progression of disease, defined as any progression that requires a change in treatment, prior to full study screening. Note: Not applicable for treatment naïve pediatric subjects with no standard of care therapies.

7. Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less except for alopecia, peripheral neuropathy, and Grade 2 laboratory values eligible per Inclusion Criterion 9.

8. Criterion modified per Amendment 3

8.1 Criterion modified per Amendment 4
8.2 For adults (≥18 years of age), ECOG performance status Grade 0 or 1 (Section 10.5).
For children and adolescents (≥6 to <16 years of age), Lansky Score of ≥70 (Section 10.6).
For adolescents (≥16 to <18 years of age), Karnofsky Score of ≥70 (Section 10.6).

9. Criterion modified per Amendment 1

9.1 Criterion modified per Amendment 2

9.2 Criterion modified per Amendment 3

9.3 Adequate bone marrow, liver, and renal function:

a. Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent transfusions in preceding 2 weeks):

- Absolute neutrophil count (ANC) ≥1,000/mm^3
- Platelet count ≥75,000/mm^3
- Hemoglobin ≥8.0 g/dL

b. Liver function:

- Total bilirubin ≤1.5 x institutional ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5x institutional ULN or ≤5x institutional ULN for subjects with liver metastases

c. Renal function: Creatinine clearance (CrCl) >30 mL/min calculated using the Cockcroft-Gault formula for adult subjects or the CKiD (Chronic Kidney Disease in Children) Schwartz formula for children and adolescent subjects (≥6 to <18 years of age) (Section 10.7)

d. Phosphate: <ULN within 14 days of treatment and prior to Cycle 1 Day 1 (medical management allowed)

10. Criterion modified per Amendment 3

10.1 Must sign an ICF (or their legally acceptable representative must sign) indicating that the subject understands the nature, significance, and purpose of the study, and procedures required for the study, and consequence of the study; and is willing to participate in the study. For children and adolescent subjects, parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign an ICF indicating that the subject understands the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study. Assent is also required of children and adolescent subjects as described in Informed Consent Process in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

11. A female of childbearing potential must have a negative pregnancy test (β-human chorionic gonadotropin [hCG]) at Screening (urine or serum).

12. Criterion modified per Amendment 1

12.1. Criterion modified per Amendment 3

12.2. Contraceptive use by male or female subjects should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

For females of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile [for the purpose of this study]. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy):

- practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

  Examples of highly effective contraceptives include

  – user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; permanently sterile; 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

- agree 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
- agree 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
- no plan to breastfeed and no plan to become pregnant during the study and for at least 3 months after the last dose of study drug

For males who are sexually active:

- agree to use a condom with spermicidal foam/gel/film/cream/suppository
- agree to not donate sperm during the study and for at least 3 months after the last dose of study drug
- no plan to father a child during the study or within 3 months after the last dose of study drug

5.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 2

   1.1 Criterion modified per Amendment 3

   1.2 Has had prior chemotherapy, targeted therapy, or treatment with an investigational anticancer agent within 15 days or <5 half-lives of the agent (whichever is longer) and up to a maximum of 30 days before the first dose of erdafitinib. Has had prior monoclonal antibody or immunotherapy within 30 days before the first dose of erdafitinib and/or has an ongoing Grade ≥2 immunotherapy-related toxicity.

2. Criterion modified per Amendment 2

   2.1 Criterion modified per Amendment 3

   2.2 The known* presence of FGFR valine 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.

3. Criterion modified per Amendment 1

   3.1 Criterion modified per Amendment 2

   3.2 Criterion modified per Amendment 3

   3.3 Criterion modified per Amendment 4

   3.4 For NSCLC subjects only - pathogenic somatic mutations in EGFR* or BRAF V600E, KRAS, 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.

   For colorectal subjects only – pathogenic somatic mutations in BRAF, KRAS, NRAS and PIK3CA.

4. Criterion modified per Amendment 2

   4.1 Histologic demonstration of urothelial carcinoma.

5. Hematologic malignancy (ie, myeloid and lymphoid neoplasms).

6. Active malignancies other than for disease requiring therapy.

7. Symptomatic central nervous system metastases (except for subjects with primary CNS tumors).

8. Criterion modified per Amendment 2

   8.1 Received prior selective FGFR inhibitor treatment.

9. Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients.

10. Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade.

11. Criterion modified per Amendment 1

    11.1 Criterion modified per Amendment 2

    11.2 Criterion modified per Amendment 3

11.3 History of uncontrolled cardiovascular disease including:

- Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-IV (Section 10.8) within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months.
- QTc prolongation (Fridericia: QTc >480 milliseconds; or for children and adolescent subjects, Bazett: QTc >440 milliseconds).

12. Known history of 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

13. Criterion modified per Amendment 1

13.1 Criterion modified per Amendment 2

13.2. Evidence of active hepatitis B or C infection (for example, subjects with history of hepatitis C infection but normal hepatitis C virus polymerase chain reaction [PCR] test and subjects with inactive hepatitis B with positive HBsAg antibody or normal PCR are allowed).

14. Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, neuropathy, hearing loss).

15. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

16. Major surgery within 4 weeks before first dose of erdafitinib.

17. Criterion modified per Amendment 2

17.1 Palliative radiation to the target lesion within 2 weeks before the first dose of erdafitinib.

18. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of drug.

19. Plans to father a child while enrolled in this study or within 3 months after the last dose of drug.

20. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Examples include ongoing active infection requiring systemic therapy and uncontrolled ongoing medical conditions.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available 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. The required source documentation to support meeting the enrollment criteria is noted in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapies, for details regarding prohibited and restricted therapy during the study.

2. Subjects should avoid consuming grapefruit or Seville oranges due to CYP 3A4/5 inhibition.

3. Subjects should check with the site prior to taking over the counter medication: 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.

4. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. Subjects should be advised on sperm banking and egg preservation, respectively, prior to entering the study, if appropriate.

5.4. Screen Failures

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 enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once for eligibility (Section 8.1.1).

5.5. Study Completion (ie, End of Data Collection Timepoint) and End of Study

5.5.1. Study Completion (ie, End of Data Collection Timepoint) Definition

The study is considered completed at the time of the end of data collection timepoint. Overall, the end of data collection timepoint is defined as the date at which the clinical cutoff for the primary analysis has been achieved. Specifically, for subjects <18 years of age, the end of data collection is defined as the timepoint when the most recently enrolled pediatric subject still participating in the study has 6 months of follow-up or the last follow-up visit of the last pediatric subject, whichever occurs first. Once the end of data collection timepoint has been achieved, follow-up of subjects will end, and data collection will conclude. Only serious adverse events will be reported in the company safety repository (See Appendix 13). The end of data collection timepoint may be extended by the Sponsor, if needed, based on health authority feedback.

Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment; during this period, only serious adverse events will be reported into the company safety repository. Section 6.7 provides details on access to study drug after the End of Data Collection timepoint is achieved.

5.5.2. End of Study Definition – Overall Study

The end of study is considered as the time when the last subject receives the last dose of study drug on the study and either all pediatric subjects are off study or until the most recently enrolled pediatric subject still participating in the study has 6 months of follow-up, whichever occurs first.

6. STUDY DRUG

6.1. Study Drug Administered

Erdafitinib will be provided as tablets for oral administration. Subjects will be instructed to take erdafitinib orally once daily for 21 days in a continuous 21-day cycle until disease progression, intolerable toxicity, withdrawal of consent decision by the investigator to discontinue treatment. For continued treatment with erdafitinib after the end of data collection timepoint has been achieved see Section 6.7. Subjects or their parent/guardian will record study drug administration in dosing diaries. Adults (aged 18 years and older) and adolescents aged ≥15 to <18 years will start with a dose of 8 mg and the dose will be up-titrated to 9 mg or maintained at 8 mg based on Cycle 1 Day 14 serum phosphate levels. Adolescent subjects aged ≥12 to <15 years will start with an erdafitinib dose of 5 mg with possible up-titration to 6 mg or further to 8 mg based on Cycle 1 Day 14 and Cycle 2 Day 7 serum phosphate levels. Children aged ≥6 to <12 years of age will start with an erdafitinib dose of 3 mg with possible up-titration to 4 mg or further to 5 mg based on Cycle 1 Day 14 and Cycle 2 Day 7 serum phosphate levels. (See Section 4.3 for information on dose justification.) Note that children and adolescent subjects will continue under the titration and dosing schedule under which they were enrolled. Each dose should be taken at approximately the same time each day, with or without food. The study drug is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact. If the subject has difficulties swallowing the tablets, tablets may be dispersed in apple juice or water, and administered via an oral syringe. Alternatively, if the subject has difficulties swallowing the tablets or the tablet

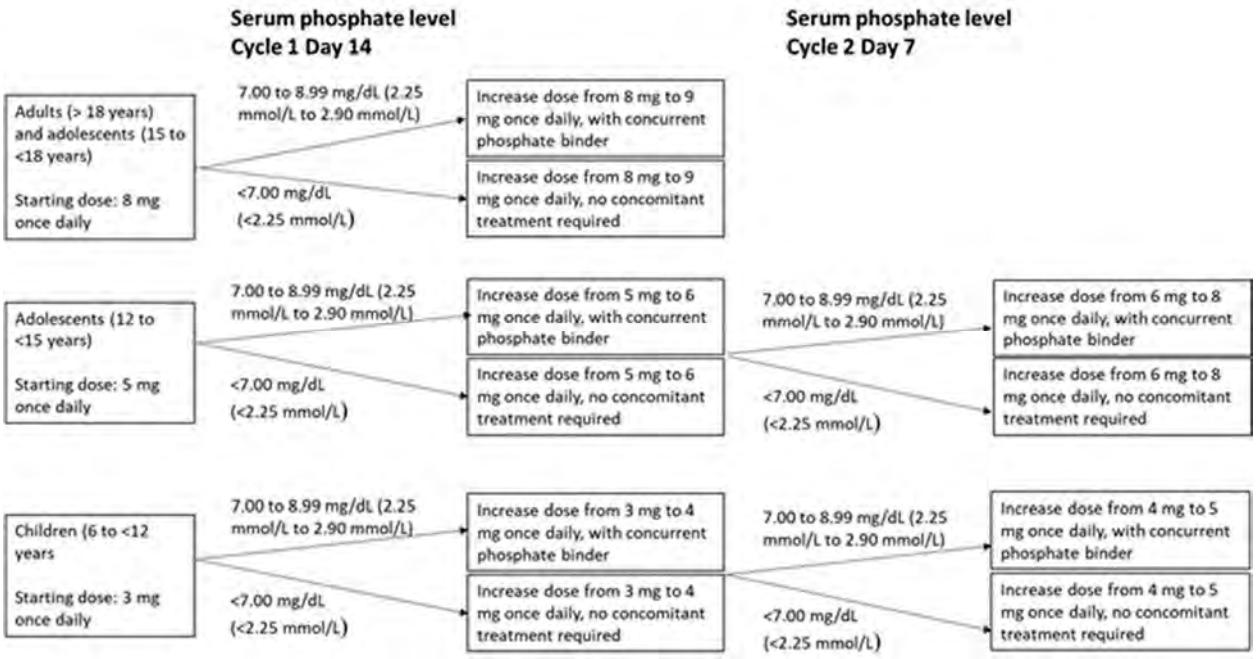
dispersion via an oral syringe, tablets may be dispersed in water and administered via a feeding tube. Refer to the pharmacy manual/study site Investigational Product Manual and the Investigational Product Preparation Instructions for additional guidance on study drug preparation, handling and storage. Subjects should avoid consuming grapefruit or Seville oranges due to CYP 3A4/5 inhibition. Study drug administration must be captured in the source documents and the case report form (CRF). Erdafitinib will be manufactured and provided under the responsibility of the sponsor.

Up-titration Guidelines

Instructions for up-titration of erdafitinib, in the absence of erdafitinib related toxicity, based on the serum phosphate level at Cycle 1 Day 14 are provided below and in Figure 5. For children aged ≥6 to <12 years and adolescents aged ≥12 to <15 years, an additional blood sample will be drawn at Cycle 2 Day 7 for determination of the serum phosphate level and the need for dose modification.

Subjects with a serum phosphate level 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 (see Table 8 for detailed guidelines regarding further treatment).

Figure 5: Instructions for up-titration of erdafitinib based on serum phosphate levels



Note: in presence of erdafitinib-related toxicities, the investigator may choose to maintain the same dose of erdafitinib without up-titration.

Adult subjects and adolescent subjects aged ≥15 to <18 years

- Adult subjects and adolescent subjects aged ≥15 to <18 years with a serum phosphate level between 7.00 to 8.99 mg/dL (2.25 mmol/L to 2.90 mmol/L) on Cycle 1 Day 14 will increase the erdafitinib dose from 8 mg once daily to 9 mg once daily, while concurrently initiating treatment with a phosphate binder such as sevelamer (see Table 8 for details).
- Adult subjects and adolescent subjects aged ≥15 to <18 years with a 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.

Adolescent subjects aged ≥12 to <15 years

- Adolescent subjects aged ≥12 to <15 years with a serum phosphate level between 7.00 to 8.99 mg/dL (2.25 mmol/L to 2.90 mmol/L) will increase the erdafitinib dose from 5 mg once daily to 6 mg once daily on Cycle 1 Day 14 or Cycle 2 Day 7, and further from 6 mg once daily to 8 mg once daily on Cycle 2 Day 7 (for those already up-titrated to 6 mg on Cycle 1 Day 14), while concurrently initiating treatment with a phosphate binder such as sevelamer (see Table 8 for details). This 2-step up-titration is step-wise, ie, no subjects will be allowed to directly up-titrate from 5 mg to 8 mg.
- Adolescent subjects aged ≥12 to <15 years with a serum phosphate level less than 7.00 mg/dL (<2.25 mmol/L) will increase the erdafitinib dose from 5 mg once daily to 6 mg once daily on Cycle 1 Day 14 or Cycle 2 Day 7, and further from 6 mg once daily to 8 mg once daily on Cycle 2 Day 7 (for those already up-titrated to 6 mg on Cycle 1 Day 14). This 2-step up-titration is step-wise, ie, no subjects will be allowed to directly up-titrate from 5 mg to 8 mg. No concomitant treatment is required.

Children aged ≥6 to <12 years

- Children aged ≥6 to <12 years with a serum phosphate level between 7.00 to 8.99 mg/dL (2.25 mmol/L to 2.90 mmol/L) will increase the erdafitinib dose from 3 mg once daily to 4 mg once daily on Cycle 1 Day 14 or Cycle 2 Day 7, and further from 4 mg once daily to 5 mg once daily on Cycle 2 Day 7 (for those already up-titrated to 4 mg on Cycle 1 Day 14), while concurrently initiating treatment with a phosphate binder such as sevelamer (see Table 8 for details). This 2-step up-titration is step-wise, ie, no subjects will be allowed to directly up-titrate from 3 mg to 5 mg.
- Children aged ≥6 to <12 years with a serum phosphate level less than 7.00 mg/dL (<2.25 mmol/L) will increase the erdafitinib dose from 3 mg once daily to 4 mg once daily on Cycle 1 Day 14 or Cycle 2 Day 7, and further from 4 mg once daily to 5 mg once daily on Cycle 2 Day 7 (for those already up-titrated to 4 mg on Cycle 1 Day 14). This 2-step up-titration is step-wise, ie, no subjects will be allowed to directly up-titrate from 3 mg to 5 mg. No concomitant treatment is required.

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 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. 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).

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. Preparation/Handling/Storage/ Accountability

Preparation/Handling/Storage

Refer to the pharmacy manual/study site Investigational Product Manual and the Investigational Product Preparation Instructions for additional guidance on study drug preparation, handling, and storage.

Accountability

The 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 (if applicable), must be documented on the intervention accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and container label, and must be stored at the study site 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 study 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 intervention return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes, vials, or infusion bags containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, 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. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization will not be used in this study. Subjects will be enrolled into the study by the Interactive Web Response System (IWRS).

6.4. Study Drug Compliance

The investigator or designated study personnel will maintain a log of the amount of study drug dispensed and returned. Subjects or their parent/guardian will also record the date and time of each daily erdafitinib dose on a diary card. Drug supplies will be inventoried and accounted for throughout the study.

Subjects will receive instructions on compliance with study treatment at the Cycle 1 Day 1 visit, including dosing and use of the diary card. On PK sampling days, record the time of erdafitinib intake as accurately as possible. On days when the subject visits the study center for dose administration or PK sampling, the investigator or designee will supervise administration of the study drug and the exact time of administration will be recorded in the CRF. During 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.

6.5. Concomitant Therapies

Concomitant therapies must be recorded at the time of full-study screening, during the study, and up to 30 days after the last dose of study drug. All therapies (prescription or over-the-counter medications) continued at the start of the study or started during the study and different from the study drug, including prior anticancer therapy, must be recorded in the CRF.

Caution should be exerted for subjects taking anti-coagulant therapies (see Section 6.5.3). 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.

6.5.1. Permitted Medications

Permitted medications are to be recorded at the time of screening (within 30 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 the treating physician's discretion, as clinically indicated.

- Prophylactic medication: 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. Subjects with breast cancer or prostate cancer who progressed while receiving hormonal therapy may continue the same hormonal therapy adjunctively, providing the same therapy was ongoing for at least 6 months prior to the first dose of study drug.
- Palliative radiotherapy: Localized radiotherapy for symptomatic control is permitted but should not include definitive radiation to target lesions.
- Surgical Procedures: Surgery or biopsy of target lesions is not permitted.
- COVID-19 vaccination: 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.

6.5.2. 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 during the Treatment Phase
- Concurrent antineoplastic agents or hormonal anticancer therapy (except as noted in Section 6.5.1) during the Treatment Phase

6.5.3. Precautions for Concomitant Medications

The following precautions are advised:

- Based on in vitro data, erdafitinib is metabolized by cytochrome CYP2C9 and CYP3A4. A clinical drug-drug interaction study showed that on average, erdafitinib exposure (C_{max} and AUC) was increased 5% and 34%, respectively, when co-administered with itraconazole (a strong inhibitor of CYP3A4) and 21% and 48%, respectively, 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 Section 10.10). Consider alternative therapies with no or minimal CYP2C9 or CYP3A4 inhibition potential during treatment with erdafitinib. If co-administration of a moderate inhibitor of CYP2C9 or strong inhibitor of CYP3A4 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 Section 10.10).

Co-administration of erdafitinib with moderate CYP3A inducers may decrease erdafitinib exposure. Caution should be exercised for concomitant administration of erdafitinib and these agents (see Section 10.10). A comprehensive list of CYP3A4/2C9 inducers is provided in Section 10.10 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.
- 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. Caution should be exercised for co-administered drugs that are P-gp substrates; separate erdafitinib administration by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic index.
- 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: use with caution in case of strong medical need and when the benefit outweigh the risk; check phosphate levels regularly during treatment.

6.6. Dose Modifications

Treatment with erdafitinib should be discontinued or modified based on erdafitinib-related toxicity as described in Table 3. For eye, skin/nail, dry mouth/mucositis, and phosphate toxicity, specific recommendations in the management guidelines are provided in Section 6.6.1.

Table 3: Erdafitinib Dose Modification Rules Based on Erdafitinib-related Toxicity Severity

Erdafitinib-related Toxicity Grade	Action	Dose modification after resolution of AE
1	None	Continue same dose.
2	None, or consider interruption if the toxicity is considered clinically significant	If interrupted, restart at same dose if toxicity is completely resolved to baseline or consider restarting at 1 dose lower[a] if not completely resolved to baseline (but resolved to Grade 1).
3	Interrupt drug	Restart at 1 dose lower[a] if recovered to baseline (to ≤Grade 1 or back to baseline for non-hematologic toxicity) within 28 days; restart at 2 doses lower[a] if not completely resolved to baseline (but resolved to Grade 1) within 28 days. Discontinue drug if unresolved for >28 days.
4	Interrupt drug	Discontinue.

[a] Please refer to Table 4.

- Subjects with any grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment where applicable.
- If erdafitinib is interrupted consecutively for 1 week or longer due to drug-related toxicity, the study drug may be reintroduced at either the same dose level or the first reduced dose level following recovery from the toxicity (see dose reduction levels in Table 4, Table 5, and Table 6). A second dose reduction may be implemented following a second occurrence of drug-related toxicity.
- If erdafitinib must be withheld for more than 28 days for a drug-related adverse event that fails to resolve to acceptable level (eg, ≤Grade 1 non-hematologic toxicity or back to baseline), treatment with erdafitinib should be discontinued except when the subject has been deriving benefit from treatment, and the investigator can demonstrate that continued treatment with erdafitinib is in the best interest of the subject. Erdafitinib may be re-started at the same or a lower dose (Table 4, Table 5, and Table 6) if the sponsor's medical monitor concurs with the assessment.
- If erdafitinib was dose-reduced and the adverse event that was the reason for this dose-reduction has completely resolved, the dose may be re-escalated to the next higher dose if the subject was deriving benefit from treatment, and the investigator can demonstrate that dose re-escalation of erdafitinib is in the best interest of the subject and the sponsor's medical monitor concurs with the assessment.
- 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 (eg, coagulation parameters) 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.

Table 4: Erdafitinib Dose Reduction Levels: Adults and Adolescents Aged ≥15 to <18 Years

Category	No up-titration at Cycle 1 Day 14	With up-titration at Cycle 1 Day 14
	Dose	Dose
Starting dose	**8 mg**	**8 mg**
Up-titration at Cycle 1 Day 14	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**

Table 5: Erdafitinib Dose Reduction Levels: Adolescents Aged ≥12 to <15 Years

For Cycle 1 Day 14			
Category		**No up-titration at Cycle 1 Day 14**	**With up-titration at Cycle 1 Day 14**
Starting Dose on Cycle 1 Day 1		**5 mg**	**5 mg**
Up-titration at Cycle 1 Day 14		None	6 mg
1st dose reduction		4 mg	5 mg
2nd dose reduction		3 mg	4 mg
3rd dose reduction		**stop**	3 mg
4th dose reduction			**stop**
For Cycle 2 Day 7			
Category	**No up-titration at Cycle 1 Day 14 and Cycle 2 Day 7**	**No up-titration at Cycle 1 Day 14 but with up-titration at Cycle 2 Day 7**	**Up-titration at Cycle 1 Day 14 followed by up-titration at Cycle 2 Day 7**
Dose on Cycle 2 Day 7	**5 mg**	**5 mg**	**6 mg**
Up-titration at Cycle 2 Day 7	None	6 mg	8 mg
1st dose reduction	4 mg	5 mg	6 mg
2nd dose reduction	3 mg	4 mg	5 mg
3rd dose reduction	**stop**	3 mg	4 mg
4th dose reduction		**stop**	3 mg
5th dose reduction			**stop**

Table 6: Erdafitinib Dose Reduction Levels: Children Aged ≥6 to <12 Years

For Cycle 1 Day 14			
Category		**No up-titration at Cycle 1 Day 14**	**With up-titration at Cycle 1 Day 14**
Starting Dose on Cycle 1 Day 1		**3 mg**	**3 mg**
Up-titration at Cycle 1 Day 14		None	4 mg
1st dose reduction		**stop**	3 mg
2nd dose reduction			**stop**
For Cycle 2 Day 7			
Category	**No up-titration at Cycle 1 Day 14 and Cycle 2 Day 7**	**No up-titration at Cycle 1 Day 14 but with up-titration at Cycle 2 Day 7**	**Up-titration at Cycle 1 Day 14 followed by up-titration at Cycle 2 Day 7**
Dose on Cycle 1 Day 14	**3 mg**	**3 mg**	**4 mg**
Up-titration at Cycle 2 Day 7	None	4 mg	5 mg
1st dose reduction	**stop**	3 mg	4 mg
2nd dose reduction		**stop**	3 mg
3rd dose reduction			**stop**

6.6.1. Guidance for Specific Erdafitinib Toxicities

6.6.1.1. Guidelines for the Management of Elevated Phosphate Levels

Hyperphosphatemia will be graded as outlined in Table 7. Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 8.

For guidance on Cycle 1 up-titration, see Section 6.1.

Table 7: Grading of Hyperphosphatemia Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hyperphosphatemia	5.50-6.99 mg/dL 1.75-2.24 mmol/L	7.00-8.99 mg/dL 2.25-2.90 mmol/L	9.00-10.00 mg/dL (2.91-3.20 mmol/L), or asymptomatic soft tissue calcification with any phosphate level	>10.00 mg/dL (>3.20 mmol/L), or symptomatic soft tissue calcification with any phosphate level

Table 8: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom 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. Adults: Start sevelamer 800 to 1,600 mg TID with food until phosphate level is <7.00 mg/dL. Children and adolescents: Start sevelamer 400 mg TID for BSA 0.75 m^2, 800 mg TID for BSA ≥0.75 to <1.2 m^2, and 1,600 mg for BSA ≥1.2 m^2 with food. Titrate up/down by 200 mg for BSA 0.75 m^2, 400 mg TID for BSA ≥0.75 to <1.2 m^2, and 800 mg for BSA ≥1.2 m^2 until phosphate level is <7.00 mg/dL. [b]
9.00-10.00 mg/dL (2.91-3.20 mmol/L) (Grade 3)	Withhold [c] 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. Adults: Sevelamer up to 1,600 mg TID with food until serum phosphate level returns to <7.00 mg/dL. Children and adolescents: Start sevelamer 400 mg TID for BSA 0.75 m^2, 800 mg TID for BSA ≥0.75 to <1.2 m^2, and 1,600 mg for BSA ≥1.2 m^2 with food. Titrate up/down by 200 mg for BSA 0.75 m^2, 400 mg TID for BSA ≥0.75 to <1.2 m^2, and 800 mg for BSA ≥1.2 m^2 until phosphate level is <7.00 mg/dL. [b]
>10.00 mg/dL (>3.20 mmol/L) (Grade 4)	Withhold [c] 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	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	Medical management as clinically appropriate.

Table 8: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom Management
function or Grade 3 hypocalcemia	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 6.6.)	

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 at 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. Pediatric dosing for sevelamer based on Fathallah-Shaykh 2018.
c. Study drug interruptions for hyperphosphatemia suggested to be 7 days in duration.

6.6.1.2. Guidelines for the Management of Dry Mouth and Mucositis

Guidelines for the clinical management of dry mouth (xerostomia) and mucositis are provided in Table 9 and Table 10, respectively.

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 9: 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 10: 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/territory 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/territory 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.

Table 10: Guidelines for the Management of Oral Mucositis

Grade	Study Drug (Erdafitinib) Management	Symptom Management
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/territory 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.		

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

Guidelines for the management of dry skin are provided in Table 11.

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 11: 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%		

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

Adverse events related to nails will be graded as outlined in Table 12. Guidelines for the management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) nail toxicity are provided in Table 13. Guidelines for the management of paronychia are provided in Table 14.

Table 12: Grading of Nail 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

ADL= activities of daily living

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 13: 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 14: 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

6.6.1.5. Guidelines for the Management of Eye Toxicity Associated With Vision Changes

If subject experiences an event of confirmed new retinal abnormality (such as retinal detachment, vitreous detachment, retinal edema, retinopathy, chorioretinopathy, detachment of retinal pigment epithelium, and detachment of macular retinal pigment epithelium) during study treatment, it must be reported as an adverse event or a serious adverse event if Grade 3 or higher. 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 in Table 15.

Amsler Grid (illustrated in Section 10.9): 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 exam at baseline (during Screening), 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.

Table 15: 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 with erdafitinib until an examination can be performed. If there is no evidence 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 Visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline	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 recurrence, then re-escalation can be considered in consultation with the medical monitor.	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.

Table 15: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 3: Severe or medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL Visual acuity worse than 20/40 or > 3 lines of decreased vision from baseline	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 Visual acuity 20/200 or worse in 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		

6.6.1.6. Guidelines for the Management of Dry Eye

- **General considerations:** Avoid unnecessary exposure to sunlight and use sunglasses in bright light.
- **Prophylactic management:** Frequent use of artificial tear substitutes and ocular demulcents is 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

6.7. Study Drug After Study Completion

Once the end of data collection timepoint (see Section 5.5) has been achieved, follow-up of subjects will end, and data collection will conclude. Only serious adverse events will be reported in the company safety repository (See Appendix 13). Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment either on this study, with only data collection of serious adverse events in the company safety repository (see Section 5.5) via LTE phase (see Appendix 13) or a post-trial access program, when permitted by local regulations. Provision may continue until the subject can commercially access study treatment within the local healthcare system, until a decision is made not to pursue the studied indication, 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.

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

A subject will be considered as having completed the study if the subject has died during the study or has not been withdrawn from the study by the end of the study.

7.1. Discontinuation of Study Drug

A subject's study drug must be discontinued if:

- The subject withdraws consent or assent to receive study drug
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study drug
- The subject becomes pregnant; discontinuation of study treatment in this instance should be discussed with the medical monitor
- Progression of disease is assessed

  Exception: if the investigator and medical monitor agree that continuation of treatment is 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.
- The subject refuses further treatment with the study drug
- The sponsor terminates the study
- Investigator decision approved by the sponsor

If a subject discontinues study drug for any reason, an End-of-Treatment Visit should be conducted 30 (+7 days) after 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 CRF. Study drug assigned to the subject who discontinued study drug may not be assigned to another subject.

7.2. Subject Discontinuation/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

When a subject withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document.

A subject (as well as guardian for children and adolescent subjects) declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the subject agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

The subject or their legal representative may withdraw consent for use of samples for 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 ICF.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3 for Adults and Section 1.4 for Children and Adolescents) summarizes the frequency and timing of safety, efficacy, PK, biomarker, and other measurements applicable to this study. Patient-reported outcome questionnaires should be completed before any other assessments at each clinic visit.

The number of samples and the blood volume will vary depending on the number of cycles of the study drug that the subject receives. The total blood volume to be collected from each subject will be approximately 230 mL for adults and 275 mL for children and adolescents over 6 cycles (including the screening and end of study visits, approximately 15 mL is collected at each additional cycle). (See Section 4.2.4 for additional information regarding the blood volume). Unscheduled blood samples may be required for safety issues of individual subjects.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Erdafitinib Investigator's Brochure
- Pharmacy manual/study site Investigational Product Manual and the Investigational Product Preparation Instructions
- Laboratory manual
- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5 or higher

- PRO completion guidelines
- Imaging Guidelines
- IWRS Manual
- Electronic data capture (eDC) Manual
- eSource Manual
- Sample ICFs

8.1. Study Procedures

8.1.1. Screening Phase

The Screening Phase will consist of a Molecular Eligibility Screening Period and a Full Study Screening Period. The consent process for the Molecular Eligibility Screening Period may occur in 1 of 3 ways:

- If archived tissue is available, the Molecular Eligibility Informed Consent Form (ICF) is signed.
- If a new tissue biopsy is required, the Full-study ICF is signed.
- If a historical report (local testing) is available indicating the subject is molecularly eligible for the study, upon sponsor review and approval, the Molecular Eligibility Screening Period is complete and the subject signs the Full-study ICF, or the Full-study ICF and Molecular Eligibility ICF are combined and signed at the same time.

The Full Study Screening Period starts within 30 days of the first dose of study drug on Cycle 1 Day 1. All subjects who are eligible for the study based on molecular screening must sign the Full-study ICF.

8.1.1.1. Molecular Eligibility Screening Period

Prior to implementation of Amendment 4, central testing for FGFR alterations was performed on subject tissue samples from the tumor histologies listed in Figure 6. Subjects with any solid tumor histology (excluding urothelial cancer) may meet molecular eligibility by submitting a local/historical test result showing an FGFR mutation or fusion. (The World Health Organization [WHO] Classification of Tumours will be used to categorize tumor histologies in this study.) 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.

During the Molecular Eligibility Screening Period, originally the protocol allowed for 2 approaches to determine eligibility for this study, ie, central or local molecular screening: (Starting with Amendment 4, central molecular testing will no longer be used for all subjects.)

Local/historical report with evidence of an FGFR mutation or fusion in any solid tumor histology (except urothelial cancer)

Results of locally performed or commercial testing from tissue or blood (NGS tests, digital counting methods, or the Qiagen therascreen FGFR RT-PCR test) performed by a CLIA-certified or regional equivalent laboratory may be used to meet molecular eligibility.

If a subject is enrolled based on local testing, a tissue sample must be submitted for: retrospective confirmation of FGFR[a] status (where applicable); diagnostic development; biomarker research.

Figure 6: Molecular Screening Approaches

	Central Molecular Screening **Note: Starting with Amendment 4, only local reports will be used for molecular screening.**	**OR**	**Local Result**
Eligible Tumor Types[a]	• Pediatric subjects with any solid tumor • High-grade glioma (glioblastoma) • Low-grade gliomas • Squamous cell head and neck cancers • Soft tissue sarcoma • Cholangiocarcinoma • Endometrial, cervical, and ovarian cancers • Squamous non-small cell lung cancer (NSCLC) • Renal cell cancer • Esophageal cancer • Gastric cancer • Breast cancer[b] • Hepatocellular carcinoma • Pancreatic cancer • Salivary gland tumors • Colorectal cancer • Thymic cancer/thymoma		**Any** solid tumor (except urothelial cancer) with an eligible FGFR mutation or fusion
Applicability	Subjects without available local FGFR testing results		Subjects with local FGFR testing results

Note: Biopsy of the brain, lung/mediastinum, pancreas, or for endoscopic procedures extending beyond the esophagus, stomach, or bowel is not permitted; please contact sponsor prior to conducting biopsy.
FGFR=fibroblast growth factor receptor
[a] For enrollment in each tumor histology, the sample size is capped at approximately 30 subjects. The tumor histology list for this cap, including a group of Other, is pre-defined in Table 16.
[b] Limited to women with hormone-sensitive, ie, estrogen receptor (ER)/progesterone receptor (PR) positive, breast cancer.

If a subject meets the molecular eligibility criteria, the subject may continue study screening under the Full-study ICF for determination of full-study eligibility.

[a] The results of retrospective central confirmation do not affect the subject's eligibility for the study. Testing results of retrospective confirmation studies will not be communicated to the site.

8.1.1.2. Full-study Screening Period

The Full Study Screening Period is 30 days before the first dose of study treatment on Cycle 1 Day 1. Subjects must meet all of the inclusion and none of the exclusion criteria in Section 5. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. To re-assess eligibility, retesting will take place during an unscheduled visit in the Screening Phase.

Subjects will be allowed to be re-screened only once for eligibility (both molecular and full study eligibility) if the investigator has a valid reason (eg, true resolution of conditions previously meeting the exclusion criteria, availability of a different tumor tissue for FGFR testing, molecular test internal quality control failure) to re-screen and after consultation with the medical monitor.

8.1.2. Treatment Phase

The Treatment Phase will begin with the administration of the first dose of erdafitinib and will continue until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or the end of data collection timepoint has been achieved. Subjects assessed with progressive disease, but for whom the treating physician strongly believes that continuation of study treatment will provide clinical benefit, may be allowed to continue treatment with erdafitinib after consultation with the medical monitor (please see guidelines in Section 8.2.2). The subject will continue to follow procedures as outlined in the Schedule of Activities and receive treatment until the treating physician and the medical monitor agree that further continuation of treatment is no longer providing benefit to the subject.

Throughout the Treatment Phase, the investigator will assess response to therapy using RECIST Version 1.1 or RANO. Efficacy evaluations are described in Section 8.2. For subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging according to the imaging schedule, until (1) the start of new anti-cancer treatment, (2) disease progression, (3) withdrawal of consent, (4) death, or (5) the end of the study, whichever occurs first.

8.1.3. End-of-Treatment Visit

The End of Treatment Visit will be performed after the last dose of study drug is administered and will include End-of-Treatment procedures as outlined in the Schedule of Activities. Subjects should have the End-of-Treatment Visit completed 30 (+7) days after the last dose of study drug, or prior to the starting any subsequent cancer treatment, except for those who have withdrawn consent, died, or have been lost to follow up.

Once the end of data collection timepoint has been achieved, follow-up of subjects will end, and data collection will conclude. Only serious adverse events will be reported in the company safety repository (See Appendix 13). Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment (see Section 6.7). During this period, only serious adverse events will be reported into the company safety repository. Additional information on reporting of adverse events is provided in Section 10.4.

8.1.4. Follow-Up Phase

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 subsequent anti-cancer therapy until death, withdrawal of consent, lost to follow-up, or the end of study (ie, the end of data collection timepoint has been achieved), whichever occurs first as outlined in the Schedule of Activities. Subjects who do not want to continue in the Follow-up Phase will be asked to complete and sign a withdrawal of consent form to specify whether or not survival data may be collected. Assessments of survival status and alternate anticancer therapies must be recorded in the eCRF. If necessary, this visit can occur by telephone. Once the end of data collection timepoint has been achieved, subjects will be considered to have completed the study, no further visits will occur and data collection through the eCRF will conclude.

8.2. Efficacy Assessments

For adult subjects, disease assessments will be performed every 6 weeks (every 2 cycles) for the first 12 months and then every 12 weeks (every 4 cycles) thereafter (±7-day window), as outlined in the Schedule of Activities.

For pediatric subjects, disease assessments will be performed every 12 weeks (every 4 cycles, ±7-day window), as outlined in the Schedule of Activities. For subjects with low-grade gliomas where a lower frequency of imaging is sufficient, a 24-week frequency (±7 days) may be adopted after a minimum of 12 months with the sponsor's approval. If a response (partial response or complete response) is observed, an additional scan for confirmation is required 4 to 8 weeks (±7-day window) after the first scan showing the response.

Assessment of responses for solid tumors will be performed according to RECIST (Version 1.1) or RANO guidelines by investigators. For subjects who discontinue study drug before disease progression, tumor assessments should continue as described in Section 8.1.2.

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 (based on global deterioration of health status) occurs without documentation of radiographic progression or disease progression as measured by skin lesion assessment and photography if applicable, 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.

8.2.1. Evaluations

8.2.1.1. RECIST and RANO Assessment of Disease

RECIST 1.1 is an accepted methodology by regulatory authorities. RECIST 1.1 will be applied by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy). The Wen 2010 Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas will be used to assess response to treatment in high-grade gliomas. The van den Bent 2011 Response Assessment in Neuro-Oncology (RANO) criteria for low-grade gliomas will be used to assess response to treatment in low-grade gliomas. After screening, imaging will be repeated during the study as indicated in the Schedule of Activities.

8.2.1.2. Radiographic Assessment

Computed tomography (CT) scans of the chest, abdomen, pelvis, and any other location where disease is present or suspected will be performed at Screening and during the study, except for primary brain tumors. 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 will be performed at baseline for all subjects with a history of brain metastasis or neurological symptoms. Brain MRI will be performed every 12 weeks during the study for subjects with a history of brain metastasis or any time during the study for new or worsening neurological symptoms. Brain MRI will be performed for all subjects with primary brain tumors at baseline and every 6 weeks for disease assessment for the first 12 months (±7-day window) and then every 12 weeks thereafter (±7-day window), as outlined in the Schedule of Activities. Imaging should be performed as scheduled irrespective of study drug interruptions. After discontinuation of treatment, subjects will have an End-of-Treatment Visit and continue in the study for follow-up as outlined in Section 8.1.4.

For skin lesions that cannot be assessed radiographically, skin lesion photography may be used to evaluate response according to RECIST 1.1 (Please refer to the Imaging Acquisition Guidelines).

8.2.2. Continuation of Treatment After Disease Progression

If the site study team makes an initial assessment of disease progression, and if the subject is clinically stable, treatment with erdafitinib may be continued. In the case of imaging-based progression (RECIST, Version 1.1 or RANO-defined disease progression) subjects may continue to receive erdafitinib treatment if the investigator and sponsor's clinical team agree and if the subject is clinically stable as defined by the following criteria: absence of signs and symptoms indicating overt disease progression, stable ECOG Performance Status grade (a comparison chart of ECOG, Karnofsky, and Lansky performance scores is provided in Section 10.6), absence of progressive tumor at critical anatomical sites (eg, spinal cord compression, new brain metastases) requiring urgent alternative medical intervention. Repeat tumor imaging at least 4 weeks but no later than 6 weeks after the first tumor imaging indicating progressive disease.

8.3. Safety Assessments

The DRC will be conducting interim analyses and further safety analyses. The details regarding the DRC are provided in the Committees Structure in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.4, Adverse Events and Serious Adverse Events and Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

In subjects with low-grade glioma and high-grade glioma, the frequency of seizure activity prior to starting trial and frequency of seizure activity while enrolled on trial will be collected in eCRF.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.3.1. History and Physical Examinations

For adult subjects, a full medical history and physical examination, including neurological examination, height, and weight will be performed at screening. If the examination occurs more than 7 days before the first dose of study drug, another examination should be conducted on Cycle 1 Day 1 prior to dosing. Limited physical examinations of involved organs, neurological examination including record of seizure activity (subjects with primary CNS tumors, CNS metastases or other subjects at the investigator's discretion, only), and body weight will be performed at subsequent visits as listed in the Schedule of Activities. New abnormalities will be recorded as AEs.

8.3.1.1. History and Physical Examinations for Children and Adolescent Subjects

A full medical history and physical examination, including neurological and hip examination, height, and weight with corresponding percentiles will be performed at screening. Height and weight with corresponding percentiles should be documented. If the examination occurs more than 7 days before the first dose of study drug, another examination should be conducted on Cycle 1 Day 1 prior to dosing. Limited physical examinations of involved organs, neurological examination including record of seizure activity (subjects with primary CNS tumors, CNS metastases or other subjects at the investigator's discretion, only), and body weight will be performed at subsequent visits as listed in the Schedule of Activities. New abnormalities will be recorded as AEs. For children and adolescents, Tanner Staging will be assessed as indicated on the Children and Adolescent Schedule of Activities (see Section 1.4) until subjects turn 18 years of age.

Slipped Capital Femoral Epiphysis (SCFE) is a hip-joint disorder characterized by the displacement of the capital femoral epiphysis from the femoral neck through the physis (growth plate), a cartilaginous region at the end of the long bone. SCFE is more common in males and occurs during adolescence, a period of increased bone growth. Given that FGFR signaling is involved in regulation of chondrogenesis, osteogenesis, and also bone homeostasis, there is growing evidence to suggest that exposure to FGFR tyrosine kinase inhibitors presents a potential risk for skeletal toxicities, such as SCFE, in adolescent subjects.

Detailed history including focus on risk factors for musculoskeletal diseases, eg SCFE (Peck 2017), should be obtained at screening; such risk factors are described below:

- Endocrine abnormalities, such as hypoparathyroidism, panhypopituitarism and hypogonadism (Kay 2014; Blethen 1996)
- Conditions associated with growth hormone deficiency or the use of growth hormone increases the risk of epiphysiolysis (SCFE) (de Andrade 2009)
- Radiation in proximal femoral epiphysis and chemotherapy in childhood increases the risk of developing SCFE (Walker 1981)
- Obesity and previous history of unilateral SCFE are both risk factors for developing SCFE (Nasreddine 2013)
- Secondary hyperparathyroidism, hypocalcemia and osteitis fibrosa in the setting of chronic kidney disease (Schmidtt 2008)
- Accelerated growth velocity (Deng 1996)

During the Treatment Phase, subjects presenting with groin, hip, thigh, or knee pain, or changes in ambulation should be evaluated for potential musculoskeletal disorders, especially among subjects with accelerated growth reflected through change in percentile curves. Referral to a pediatric orthopedic surgeon should be considered.

8.3.2. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and temperature will be assessed. All clinically significant abnormalities will be recorded as AEs. For children and adolescents aged ≥6 to <18 years, height will be measured using a stadiometer and should be documented with corresponding percentiles with weight.

8.3.3. Electrocardiograms

The 12-lead electrocardiograms (ECGs) will be performed at any time during the screening period, as well as Cycle 2 Day 1 and Cycle 4 Day 1. If possible, postdose ECGs should be recorded 2 to 4 hours after the erdafitinib dose on Cycle 2 Day 1 and on Cycle 4 Day 1. Additional ECGs may be performed during the study as clinically indicated.

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. A printout of the ECG should be produced and stored in the subject's source documents. The 12-lead ECG recorder device used 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. For children and adolescent subjects (aged <18 years), QTc (Bazett) may be used for assessment of QTc interval. The investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings).

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, and pregnancy testing will be collected as noted in Section 10.2, Clinical Laboratory Tests. 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 CRF.

8.3.5. Ophthalmologic Examination

All subjects must 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), and slit lamp biomicroscopy; an Optical Coherence Tomography (OCT) must also be performed at Screening (see the OCT Manual for details). 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 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 scan and fluorescein angiography (if performed) must be stored in the subject's records and a redacted copy sent to the sponsor-selected central vendor for possible future independent assessment. If only a PDF is available, please review with sponsor prior to enrollment (refer to the central vendor manual).

Amsler grid (Section 10.9) testing will be administered to all subjects at Screening and during the treatment phase according to the Schedule of Activities. 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 examination 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.

8.3.6. Performance Status

Performance status will be determined at pre-specified time points listed in the applicable Schedule of Activities (Adult or Children and Adolescent) using one of the following scales:

- ECOG performance status for adults, ie, ≥18 years of age (Section 10.5),
- Karnofsky Performance Scale for adolescents ≥16 to <18 years of age (Section 10.6), or
- Lansky Performance Scale for children and adolescents aged ≥6 to <16 years of age (Section 10.6).

Subjects should have a repeated performance assessment at Cycle 1 Day 1 prior to dosing if the previous one during screening occurred more than 7 days before first dosing.

8.3.7. Bone-related Assessments (Children and Adolescents)

For assessment of bone-related toxicities (growth plate assessment), children and adolescent subjects (≥6 to <18 years) will undergo a plain anteroposterior (AP) radiograph of the (left or right) tibia and AP and frog leg lateral of both hips prior to Cycle 1 Day 1.

- If subjects are found to have a closed growth plate, no further radiographs will be required.

- While on study treatment, tibia imaging will be required. If subjects are found to have an open growth plate, repeat plain AP radiographs of the same growth plate will be performed every 3 months for 6 months, and, thereafter, every 6 months.

- While on study treatment, hip imaging will continue to be performed every 6 months. Additional imaging may be performed if clinically indicated (groin, hip, thigh, knee pain, and/or difficulty ambulation). If x-ray imaging is inconclusive and symptoms persist, an MRI should be performed for further evaluation. Referral to a pediatric orthopedic surgeon should be considered.

Subjects with evidence of growth plate changes should have additional detailed imaging (MRI, etc) performed to assess the degree of pathology.

For assessment of bone-related toxicities (bone age), children and adolescent subjects (≥6 to <18 years) will undergo a plain posteroanterior (PA) radiograph of the nondominant hand and

wrist prior to Cycle 1 Day 1. Assessments will be conducted every 3 months for 6 months, and, thereafter, every 6 months.

Also, for children and adolescent subjects (≥6 to <18 years), bone densitometry (DEXA scan) should be conducted at baseline, at 6 months, at 12 months, and, thereafter, every 12 months, as clinically indicated.

Abnormalities identified during imaging must be recorded as AEs. The investigator must consult with the sponsor regarding any dose modification and/or discontinuation of treatment related to these abnormalities.

8.4. Adverse Events and Serious Adverse Events

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.

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.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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 is obtained until 30 days after the subject's last dose of study drug. 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.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately but no later than 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).

A possible Hy's law Case is defined by the occurrence of ALT/AST ≥3 × ULN, alkaline phosphatase <2 × ULN together with total bilirubin ≥2 × ULN or INR >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported as an SAE to the sponsor in an expedited manner (Appendix 10.2), even before all other possible causes of liver injury have been excluded.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

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 suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.4.5. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) 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 and discontinue further study drug. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be requested. Follow-up information may continue to be collected up to 12 months after the birth of a baby, if a congenital anomaly or significant medical condition is diagnosed at birth.

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

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

Progression of disease should not be considered an AE (or SAE). 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 (Section 10.4).

8.4.7. Adverse Events of Special Interest

Central serous retinopathy (CSR) is considered an adverse event of special interest. Retinal abnormalities should be reported as adverse events or as serious adverse events if the severity is Grade 3 or higher. Instructions for assessing vision abnormalities during the study are provided in Section 8.3.5.

Growth disorders (including accelerated bone growth and SCFE) and fractures in children and adolescent subjects (≥6 to <18 years) is an adverse event of special interest for erdafitinib. Growth disorder-related and fracture-related AEs of Grade 3 or higher severity in children and adolescents, regardless of seriousness, will be reported to the sponsor within 24 hours (see Section 10.4.).

8.5. Pharmacokinetics

Venous blood samples (2 mL per visit) will be collected for the determination of plasma concentrations of erdafitinib at the time points specified on the Schedule of Activities (Section 1.3 for Adults and Section 1.4 for Children and Adolescents). On PK sampling days Cycle 1 Day 14, and Cycle 2 Day 14 (children and adolescents only), for morning clinic visits, morning dosing should be withheld until after the PK sample has been obtained in the clinic. For afternoon clinic visits, subjects should take their dose as usual and a postdose sample should be collected during the visit. On Cycle 2 Day 1, Cycle 3 Day 1 (children and adolescents only), and Cycle 4 Day 1 (children and adolescents only), the dose should be taken in the clinic after the predose PK sample. On Cycle 2 Day 1, a 2- to 4-hour blood sample will be collected for adults, children, and adolescents. An approximate 1-4-mL venous blood sample will be taken together with the postdose PK samples on Cycle 2 Day 1, 2- to 4-hour postdose (for adults), and Cycle 3 Day 1, 2-hour postdose (for children and adolescents) for the determination of plasma protein binding data of erdafitinib (ie, alpha-1-acid glycoproteins, total protein, and fraction unbound) (Section 1.3 for adults and Section 1.4 for children and adolescents). On Cycle 3 Day 1, serial PK samples will be collected at predose, and at 1h, 2h, 4h, 6h, 12h postdose in children and adolescents. The 12h postdose sample can alternatively be collected at 24h postdose (see Section 1.4). The time of dosing, and the time of the PK sample and protein binding sample must be recorded accurately. If indicated by the emerging safety findings or if the scheduled PK samples are not collected due to treatment interruption, blood samples may be collected at a later site visit (on Cycle 2 Day 14 [adults only], Cycle 3 Day 1 [adults only], or Cycle 3 Day 14). In the event of a treatment interruption of 2 consecutive weeks or more, PK samples do not need to be collected. The Laboratory Manual provides further information regarding handling and shipment of blood/plasma samples.

Germline DNA will be collected for subjects on erdafitinib (see Schedule of Activities in Section 1.3 for Adults and Section 1.4 for Children and Adolescents) from a blood sample (2 mL) on Cycle 1 Day 14 (or later timepoint) for the purpose of CYP2C9 genotyping to allow exploration of the effect of CYP2C9 polymorphism on the PK of erdafitinib.

To assess the distribution of erdafitinib in the CSF in subjects with CNS tumors, one CSF sample will be collected from a routinely scheduled CSF evaluation from subjects when feasible during the Treatment Phase. A 2 mL sample for PK evaluation will be collected at the time of the CSF evaluation during the treatment phase.

8.5.1. Analytical Procedures

Blood samples will be processed to obtain plasma for measurement of erdafitinib concentration by a validated analytical method under the direction of the sponsor. Plasma protein binding, if needed, will be determined by equilibrium dialysis. After dialysis, the buffer and plasma samples will be analyzed for erdafitinib content using a qualified liquid chromatography/mass spectrometry method by the sponsor's Bioanalytical Laboratory. The α1-AGP and other proteins will also be measured in the plasma protein binding samples. CSF samples will be analyzed for erdafitinib concentrations using a qualified liquid chromatography/mass spectrometry method by the sponsor's Bioanalytical Laboratory.

8.6. Biomarkers

Biomarker investigations in this study include but are not limited to assessment of:

- Circulating tumor DNA (ctDNA) from plasma to screen for changes in the levels or types of genetic alterations observed over time, and to identify markers of intrinsic and acquired resistance to erdafitinib
- Assessment of alterations in non-FGFR genes in pre-treatment/archival samples and association with response or resistance to erdafitinib
- Serum phosphate levels as a marker of target engagement

Tumor Tissue Assessments

Tissue collected on study at screening will be used to assess biomarkers relevant to specific tumor histologies and to determine co-occurring genomic alterations from tumor samples by DNA sequencing analysis or alternate method.

Circulating Biomarkers

Blood samples for circulating biomarkers should be collected predose at timepoints specified in the Schedule of Activities.

Serum phosphate levels may be monitored in subjects treated with erdafitinib as a marker of target engagement. The Phase 1 (JNJ42756493EDI1001) and Phase 2 (JNJ42756493BLC2001) studies of erdafitinib demonstrated that phosphate levels are a robust PD biomarker of erdafitinib target engagement, and that achieving target increases in serum phosphate may be associated with clinical response to erdafitinib.

Circulating Tumor DNA

Blood for analysis of ctDNA will be collected at multiple time points on the study. Circulating tumor DNA are fragments of DNA shed in the bloodstream during cell turnover. In cancer, a

fraction of the circulating DNA is from DNA shed by tumor cells. This ctDNA often harbors somatic alterations which are reflective of the original tumor.

Circulating tumor DNA may be used to track response to treatment and the emergence of resistance by monitoring changes in target ctDNA levels over time. Samples collected prior to and during treatment may be screened for changes in the levels or types of genetic alterations observed over time, and to monitor for the emergence of potential markers of resistance to erdafitinib.

Sample Collection and Analysis

Additional biomarkers (DNA, RNA, and protein) relevant to cancer may also be assessed in blood and tissue samples collected on the study to better understand the disease and the mechanisms of response or resistance to erdafitinib.

Adjustments in the timing of biomarker collections may be made during the study based on emerging data.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and emerging data. Biomarker analyses may be deferred if, during or at the end of the study, it becomes clear that the analysis will have no scientific value, that there are not enough samples, or that there are not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.7. Tumor Markers

If applicable for the underlying tumor type and when permitted by local regulations, serum tumor markers (eg, carbohydrate antigen 19-9, carcinoembryonic antigen, alpha-fetoprotein) that are assessed as part of routine care will be captured in the eCRF at baseline and until treatment discontinuation.

8.8. Patient-reported Outcomes

Patients' health-related quality of life, symptoms, functioning, and general well-being will be captured using PRO measures (the assessments should be conducted in this order): PGIS, PGIC, EORTC-QLQ-C30 (for subjects ≥18 years of age) or Peds FACT-Br (for subjects <18 years of age), and EQ-5D-5L utility and VAS. The PRO measures will be electronically collected, according to the Schedule of Activities, to understand change over time in each cohort.

The PGIS is a single question regarding the subject report of disease severity: Considering all aspects of your cancer symptoms right now would you say your cancer symptoms are none, mild, moderate, severe, or very severe? The PGIS is an anchor question that will be used to establish the magnitude of meaningful change in this study.

The PGIC is the PRO counterpart to the Clinical Global Impressions scale, (CGI), which was published in 1976 by the National Institute of Mental Health (US) (eProvide 2019, Guy 1976). It consists of one item taken from the CGI and adapted to the patient.

The EORTC-QLQ-C30 (for subjects ≥18 years of age) consists of 30 core items, with the 4-point Likert scales ranging from 1: "Not at all" to 4: "Very much" (Michelson 2000, Schwarz 2001). There are 2 items for global health status/quality of life. Functional scales include: Physical functioning (5 items), Role functioning (2 items), Emotional functioning (4 items), Cognitive functioning (2 items), and Social functioning (2 items). Symptom scales/items include Fatigue (3 items), Nausea and vomiting (2 items), Pain (2 items), Dyspnea; Insomnia; Appetite loss; Constipation; Diarrhea; and Financial impact (1 item each). For subjects <18 years of age, the Peds FACT-Br should be used. Peds FACT-Br consists of 4 sets of disease-specific questions pertaining to brain neoplasms (a set of 34 to 37 questions each for child, parent of child, adolescent or parent of adolescent; Peds FACT-Br, 2021).

The EQ-5D-5L is a generic measure of health status (Herdman 2011). For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L asks respondents to select their response based on their current health ("today") and takes less than 5 minutes to complete.

8.9. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects at the disease assessment visits. Protocol mandated procedures, tests, and encounters are excluded. The data collected will be used to conduct exploratory analyses that may be used to support the value story and cost-effectiveness modeling for market access. The data collected may include:

- Number and characteristic of diagnostic and therapeutic tests procedures (inpatient and outpatient)
- Number and duration of hospitalization (total length of stay [days]), including duration by each hospital unit (intensive care unit)
- Outpatient medical encounters (including physician, nurse practitioner or emergency room visits, tests and procedures)
- Please see eDC manual for more details.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be performed 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.

9.1. Statistical Hypothesis

The primary hypothesis of this study is that treatment with erdafitinib will improve ORR with a target rate of 35% over a null rate of 15% in subjects with advanced solid tumors that harbor target FGFR alterations in the Broad Panel Cohort, the Core Panel Cohort, or both cohorts. The corresponding null and alternative hypotheses are as follows:

H_0: ORR ≤15% vs Ha: ORR ≥35%.

9.2. Sample Size Determination

Approximately 280 subjects ≥12 years of age with FGFR genetic alterations will be enrolled in the Broad Panel Cohort (approximately 240 subjects for 200 response-evaluable subjects, note that adolescent subjects will be enrolled in the Broad Panel Cohort until the cohort is full or the sample size cap of 30 for the tumor histology is met) and the Exploratory Cohort (approximately 40 subjects).

The primary analysis will be conducted 6 months after the first dose of the last Broad Panel Cohort subject.

9.2.1. Broad Panel Cohort

The sample size of 200 response-evaluable subjects for the Broad Panel Cohort is selected based on extensive simulations with various Bayesian hierarchical model designs to achieve approximately 80% power to select 80% tumor histologies (eg, ≥12 of 15 tumor histologies) for the final analysis if the true ORR is 35% for each tumor histology. For enrollment in each tumor histology, the sample size is capped at approximately 30 subjects. For comparison, a Simon minimax 2-stage design requires 28 subjects for Type I error rate of 0.05 and Type II error rate of 0.20. The tumor histology list for this cap, including a group of Other, is pre-defined in **Table 16**.

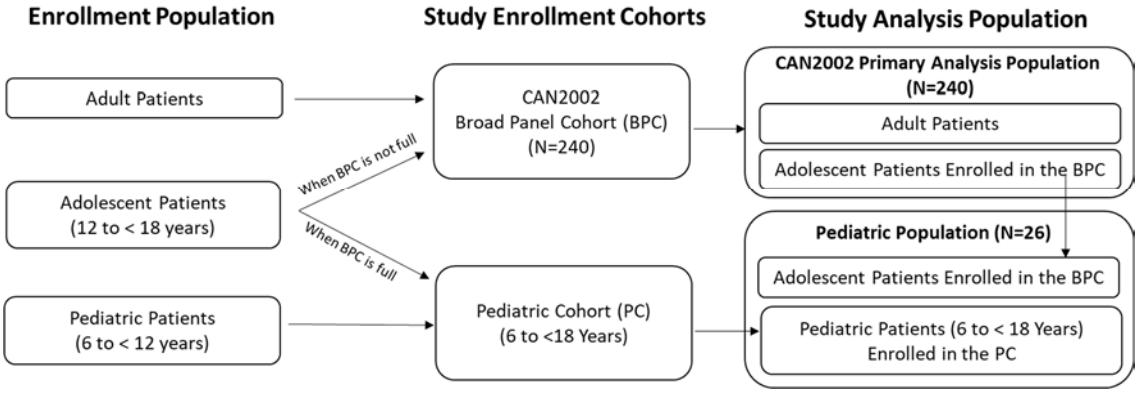
For the tumor histology that is identified as active and safe, further enrollment beyond the cap of approximately 30 subjects may be allowed at the discretion of the DRC. These subjects will be enrolled in separate cohorts and not included in the primary efficacy analysis of the Broad Panel Cohort.

9.2.2. Cholangiocarcinoma Expansion Cohort

A DRC meeting was triggered by the cholangiocarcinoma histology approaching the predefined cap of approximately 30 subjects. In July 2020, a DRC meeting was convened to consider expansion of enrollment of subjects with cholangiocarcinoma. Based on review of safety and efficacy data, the DRC recommended to continue the study and to allow expanded enrollment in the cholangiocarcinoma histology. As a result, a Cholangiocarcinoma Cohort was added to enroll subjects outside the Broad Panel Cohort. Approximately 30 additional subjects are intended to be enrolled in the Cholangiocarcinoma Expansion Cohort to further characterize the clinical activity for this histology.

9.2.3. Pediatric Cohort

A separate Pediatric Cohort will enroll subjects ≥6 to <18 years of age with locally advanced or metastatic solid tumors harboring FGFR alterations. These subjects include 1) those who have either progressed following prior therapies and who have no acceptable standard therapies, or 2) those who have newly diagnosed solid tumors and who have no acceptable standard therapies. A sample size of 20 children and adolescent subjects who have either progressed following prior therapies and who have no acceptable standard therapies (including adolescent subjects enrolled in the Broad Panel Cohort) will be planned. CCI [redacted]. With an observed ORR of 35%, the 20 children and adolescent subjects will provide a 95% Clopper-Pearson CI of 15.4% to 59.2%. In addition, approximately 6 children and adolescent subjects who have newly diagnosed solid tumors and who have no acceptable standard therapies are anticipated to be enrolled. Note that the enrollment in the Pediatric Cohort will be unaffected by any futility analysis for the Broad Panel Cohort.



Note: Eligibility of adolescents ≥12 to <18 years to enroll in the Pediatric Cohort will be based on molecular eligibility as well as whether the Broad Panel Cohort is full or the enrollment cap for a tumor type is met.

9.3. Populations for Analyses

9.3.1. Broad Panel Cohort

The alterations eligible for inclusion in the Broad Panel Cohort consist of target FGFR mutations and any FGFR fusion. The List of Target FGFR Mutations eligible for the Broad Panel Cohort is provided in Section 10.11. The Broad Panel Cohort will represent the primary cohort of interest for analysis. Populations for analysis of the Broad Panel Cohort are specified below:

- The Treated Population will consist of all subjects (FGFR+) who receive at least 1 dose of study drug. The Treated Population is the primary population for efficacy and safety analyses.
- The Response-evaluable Population will include all subjects (FGFR+) who satisfy the following criteria:
  - 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 radiological disease evaluation, or had clinical signs or symptoms of disease progression, or died prior to the first posttreatment disease evaluation (these subjects will be considered non-responders). Adequate disease assessment is defined as having enough evidence to indicate that progression has or has not occurred.

- The Core Panel Cohort, which is a subgroup of the Treated Population in the Broad Panel Cohort with a selected panel of pre-specified FGFR markers, will be assessed as part of the final analysis. The subset of FGFR markers was selected based on observed clinical activity in previous studies or a high level of recurrence of these alterations across tumor histologies; the subset of FGFR markers is outlined below:
  - FGFR3 mutations: S249C; Y373C; R248C; G370C
  - FGFR2 mutation: C382R
  - FGFR3 fusion: FGFR3-TACC3
  - FGFR2 fusions: FGFR2-BICC1; FGFR2-TACC2

The Treated Population will be used to summarize the study population and characteristics, efficacy, and PRO data; the efficacy and safety analyses will be conducted in the Treated Population in the Broad Panel Cohort and the Core Panel Cohort. The Response-evaluable Population will be used for the interim analysis, and supplementary efficacy analysis on key endpoints such as ORR and DOR.

9.3.2. Exploratory Cohort

Subjects enrolled in Exploratory Cohort who receive at least 1 dose of study drug, will be evaluated for efficacy and safety as the exploratory analysis.

9.3.3. Cholangiocarcinoma Expansion Cohort

Subjects enrolled in Cholangiocarcinoma Expansion Cohort with target FGFR mutations or any FGFR fusion who receive at least 1 dose of study drug, will be evaluated for efficacy and safety as a separate analysis. The Cholangiocarcinoma Expansion Cohort will be evaluated separately from the Broad Panel Cohort.

9.3.4. Pediatric Cohort

Subjects in the Pediatric Cohort with locally advanced or metastatic solid tumors harboring FGFR mutations, any gene fusions or FGFR internal tandem duplication who have either progressed following prior therapies and who have no acceptable standard therapies, or who have a newly diagnosed solid tumors and who have no acceptable standard therapies, and receive at least 1 dose of study drug, will be evaluated separately from the Broad Panel Cohort.

9.4. Statistical Analyses

9.4.1. Primary Endpoint

ORR assessed by IRC: the proportion of subjects who achieve a CR or PR based on RECIST v1.1 or RANO as assessed by IRC.

9.4.2. Secondary Efficacy Endpoints

- ORR assessed by investigator: the proportion of subjects who achieve a CR or PR based on RECIST v1.1 or RANO as assessed by investigator.
- DOR: the duration 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, whichever comes first, for subjects. Data from subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment
- DCR: the proportion of subjects with CR, PR or SD
- CBR: the proportion of subjects with CR, PR or durable SD (defined as a duration of at least 4 months)
- PFS: 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, for subjects. Data from subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment
- OS: 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

Details for the PRO endpoints will be provided in a separate Statistical Analysis Plan.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analysis

The primary analysis for the Broad Panel Cohort will be conducted approximately 6 months after the first dose of the last Broad Panel Cohort subject (reaching approximately 200 response-evaluable subjects) and the analysis will be based on Treated Population in the Broad Panel Cohort.

The primary efficacy analysis will be performed on the pooled data of all tumor histologies that did not meet the futility for the Treated Population in the Broad Panel Cohort and the Core Panel Cohort. The primary endpoint ORR (CR or PR) according to RECIST v1.1 or RANO criteria assessed by the IRC will be calculated with 95% 2-sided exact CI. Statistical inference on ORR by IRC will be tested at 0.025 one-sided level, unless otherwise specified. To adjust for multiplicity, an error-spending function approach (Spiessens 2010) will be used to split the significance level using the observed size of the Core Panel Cohort relative to the size of the Broad Panel Cohort.

Refer to the SAP for details of the supplementary and sensitivity analyses.

Other efficacy analyses that will be focused on the Broad Panel Cohort and the Core Panel Cohort include:

- ORR (CR or PR) according to RECIST v1.1 or RANO criteria assessed by the investigator will be calculated with 95% 2-sided exact CI
- The distributions of DOR will be summarized using Kaplan-Meier estimates based on responding subjects. The estimated median will also be reported along with a 95% CI
- DCR and CBR will be calculated with 95% 2-sided exact CI
- PFS and OS will be summarized using similar Kaplan-Meier methods

Safety and efficacy analyses will be conducted on the Cholangiocarcinoma Expansion Cohort and the Exploratory Cohort at the same time as the primary analysis of the Broad Panel Cohort.

Primary Analysis for the Pediatric Cohort

The treated subjects (approximately 20) who have either progressed following prior therapies and who have no acceptable standard therapies in the proposed Pediatric Cohort (including the adolescent subjects enrolled in the Broad Panel Cohort) will be the primary analysis population for the Pediatric Cohort. The additional approximately 6 subjects who have a newly diagnosed solid tumors and who have no acceptable standard therapies will be analyzed separately from the Broad Panel Cohort.

The Pediatric Cohort will have the same primary and secondary endpoints as the Broad Panel Cohort. In general, all interval estimation will be reported using 2-sided 95% CIs. Disease progression and response will be primarily based on IRC assessment and secondly based on investigator assessment, using RECIST v1.1. or RANO criteria. The ORR and its 2-sided 95% Clopper-Pearson CI will be provided. For time-to-event variables, Kaplan-Meier estimates will be provided.

9.4.3.2. Final Analysis

The final analysis will be performed for all cohorts when the end of data collection timepoint (defined in Section 5.5) is reached for all cohorts. All efficacy and safety analyses will be updated.

9.4.4. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic data will be summarized and listed for all subjects with available plasma and CSF erdafitinib concentrations. Additionally, the erdafitinib CSF-to-plasma concentration ratios will be calculated with CSF and plasma PK samples collected in pair, if the sample collections of PK plasma samples and PK CSF are within 2 hours of each other. The CSF-to-plasma concentration ratios will be summarized and listed.

In addition, for children and adolescents only, the following PK parameters will be derived after serial PK sampling at Cycle 3 Day 1: C_{max}, t_{max}, $AUC_{0\text{-}24h}$, CL/F.

C_{max}	maximum observed analyte concentration
t_{max}	the actual sampling time to reach the maximum observed analyte concentration
AUC_{0-24h}	AUC from time of dose to 24h[a] post-dose
CL/F	total apparent clearance

[a] The predose (C_{min}) sample at Cycle 4 Day 1 or other cycles in which erdafitinib has reached steady-state can be used as surrogate for 24-hour postdose PK to derive AUC_{0-24}.

An interim Bayesian population PK and, if appropriate, noncompartmental analysis of plasma concentration-time data of erdafitinib and markers of pharmacological activities (serum phosphate) will be performed after 5 children or adolescents (<18 years of age) are enrolled and have completed Cycle 3 Day 1 in the study. Assessment of the accuracy of the existing population PK/PD model and model parameters to predict the pediatric population PK and PK serum phosphate relation will be performed to justify or, if needed, update the age guided dose selection and phosphate guided dose titration of children and adolescent subjects.

Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Population PK analysis of plasma concentration-time data of erdafitinib may be performed using nonlinear mixed-effect modeling. Previously developed PK models may be used and updated as considered appropriate. Relationships between plasma concentrations or metrics of systemic exposure and CYP2C9 polymorphism, markers of pharmacological activities (serum phosphate), efficacy or treatment-emergent adverse events may also be explored as data allow using population approaches. If relevant, results of the analyses will be provided in a separate report.

9.4.5. Biomarker Analyses

Changes in molecular markers (FGFR or other genes), disease relevant biomarkers, and phosphate levels over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and clinical response will be explored.

Results of exploratory biomarker analyses may be presented in a separate report. Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

9.4.6. Medical Resource Utilization and Patient-reported Outcomes Analyses

Medical resource utilization and PRO measures will be summarized descriptively (ie, mean, standard deviation including change from baseline) at each assessment time point. Additional analyses may be conducted; details and results of any additional analyses will be presented in a separate report.

9.4.7. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent adverse events 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 intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue intervention 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 used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided. Parameters with predefined NCI-CTCAE 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

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT corrected according to Fridericia's formula (QTcF). The Bazett formula may be used for children and adolescent subjects. Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds. All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

ECOG

ECOG grade will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

Bone-related Assessments

Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

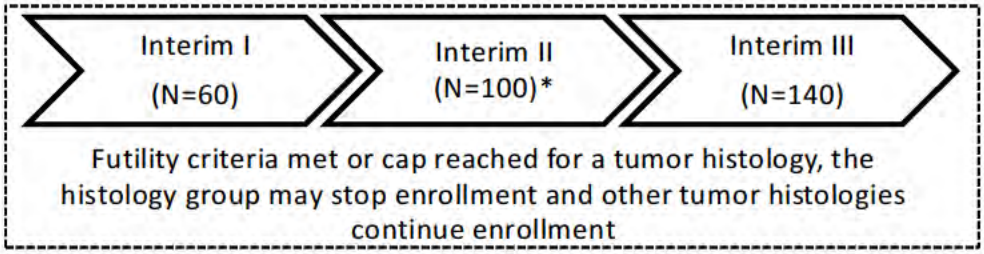
9.5. Interim Analyses

Broad Panel Cohort

Three interim futility analyses are planned for the Broad Panel Cohort when 30%, 50%, and 70% of the subjects (ie, approximately 60, 100, and 140 subjects) have been treated and are considered response-evaluable by investigator assessment, irrespective of the tumor histologies and the distribution among the tumor histologies (Figure 7, N represents the number of response-evaluable subjects). The tumor histology list for futility analysis is pre-defined in **Table 16** (except for the group Other including all other tumor histologies not listed). In addition, an interim efficacy analysis will be conducted for the Broad Panel Cohort after 50% subjects being treated and considered response-evaluable (at the same time as the second interim futility analysis, Figure 7). An early success may be declared if the observed ORR is 50% or higher, with consistent effect across histologies and few tumor histologies were stopped (ie, for enrollment) due to the futility analyses. Regardless of the outcome of the interim efficacy analysis, study enrollment will continue to better characterize the efficacy for active tumor histologies. The results of the interim analyses will be reviewed by the DRC.

The interim futility analyses will be based on the ORR assessed by investigator using a Bayesian hierarchical model (BHM), implemented in FACTS v6.2 Enrichment Design – Dichotomous (Berry 2013, Chugh 2009). The BHM borrows information across tumor histologies and allows for evaluation of each tumor histology individually given the often-unique features of each group. At least 5 subjects in a tumor histology are required for the futility analysis for the given tumor histology. The futility criteria will be met if the posterior probability (ORR >25%) is <40% in the Broad Panel Cohort for a given tumor histology. More details are in the Appendix to the draft Statistical Analysis Plan provided with this submission. All available data (eg, efficacy, safety, and biomarker data) will be assessed to determine whether enrollment in a given tumor histology should continue, including the representativeness of biomarker alterations (the expected variant representation by tumor histology based on genomic database assessment). If a tumor histology is deemed futile by the DRC, further enrollment in the group will stop; subjects who have been enrolled in the tumor histology group will continue treatment and evaluation as per the protocol. Details of the composition of the DRC and the operational procedures will be specified in the DRC charter.

Figure 7: Interim Analyses for the Broad Panel Cohort



* At Interim Analysis II both futility and efficacy will be assessed.

Table 16: List of Tumor Histologies for Futility and Cap

Number	Tumor Histologies
1	Cholangiocarcinoma
2	High-grade Glioma
3	Squamous NSCLC
4	Squamous cell head and neck cancers
5	Gastric Cancer
6	Breast Cancer
7	Endometrial Cancer
8	Low-grade Glioma
9	Ovarian Cancer
10	Non-squamous NSCLC
11	Colorectal Cancer
12	Pancreatic Cancer
13	Cervical Cancer
14	Esophageal
15	Other

Note: The group Other will enroll all other tumor histologies not listed. The group Other shares the same cap of approximately 30 and will be included in the BHM evaluation for information borrowing only but will not be deemed futile early in the interim analyses and will continue enrollment until cap is reached.

Pediatric Cohort

An interim Bayesian population PK and, if appropriate, noncompartmental analysis of plasma concentration-time data of erdafitinib and markers of pharmacological activities (serum phosphate) will be performed after 5 children or adolescents (<18 years of age) are enrolled and

have completed Cycle 3 Day 1 in the study (see Section 9.4.4). In addition, further interim analyses may be conducted after enrollment of additional subjects.

9.6. Data Review Committee

A DRC will be established as noted in Committees Structure in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

α1-AGP	α1-acid glycoprotein
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	anteroposterior
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta-human chorionic gonadotropin
BPC	Broad Panel Cohort
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma drug concentration
CNS	central nervous system
CNV	copy number variation
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CSF	cerebrospinal fluid
CSR	central serous retinopathy
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
CXDX	Cycle X Day X
DCR	disease control rate
DEXA	dual-energy X-ray absorptiometry
DNA	deoxyribonucleic acid
DOR	duration of response
DRC	Data Review Committee
ECGs	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
EQ-5D-5L	European Quality of Life – 5 Dimensions-5 Levels
EU	European Union
FGFR	fibroblast growth factor receptor
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
GENIE	Genomics Evidence Neoplasia Information Exchange [database]
HGG	high grade glioma
HNSCC	head and neck squamous cell carcinoma
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IEC	Independent Ethics Committee
INR	international normalized ratio
IRC	Independent Review Committee
IRB	Institutional Review Board

LTE	long-term extension
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-COG Pediatric MATCH studies	National Cancer Institute and Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice [Substudy for Erdafitinib]
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	overall response rate
OS	overall survival
PA	posteroanterior
PCC	protocol clarification communication
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD-L1	programmed death-ligand 1
Peds FACT-Br	Pediatric Functional Assessment Of Cancer Therapy - Brain
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Symptom Severity
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PR	partial response
PRO	Patient-reported Outcome
PTH	parathyroid hormone
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RPED	retinal pigment epithelial detachment
RT-PCR	reverse transcription polymerase chain reaction
RVO	retinal vein occlusion
SCFE	slipped capital femoral epiphysis
SD	stable disease
TCGA	The Cancer Genome Atlas [database]
ULN	upper limit of normal
US	United States
VAS	visual analog scale

10.2. Appendix 2: Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected according to the Schedule of Activities. 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.

The following tests will be performed by the local laboratory:

Hematology Panel

-hemoglobin
-platelet count
-white blood cell (WBC) count and absolute neutrophil count (ANC) only

Serum Chemistry Panel

-alanine aminotransferase (ALT)
-aspartate aminotransferase (AST)
-total bilirubin
-chloride
-bicarbonate (if feasible)
-creatinine (including calculated creatinine clearance)
-calcium
-phosphate
-potassium
-sodium
-magnesium
-alkaline phosphatase
-albumin

Possible Hy's Law case reporting requirements are defined in Section 8.4.1

Parathyroid hormone

Thyroid hormones (children and adolescents only)

- Thyroid stimulating hormone (TSH), free thyroxine (T4), and total triiodothyronine (T3)

Insulin-like growth factor 1 (IGF-1) (children and adolescents only)

Creatinine or creatinine clearance will be determined per institutional standard.

A urine or serum sample will be obtained for a pregnancy test (β-hCG) in sexually active female subjects of childbearing potential at screening within 7 days of the first dose, or at Cycle 1 Day 1 prior to the first dose, and at End-of-Treatment. Additional serum or urine pregnancy tests will be performed on Day 1 of every cycle (starting with Cycle 2 Day 1), to establish the absence of pregnancy at any time during the subject's participation in the study.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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, Clinical Trial Managers, and/or Contract Research Organizations who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with 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.

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) involve only logistic or administrative aspects of the study, the IEC/IRB (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 listed in the Contact Information page(s), which will be provided as a separate document. 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 CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy 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 (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, 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 subinvestigators
- Documentation of subinvestigator qualifications (eg, 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 (eg, accreditation/license), if applicable

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)
- IB (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, unless required locally), 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.

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 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, where required.

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

Long-Term Extension and Post-trial Access

Once the end of data collection timepoint (see Section 5.5) has been achieved, follow-up of subjects will end, and data collection will conclude. Subjects in the Treatment Phase who are continuing to derive benefit from study treatment as determined by their investigator may continue to receive access to study treatment either on this study, with only data collection of serious adverse events in the company safety repository (see Section 5.5 and **Error! Reference source not found.**) via LTE phase or a post-trial access program, when permitted by local regulations. Provision may continue until the subject can commercially access study treatment within the local healthcare system, until a decision is made not to pursue the studied indication, 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.

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.4, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.4.

10.3.2. 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 (above) for details on financial disclosure.

10.3.3. Informed Consent Process and Assent Form

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature, significance, and purpose of the study, and procedures required for the study, and consequence of the study, have been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form 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 the subject will receive for the treatment of his or her disease. 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, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The 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 either 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.

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.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies; children ≥6 to <12 years of age, adolescents 12 years of age and above and adults will be enrolled in this study. Written Assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for children and adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent(s) or if applicable legally acceptable representative. Minors who reach the age of majority (per local regulations) during study will need to (re)sign an ICF.

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.

10.3.4. Data Protection

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 information about, and where required per applicable regulations, 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. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

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, or make requests concerning his or her personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory biomarker and PK 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.

10.3.5. 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 advanced solid tumors with FGFR aberrations, to understand differential intervention responders, and to develop tests/assays related to erdafitinib and advanced solid tumors with FGFR aberrations. 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 7.2.1, Withdrawal From the Use of Research Samples).

10.3.6. Committee Structure

Data Review Committee

A DRC will be established for review of safety data and for monitoring of interim efficacy data, to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data including safety data. After the review, the DRC will make recommendations regarding the continuation of enrollment in each histology or the continuation of the study. The DRC will also determine whether to enroll more subjects into a tumor histology when the prespecified cap of approximately 30 subjects is reached. Details of the composition of the DRC and their operational procedures will be specified in the DRC Charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding erdafitinib or the sponsor's operations (eg, 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 exploratory PK or 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 as per protocol. 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 for the study. Results of exploratory PK or 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 (ICMJE) 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 sub-study 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 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 conception or 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 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.

10.3.8. Data Quality Assurance

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 CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF 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.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

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

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and 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).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: 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; intervention 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.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document). Missing PRO data form will be recorded directly into the CRF and will be considered as source data.

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, 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. This data is 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.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

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 CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF 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 documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review 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 documents 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.

10.3.12. 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. 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.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF 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.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

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

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is specifically not questioned.

10.4.1. 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 intervention. 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 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 Full-study ICF (refer to All Adverse Events under Section 8.4.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU 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 IB.

Assessment of Causality

The causal relationship to study treatment is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.2. 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 or higher. Any adverse event or serious adverse event not listed in the NCI-CTCAE, Version 5 or higher 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].

- 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[b].

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

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

[b] Self-care ADL refers to bathing; dressing and undressing; feeding self; using the toilet; taking medications; and not bedridden.

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

10.4.3. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

Retinal abnormalities should be reported as adverse events or as serious adverse events if the severity is Grade 3 or higher. Instructions for assessing vision abnormalities during the study are provided in Section 8.3.5.

In addition, growth disorder (including accelerated bone growth and SCFE) and fractures in children and adolescents (≥6 to <18 years) is an adverse event of special interest for erdafitinib. Growth disorder-related and fracture-related AEs of Grade 3 or higher severity in children and adolescents, regardless of seriousness, will be reported to the sponsor within 24 hours.

10.4.4. Procedures

All Adverse Events

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 CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF 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.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- 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)

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 (eg, 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 CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- 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 (eg, 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.

Expected progression of disease should not be considered or reported as an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked progression (ie the treatment-invoked signs/symptoms of such progression) should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Death that is attributed by the investigator explicitly to progression of disease should not be considered nor reported as an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked death due to progression should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Section 10.4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form).

Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure, should be documented on the appropriate eCRF forms (eg, the Clinical Progression form).

10.4.5. 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 in the Contact Information page(s), which will be provided as a separate document.

10.4.6. 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.

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 8.4.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.5. Appendix 5: ECOG Performance Status Scale

Grade	ECOG Performance Status Grade
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.

10.6. Appendix 6: ECOG/Karnofsky/Lansky Performance Scales

The Karnofsky Scale is designed for those aged 16 years and older. The Lansky Scale is designed for those less than 16 years of age.

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

The Karnofsky (Karnofsky 1948) and Lansky (Lansky 1987) Performance Scales with adaptation by the National Marrow Donor Program® and The Medical College of Wisconsin.

Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Evaluation of chemotherapeutic agents. Edited by MacLeod CM. New York: Columbia University Press; 1949:191-205.

Source: Lansky et. al: Toward the Development of a Play Performance (PPSC), Cancer; 56: 1837-1840.

10.7. Appendix 7: Cockcroft-Gault (Adults) and CKiD Schwartz (Children [≥6 to <12 years] and Adolescents [≥12 to <18 years]) Formulas for Estimated Creatinine Clearance

Cockcroft-Gault Formula for Estimated Creatinine Clearance for Adults

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

OR

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

Where Constant = 1.23 for men and 1.04 for women

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

CKiD[a] Schwartz Formula for Estimated Creatinine Clearance for Children (≥6 to <12 years) and Adolescents (≥12 to <18 years)

GFR (ml/min per 1.73 m(2)) =39.1[height (m)/Scr (mg/dl)](0.516) x [1.8/cystatin C (mg/L)](0.294)[30/BUN (mg/dl)](0.169)[1.099](male)[height (m)/1.4](0.188)

Reference: Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629-637.

[a]CKiD=Chronic Kidney Disease in Children

10.8. Appendix 8: 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.

Reference: 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.

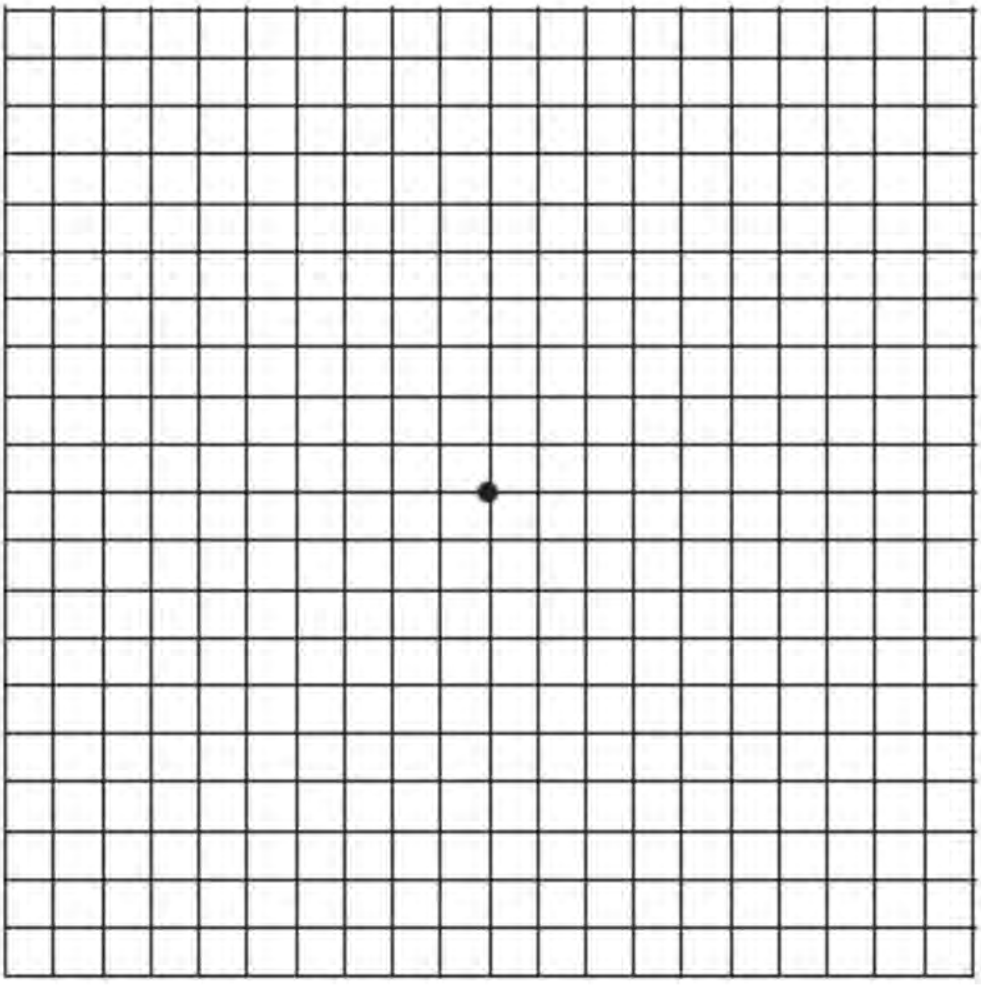
10.9. Appendix 9: Amsler Grid

Study Number: _____

Subject ID: _____

Date: _____

Examiner: _____



10.10. Appendix 10: 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	Conivaptan
Saquinavir	Boceprevir
Telaprevir	Clarithromycin
Telithromycin	Erythromycin
Voriconazole	Troleandomycin
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	Atacigual
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.

10.11. Appendix 11: 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.

10.12. Appendix 12: 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 and for molecular eligibility screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent.

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 (NCCN). 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 European Society for Medical Oncology 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.

10.13. Appendix 13: Long-term Extension Phase

The purpose of the long-term extension (LTE) phase is to provide continued study drug to subjects, while minimizing data collection burden; only data of serious adverse events will be collected in the company safety repository. Subjects in the Treatment Phase who are continuing to derive benefit from study drug, as determined by their investigator, may have continued access to study drug in the LTE Phase of this study (see Section 6.7). As an alternative to entering the LTE Phase, subjects may exit the study and continue to receive treatment on a post-trial access program, when permitted by local regulations.

For adult subjects, the LTE Phase begins with the approval of Amendment 6. For pediatric subjects, the LTE Phase begins when the most recently enrolled pediatric subject still participating in the study has 6 months of follow up or the last follow-up visit of the last pediatric subject, whichever occurs first. Upon initiation of the LTE Phase, participation in the Follow-Up Phase will end and study data collection will conclude in the clinical database. During this LTE Phase, only serious adverse events will be reported to the company safety repository, which will be conducted as specified in Section 8.4 using the appropriate serious adverse event reporting method. No analyses other than routine periodic safety review encompassing reported serious adverse events are planned for the LTE.

Study Treatment Administration

Erdafitinib may continue to be administered as described in Sections 6.1 and 6.7 of the protocol.

Prohibitions and Restrictions

Refer to protocol Section 6.5.

Study Procedures for the Long-term Extension

All subjects continuing in the LTE Phase will follow the Schedule of Activities provided in Table 17. Clinical assessments will be conducted according to the standard of practice. Serious adverse events will be reported to the company safety repository as specified in Table 17. Specific safety assessments may be performed if required by local Health Authorities.

Discontinuation Criteria for the Long-term Extension

Subjects continue on study drug as defined in Section 6.7.

The assessments and timing are specified in the Schedule of Activities provided in Table 17.

Case Report Form Completion

No data will be collected in the eCRF during the LTE Phase. However, documentation of assessments performed should be done in the subject file/source notes.

Table 17: Schedule of Activities (Long-term Extension Phase)

Procedures	Continuing to Receive Erdafitinib
Informed Consent	
	Subjects must sign the updated informed consent prior to entering LTE Phase.
Study Drug Dispensing	
Erdafitinib	Continuous. See Sections 6.1 (Study Drug Administered) and 6.7 (Study Drug after the End of Study) of the protocol.
Study drug accountability	Drug accountability will be done.
Safety	
Hematology and chemistry	Assessments for erdafitinib as per local prescribing information. (If erdafitinib is not approved in a country, the Erdafitinib Investigator's Brochure will be utilized.) In addition, as clinically indicated.
Other safety assessments	Assessments for erdafitinib as per local prescribing information. (If erdafitinib is not approved in a country, the Erdafitinib Investigator's Brochure will be utilized.) In addition, safety assessments as clinically indicated. Only serious adverse events will be reported to the company safety repository; see Section 8.4.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) of protocol. Pregnancy reporting should continue as described in Section 8.4.5 (Pregnancy). No other safety data are collected.
Efficacy	
	Per local practice. No data is collected.

AE=adverse events; LTE=long-term extension.

10.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (10 November 2022)

Overall Rationale for the Amendment: The end of study for each cohort is defined as approximately 12 months from enrollment of the last subject into the respective cohort or the last follow-up visit of the last subject in the respective cohort, whichever occurs first. The end of study for each cohort is also considered the "end of study data collection timepoint" for the respective cohort. The amendment also modifies data collection during continued treatment with erdafitinib (ie, after the end of study data collection timepoint for a cohort is reached).

The changes made to Clinical Protocol 42756493CAN2002 as part of Protocol Amendment 5 are listed below, including the rationale for each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.14 Appendix 14: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall Design, Intervention Groups and Duration; 1.3 Schedule of Activities: For Adults (≥18 years of age); 4.1 Overall Design; 4.3 Justification for Dose, Adult Dose Justification; 5.5.End of Study Definition; 6.1 Study Drug Administered; 6.7 Study Drug After the End of Study; 8.1.2 Treatment Phase; 8.1.3 End-of-Treatment Visit; 8.1.4 Follow-Up Phase; 9.4.3.2 Final Analysis; 10.3.1 Regulatory and Ethical Considerations	The end of study for each cohort is defined as approximately 12 months from enrollment of the last subject into the respective cohort or the last follow-up visit of the last subject in the respective cohort, whichever occurs first. The end of study for each cohort is also considered the "end of study data collection timepoint" for the respective cohort. The end of study is defined as the end of study data collection timepoint for the last open cohort. Section 5.5 was divided in subsections: 5.5.1, End of Study Definition Per Cohort, and 5.5.2 End of Study Definition – Overall Study. In the applicable sections, it was clarified that the subject follow-up and data collection will end once the end of study data collection timepoint has been achieved for a cohort. Subjects who continue to derive benefit from study treatment will be allowed to receive study treatment and only serious adverse events will be monitored and stored in the company safety repository.	To revise the end of study definition for each cohort and the overall study, and to modify data collection during continued treatment with erdafitinib after the study data collection timepoint. To clarify monitoring of adverse events for subjects continuing study treatment.
1.3 Schedule of Activities: For Adults (≥18 years of age);	Erdafitinib administration was indicated for the end of treatment visit and Footnote 'a' in Section 1.3 and Footnote 'b' in Section 1.4 were modified to include the end of study data collection.	To indicate treatment administration at the end-of-treatment visit for subjects who

Section Number and Name	Description of Change	Brief Rationale
1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)		continue to benefit from study treatment.
1.1 Synopsis (Evaluations); 1.3 Schedule of Activities: For Adults (≥18 years of age); 3 Objectives and Endpoints; 4.1 Overall Design; 8.6 Biomarkers; 9.4.5 Biomarker Analyses	Modified the exploratory biomarker objective and related text. Added that the evaluation of paired biopsies will be removed from Amendment 5.	To reflect analysis deemed meaningful for the study. As the study continued, it became apparent that some of the sample collections were not feasible.
1.3 Schedule of Activities: For Adults (≥18 years of age)	For adult subjects remaining on treatment, PRO assessments were discontinued at Cycle 49.	The PRO measures are reflective of efficacy and the primary analysis is complete for adult subjects.
1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age)	Clarified that there will be separate FACT-Br caregiver versions for child/adolescent and parent of the child/adolescent.	To provide clarity to the site.
1.3 Schedule of Activities: For Adults (≥18 years of age	During the Follow-up Phase, the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC-QLQ-C30) and the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) are conducted for the first 3 visits or until the start of subsequent therapy.	Provided additional guidance for the timing of patient reported outcome (PRO) assessments.
10.12 Appendix 12: Study Conduct After End of Study Data Collection for Each Cohort	Deleted the appendix on continuation of treatment after clinical cutoff for each cohort. Succeeding appendices were re-numbered.	To avoid repetitive information.
Throughout the protocol	Minor formatting changes were made.	Minor errors were noted.

Amendment 4 (29 August 2022)

Overall Rationale for the Amendment: The overall rationale for this amendment is to remove central molecular screening for all subjects, to add new safety assessments and palatability testing for pediatric subjects, and to decrease the frequency of efficacy assessments for pediatric subjects. The end of study definition has also been revised and minor clarifications have been made throughout the protocol.

The changes made to the clinical protocol 42756493CAN2002 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.14 Appendix 15: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Overall Design; 1.2 Schema; 8.1.1.1 Molecular Eligibility Screening Period; Figure 6	Central molecular testing will no longer be used and only local reports will be used for molecular screening.	Review of enrollment to date has shown that the majority of enrolled subjects were deemed molecularly eligible based on local reports. Therefore, central molecular testing is being removed.
1.4 Schedule of Activities for Children and Adolescents (≥6 to <18 Years of Age); 8.3.1 History and Physical Examinations; 8.3.1.1, History and Physical Examinations for Children and Adolescent Subjects; 8.3.2 Vital Signs; 8.3.7 Bone-related Assessments (Children and Adolescents); 8.4.7 Adverse Events of Special Interest; 10.4.3 Special Reporting Situations; 11 References	Additional Safety Assessments were added. In Sections 8.4.7 and 10.4.3, the Adverse Event of Special Interest for children and adolescent subjects was revised to include slipped capital femoral epiphysis (SCFE) and fractures, ie, now termed "Growth disorders (including accelerated bone growth and SCFE) and fractures". Expedited reporting was revised accordingly, ie, growth disorder-related and fracture-related adverse events of Grade 3 or higher severity in children and adolescents, regardless of seriousness, will be reported to the sponsor within 24 hours. Added new Section 8.3.1.1, History and Physical Examinations for Children and Adolescent Subjects. Information regarding Tanner Staging previously in Section 8.3.1 relocated to this new section. Also, in Section 8.3.1, the text clarifies that a full medical history will be conducted for adults.	Hip examinations and assessment for risk factors of musculoskeletal conditions were added to ensure identification of pre-existing conditions and potential risks, given the potential risk for bone growth abnormalities with erdafitinib treatment. The name of the Adverse Event of Special Interest was revised to reflect recent safety information. Clarification added for the medical history section for adults.
1.4 Schedule of Activities for Children and Adolescents (≥6 to <18 Years of Age); 3. Objectives and Endpoints; 8.1.2 Treatment Phase; 9.4.8, Other Analyses (new); 10.14, Appendix 14, Pediatric Cohort Medicine Palatability Testing; 10.15, Appendix 15, Protocol Amendment History	The palatability assessment was added to the schedule of activities, and the other noted sections. Acceptability and palatability were added to Section 3.	Palatability testing was added to assess a newly added exploratory objective. Acceptability and palatability added as exploratory objectives to evaluate subject compliance with the study drug tablet in the Pediatric Cohort in order to ensure compliance with the Pediatric Investigational Plan commitment.
1.4 Schedule of Activities for Children and Adolescents (≥6 to <18 Years of Age);	For pediatric subjects, radiological assessments were reduced to every 12 weeks. In Section 8.2, it was clarified that the first sentence pertains to adults.	Frequency of efficacy assessments was decreased for pediatric subjects to reduce the burden of assessments.

Section Number and Name	Description of Change	Brief Rationale
8.2 Efficacy Assessments; 8.5 Pharmacokinetics	In the Schedule of Activities for Children and Adolescents, some pharmacokinetic (PK) and biomarker information was aligned with the body of the protocol.	Description of the PK and Biomarker assessments in the Schedules of Activities was adjusted to align with the text in the body of the protocol.
Table 1: Frequency of FGFR Mutations and Fusions in Advanced Cancer	Updated mutation data was provided.	Updated information based on last database access.
3. Objectives and Endpoints	Changes were made to the first Exploratory Endpoint of the Exploratory Cohort.	Details have been added to the protocol to specify the endpoints in the Exploratory Cohort.
5.1 Inclusion Criterion Number 6	Text was added to specify that the criterion does not apply to treatment naïve pediatric subjects with no standard of care therapies.	The change was made for clarification.
5.1 Inclusion Criterion Number 8	The cutoffs for the Lansky Score and the Karnofsky Score were adjusted.	Lansky/Karnofsky ≥70 is consistent with Eastern Cooperative Oncology Group (ECOG) 0-1 (Appendix 10.6)
5.5 End of Study Definition	The end of study was defined as 1 year from enrollment of the last subject into the study or the last follow-up visit of the last subject, whichever occurs first	The end of study definition was revised to align with compound development plans.
6.7 Study Drug After the End of the Study; 10.3.1 Regulatory and Ethical Considerations	Additional information regarding the continuation of treatment after the study was provided.	Clarified the continuation of treatment after the study.
1.4 Schedule of Activities for Children and Adolescents (≥6 to <18 Years of Age)	During the Follow-up Phase, the Pediatric Functional Assessment of Cancer Therapy - Brain (Peds FACT-Br) and European Quality of Life - 5 Dimensions-5 Levels (EQ-5D-5L) are conducted for the first 3 visits or until the start of subsequent therapy.	Provided additional guidance for the timing of patient reported outcome (PRO) assessments.
8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	"Immediately" was added to the instruction regarding reporting of serious adverse events, ie, reported immediately but no later than 24 hours of their knowledge of the event.	Updated with new protocol template wording.
6.6.1.5 Guidelines for the Management of Eye Toxicity Associated with Vision Changes	Text was adjusted to specify the reporting process for a new retinal abnormality.	Text was corrected as described in the Protocol Clarification Letter, issued 10 Sept 2021.
Table 15: Guidelines for Management of Eye Toxicity	Visual acuity values were added to the definition of Grade 2, Grade 3, and Grade 4 eye toxicity.	For clarity, added visual acuity values to the definition of grades for eye toxicity.

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Number of Subjects; 9.2 Sample Size Determination; 9.4.3.1 Primary Analysis	The timing of the primary analysis was clarified. "Approximately" was added to the planned number of subjects in the Broad Panel Cohort and the Exploratory Cohort, ie, approximately 240 subjects and approximately 40 subjects, respectively. In Section 9.2, additional information was provided regarding the response-evaluable subjects and the enrollment of adolescent subjects in the Broad Panel Cohort.	Clarification was added regarding the timing of the primary analysis. Clarification was added regarding the number of subjects enrolled in the study (and the response-evaluable subjects in the Broad Panel Cohort), as well as adolescent subjects enrolled in the Broad Panel Cohort.
9.5 Interim Analyses	By the discussion of interim Bayesian population PK and noncompartmental analysis of plasma concentration-time data of erdafitinib and markers of pharmacological activities after the enrollment of 5 children or adolescent subjects, added that further interim analyses may be conducted after the enrollment of additional subjects.	Provided clarification regarding the interim analysis for the Pediatric Cohort.
10.3.4 Data Protection	Aligned section with template text.	Aligned with protocol template
5.2 Exclusion Criteria	The criterion number for modified Exclusion Criterion 3 was moved to top of the criterion.	Corrected number of criterion text.
2.2.1 Erdafitinib	The National Cancer Institute and Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice (NCI-COG Pediatric MATCH), the erdafitinib substudy, text was updated based on recent information.	Updated study information.
Throughout the protocol	Minor updates or grammatical, formatting, abbreviation, or spelling changes were made.	Minor errors were noted and minor clarifications were needed.

Amendment 3 (12 August 2021)

Overall Rationale for the Amendment: To add a Pediatric Cohort (≥6 to <18 years of age) for children and adolescents with locally advanced or metastatic solid tumors harboring FGFR alterations who have either progressed following prior therapies and who have no acceptable standard therapies, or who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. This cohort also includes children and adolescent subjects who are enrolled in the Broad Panel Cohort.

The dosing and titration schedule was amended to include dosing instructions for subjects ≥6 to <12 years of age (added due to addition of this age group within the protocol) and to amend the titration schedule for subjects ≥12 to <15 years of age in order to align with PK-PD simulation and modelling. Based on the PK and PD model, a 2-week dosing interval was selected as it allows PK and PD to reach steady-state and leads to satisfactory efficacy and safety proportions.

Section number and Name	Description of Change	Brief Rationale
Synopsis (Objectives, Overall Design, Number of Subjects,	Addition of a Pediatric Cohort (≥6 to <18 years of age) to include 20 children and	To extend the lower age limit of subjects included

Section number and Name	Description of Change	Brief Rationale
Intervention Groups and Duration, Statistical Methods), 1.2 Schema, 1.4 Schedule of Activities, 2.2.3 Fibroblast Growth Factor Receptor Alterations in Solid Tumors, 3 Objectives and Endpoints, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 4.3 Justification for Dose, 5.1 Inclusion criteria, 6.1 Study Drug Administered, 6.6 Dose Modifications, 8.5 Pharmacokinetics, 9.2 Sample Size Determination, 9.3.4 Pediatric Cohort, 9.4.3.1 Primary Analysis, 9.4.4 Pharmacokinetic and Pharmacodynamic Analyses.	adolescent subjects who have progressed following prior therapies and who have no acceptable standard therapies, and approximately 6 additional children and adolescent subjects who have a newly-diagnosed solid tumor and who have no acceptable standard therapies. Clarification that adolescent subjects enrolled in the Broad Panel Cohort will be analyzed as part the Broad Panel Cohort and the Pediatric Cohort. Other sections were revised to add specific aspects of the Pediatric Cohort. In Section 2.2.3, Justification for inclusion of Pediatric Cohort was added. In the synopsis and Section 3, the objective for the Pediatric Cohort was added. To the listed dosing sections, added dosing information for subjects ≥6 to <12 years of age. To the synopsis and Sections 4.1 and 9.3.4, added endpoints for the Pediatric Cohort, and clarified that subjects in the Pediatric Cohort will be analyzed as part of the Broad Panel Cohort and Pediatric Cohort. Statistical analyses for Pediatric Cohort added to Section 9. Pharmacokinetic sampling instructions added to Section 8.5 for subjects ≥6 to <12 years of age.	in the study from ≥12 to ≥6 years, and to include a broader range of FGFR alterations to ensure that an adequate selection of pediatric subjects will be treated with erdafitinib.
Synopsis Intervention Groups and Duration, 1.2 Schema, 1.4 Schedule of Activities, 4.1 Overall Design, 4.3 Justification for Dose, 6.1 Study Drug Administered, 6.6, Dose Modifications, 8.5 Pharmacokinetics.	Change to dose titration schedule for ≥12 to <15 years of age, with first possible up- titration at Cycle 1 Day 14 (previously Cycle 1 Day 7) and second possible up-titration at Cycle 2 Day 7 (previously Cycle 1 Day 14). Pharmacokinetic sampling frequency amended from Cycle 1 Day 7 and Cycle 1 Day 14, to Cycle 1 Day 14 and Cycle 2 Day 14.	Based on PK-PD modeling, a 2-week dosing interval was selected for subjects ≥12 to <15 years of age. This interval allows PK and PD to reach steady-state and leads to satisfactory efficacy and safety proportions.
1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age), 4.2.3 Patient-reported Outcomes Research, 8.7 Patient-reported Outcomes	Addition of Pediatric Functional Assessment Of Cancer Therapy – Brain (Peds FACT-Br) for use in subjects <18 years of age.	To be used for subjects <18 years of age as EORTC-QLQ-C30 is not validated for pediatric use.
Synopsis Objectives and Statistical Methods, 3 Objectives And Endpoints, 9.4.2 Secondary Efficacy Endpoints, 9.4.3.1 Primary Analysis.	Addition of clinical benefit rate (CBR) as a measure of efficacy.	Clinical benefit rate is a clinically-relevant measure of efficacy in this study.
Synopsis Statistical Methods, 4.1 Overall Design, 9.3.3 Cholangiocarcinoma Expansion Cohort	Clarification that Cholangiocarcinoma Expansion Cohort will be evaluated separately from the Broad Panel Cohort.	Amended for clarity.
Synopsis Overall Design, 6.7 Study Drug After the End of the Study,	Language added relating to post-trial access to study treatment.	To clarify that the sponsor will ensure subjects who

Section number and Name	Description of Change	Brief Rationale
10.3.1. Regulatory and Ethical Considerations, 10.12. Appendix 12: Continuation of Treatment After Clinical Cutoff for the Final Analysis.		are benefiting from study treatment will have continued access to study drug.
1.3 Schedule of Activities: For Adults (≥18 Years of Age), 1.4 Schedule of Activities: For Children and Adolescents (≥6 to <18 Years of Age).	Addition that history of seizure activity should be included within the neurological examination and detailing relevant subjects for this assessment. Addition that for Radiological assessment and/or skin photography, as applicable, after Week 48, the next radiological assessment will be performed at Week 60.	Clarification regarding neurological exam and timing of assessments.
5.2 Exclusion criteria, 10.11 Appendix 11 List of Target Fibroblast Growth Factor Receptor (FGFR) Mutations	List of eligible FGFR mutations to be included was revised. Update to exclusion criteria for NSCLC and colorectal subjects.	Change to eligibility criteria of the study based on predicted likelihood for pathogenicity.
2.3 Benefit-Risk Assessment	Addition of text relating to subjects <6 years of age	These subjects will not be included in the study as an age-appropriate formulation is not yet available.
4.1 Overall Design, 8.1.1.1 Molecular Eligibility Screening Period, 9.2 Sample Size Determination, 9.5 Interim Analyses	Clarification regarding sample size cap for each tumor histology.	Additional detail included regarding tumor histology cap.
2.2.1 Erdafitinib	Summary of subprotocol of the NCI-COG-sponsored Pediatric MATCH Trial APEC1621B added.	To add details of this pediatric study of erdafitinib.
6.1 Study Drug Administered	Guidance for subjects with CYP2C9 *3/*3 genotype added.	To provide guidance for subjects with CYP2C9 *3/*3 genotype
6.5.3 Precautions for Concomitant Medications	Updated precautions to specify that moderate CYP2C9 (strength previously not stated) inhibitors should be used with caution. Guidance for use with CYP3A4 substrates and OCT2 substrates added.	Aligned with updates to Investigator's Brochure Edition 10.
6.1 Study Drug Administered	Presentation of information for adolescents and adults updated to group information for each age category and flow-chart added to illustrate titration schedule.	Amended for clarity.
8.4.7 Adverse Events of Special Interest, 10.4.3 Special Reporting Situations	Corneal or retinal abnormalities were removed as adverse events of special interest.	Corneal or retinal abnormalities are no longer considered adverse events of special interest but should continue to be reported as adverse events or as serious adverse events if the severity is Grade 3 or higher.
6.6.1.1 Guidelines for the Management of Elevated Phosphate Levels	Pediatric dosing guidance added for sevelamer.	Dosing guidance for pediatric subjects added in line with addition of Pediatric Cohort.
8.7 Tumor Markers	New section added.	To ensure capture of data

Section number and Name	Description of Change	Brief Rationale
		relating to tumor markers were collected as part of routine care.
6.5.1 Permitted Medications	Text added relating to coronavirus disease 2019 (COVID-19) vaccination.	Guidance added relating to COVID-19 vaccination.
6.5.3 Precautions for Concomitant Medications	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.	Text added in line with updated Investigator's Brochure Edition 10.
9.4.3.1 Primary Analysis	Clarification that the primary analysis will be conducted 6 months after enrollment of 200 response-evaluable subjects have been treated.	Previously described as 240 subjects.
6.6.1.2 Guidelines for the Management of Dry Mouth and Mucositis, 6.6.1.3 Guidelines for the Management of Dry Skin and Skin Toxicity, 6.6.1.4 Guidelines for the Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia), 6.6.1.5 Guidelines for the Management of Eye Toxicity Associated With Vision Changes	Minor edits were added throughout these tables.	Harmonization of presentation of toxicity management guidance across the development program.
4.2.5 Participant Input Into Design	Explanation of how the results of the study may be made available to participants.	To comply with an update to the company template.
8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, 10.2. Appendix 2: Clinical Laboratory Tests	Definition of potential Hy's Law case added.	Per update to company protocol template.
10.3.1 Regulatory and Ethical Considerations	Addition of text relating to protocol clarification communications	Per update to company protocol template.
10.4.2 Severity Criteria	Alignment of text with most recent company protocol template.	Per update to company protocol template.
10.4.4 Procedures	Clarification of text regarding disease progression.	Per update to company protocol template.
10.13 Appendix 13: Guidance on Study Conduct During a National Disaster for Enrolled Subjects	Guidance relating to administration of non-live vaccines added.	Per update to company protocol template.
Title page	Addition of IND number.	Per company template.
5.2 Exclusion criteria	Timeframe for exclusion based on prior therapy amended to <5 half-lives of the agent.	Correction of typographical error.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. "He" or "she" were replaced by "the subject".	Minor errors were noted. To adhere to the current company standards for gender inclusivity.

Amendment 2 (19 Aug 2020)

Overall Rationale for the Amendment: Revised inclusion and exclusion criteria based on new insights related to eligibility; expanded enrollment for subjects with cholangiocarcinoma histology.

Section Number and Name	Description of Change	Brief Rationale
Synopsis; 1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents; 5.1. Inclusion Criteria (Number 2.2); 8.1.1.1. Molecular Eligibility Screening Period	Updated the list of local molecular testing methods to include direct digital counting methods and the Qiagen *therascreen*® FGFR RT-PCR test Specified FGFR gene fusions must have an intact FGFR kinase domain as follows (formerly included exon 16, 17 or 18): • **FGFR fusion with a 3-prime partner (FGFR gene is listed first, eg FGFR-GENE or FGFR3-TACC3); FGFR portion of fusion must involve exon ≥17** • **FGFR fusion with a 5-prime partner (Partner gene is listed first and FGFR gene is second, eg GENE-FGFR or KLK2-FGFR2); FGFR portion of fusion must involve exon ≤11** • **Named FGFR fusion partner gene (self-fusions or rearrangements, eg FGFR-FGFR, are not eligible)** The gene identifiers table was updated for correctness and clarity. Other FGFR mutations for enrollment in the Exploratory Cohort were further defined **as protein-coding single nucleotide variant (SNV) and insertions or deletions (indels)**:	To provide updates and clarify molecular eligibility methods and criteria; update FGFR gene identifiers and canonical transcript identifiers
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents; 8.1.1.1. Molecular Eligibility Screening Period; Figure 3	The following was added: Biopsy of the brain, lung/mediastinum, pancreas, or for endoscopic procedures extending beyond the esophagus, stomach, or bowel is not permitted; please contact Sponsor prior to conducting biopsy.	To restrict biopsy of the brain, lung/mediastinum, pancreas, or for endoscopic procedures extending beyond the esophagus, stomach, or bowel
5.2. Exclusion Criteria (Number 2.1)	The following was added: 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.	To define "known" FGFR gatekeeper/resistance alterations
5.2. Exclusion Criteria (Number 3.2)	Updated as follows: For NSCLC subjects only – pathogenic somatic mutations in EGFR* or BRAF	To clarify NSCLC molecular screening methods and update exclusionary mutations and gene fusions

Section Number and Name	Description of Change	Brief Rationale
	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	
5.1 Inclusion Criteria (Number 2.2)	Deleted note that central screening for breast cancer is limited to women with hormone-sensitive (ie, estrogen positive [ER]/progesterone positive [PR]) breast cancer.	Not applicable for study eligibility; selective tumor histologies for central screening is fully described in other sections of the protocol
5.1. Inclusion Criteria (Number 4.1)	Updated inclusion criterion to include advanced and unresectable settings	To align with 5.1 Inclusion Criteria (Number 2.1)
5.1. Inclusion Criteria (Number 9.2)	Deleted the following: /1.73m^2 either directly measured via 24 hour urine collection or	Minor revision
5.2. Exclusion Criteria (Number 1.1)	Updated the washout for prior chemotherapy, targeted therapy, or treatment with an investigational anticancer agent to: within **15 days** (previously 30 days) or ≥5 half-lives (whichever was longer) **and up to a maximum of 30 days**; added restriction for prior **monoclonal antibody** within 30 days	A shorter minimum washout period may be sufficient for some prior therapies (ie, shorter than 30 days). Monoclonal antibody therapy washout was previously inadvertently omitted.
5.2. Exclusion Criteria (Number 4.1)	Updated to exclude all urothelial carcinoma (previously specified transitional cell carcinoma of the urothelium).	To align with indication statement
5.2. Exclusion Criteria (Number 8.1)	Clarified that prior **selective** FGFR inhibitor treatment is not permitted	To specify only selective FGFR inhibitors are exclusionary
5.2. Exclusion Criteria (Number 11.2)	Revised exclusion for heart failure to Class III-IV (previously Class III-V)	Minor revision
5.2. Exclusion Criteria (Number 13.2)	Updated to allow enrollment of subjects with **inactive** hepatitis B with a positive HBsAg antibody **or normal PCR**	To allow subjects with inactive hepatitis to be eligible for study participation
5.2. Exclusion Criteria (Number 17.1)	Clarified to specify that palliative radiation **to the target lesion** within 2 weeks before the first dose of erdafitinib was not permitted.	To clarify palliative radiation was restricted for only the target lesion
Synopsis; Figure 1; 3.1. Cholangiocarcinoma Expansion Cohort; 4.1 Overall Design; Figure 2; 4.2.1 Cohort Design; 9.2 Sample Size Determination; 9.3.3 Cholangiocarcinoma Expansion Cohort	Added a Cholangiocarcinoma Expansion Cohort and removed text specifying further enrollment "up to 60 subjects per each tumor histology"	To allow expanded enrollment of subjects with cholangiocarcinoma in a separate cohort
2.2.3. Fibroblast Growth Factor Receptor Alterations in Solid Tumors, Table 1	Updated to add central testing for salivary gland tumors, colorectal cancer, and thymic cancer/thymoma; specify **high-grade gliomas (eg, glioblastoma)** and **low-grade** gliomas	To allow central molecular testing for subjects with salivary gland tumors, colorectal cancer, and thymic cancer/thymoma; to clarify low- and high-grade

Section Number and Name	Description of Change	Brief Rationale
	Predominant alteration types column is added to Table 1.	gliomas; to add alteration types information
2.2.3. Fibroblast Growth Factor Receptor Alterations, Pediatric Solid Tumors	Updated references	Minor revision
4.1. Overall Design; Figure 3	Central molecular screening updated to add salivary gland tumors, colorectal, and thymic cancer/thymoma; to specify **high-grade gliomas (eg, glioblastoma)**, **low-grade** gliomas; and **squamous** NSCLC; to specify **hormone-sensitive** breast cancer **(estrogen positive [ER]/progesterone positive [PR])** The following text is also added: Central screening for any tumor type will be allowed for pediatric subjects or if a local report is deemed insufficient. Added that central molecular testing should be performed for subjects who can be eligible for study participation within 6 months of testing.	To allow central molecular testing for subjects with salivary gland tumors, colorectal cancer and thymic cancer/thymoma, to clarify low- and high-grade gliomas; to specify squamous NSCLC and hormone-sensitive breast cancer; to allow central molecular testing for any tumor type in pediatric subjects and subjects with an insufficient local report; To limit central testing to patients who can participate
6.5.1. Permitted Medications; 6.5.2. Prohibited Medications	Updated to allow ongoing adjunct hormonal therapy in subjects with breast cancer or prostate cancer who progressed while receiving the hormonal therapy and had been receiving the therapy for at least 6 months	To allow ongoing, long-term adjunctive hormonal therapy for subjects with breast cancer or prostate cancer
6.5.3. Precautions for Concomitant Medications; 10.10	Updated fluconazole as a moderate CYP2C9 inhibitor (previously considered a strong inhibitor); updated to state that caution should be used with moderate CYP3A inducers. Added the following: 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	To align with updated FDA classification of inhibitors or inducers of CYP2C9 and CYP3A
8.2. Efficacy Assessments; 8.2.2 Continuation of Treatment	Updated the investigator assessment of suspected progression to include IRC confirmation; removed the requirement for treatment discontinuation if the repeat imaging meets the threshold of progressive disease.	To allow consideration of IRC assessment prior to treatment discontinuation and remove the requirement for discontinuation if repeat imaging meets threshold of progressive disease
8.2.1.1. RECIST and RANO Assessment of Disease; References	Updated RANO references (Wen 2010 and van den Bent 2011), including assessment criteria for both low- and high-grade gliomas	To provide assessment reference for low- and high-grade gliomas

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents; 8.2. Efficacy Assessments; 8.2.1.2. Radiographic Assessment	Added skin lesion photography as an efficacy assessment as applicable	To allow for photography assessments when radiological assessment is not feasible
Synopsis; 1.4. Schedule of Activities for Adolescents; 3. Objectives; 8.5. Pharmacokinetics; 9.4.4. Pharmacokinetic and Pharmacodynamic Analyses	Added serial PK samples for adolescents on Cycle 3, Day 1 and Cycle 4 Day 1; deleted samples on Cycle 2, Day 1 Moved protein binding sample to Cycle 3, Day 1 (previously Cycle 2, Day 1) Updated the PK endpoints to indicate both adults and pediatric subjects; removed population PK analysis from the secondary endpoint	To fully characterize the PK profile in adolescents To align with PK sampling To remove a secondary endpoint linked to an optional analysis (population PK)
1.3. Schedule of Activities	Changed fresh tumor biopsy assessment to read as **optional** (previously 'where clinically feasible'); specified sampling at the time of disease progression (previously end of treatment)	To clarify that fresh tumor biopsy is optional and timepoint for sampling
Figure 2	Added a footnote that the Exploratory Cohort is closed for enrollment	To indicate that the Exploratory Cohort enrollment is completed
4.2.4. Study-Specific Ethical Design Considerations	Updated total blood volume collected for adolescents on Cycle 1 Day 1 visit	To indicate that collection exceeds the maximum 30 mL on Cycle 1 Day 1
4.3. Justification for Dose	Updated for flow and to strengthen justification for adult dosing	Updated for flow and to strengthen justification for adult dosing
5.3. Lifestyle Considerations	The following was added: Male and female subjects should be advised on sperm banking and egg preservation, respectively, prior to entering the study, if appropriate.	To address a request from a regulatory authority in the clinical program
6.5.1. Permitted Medications	Added that surgery or biopsy of target lesions is not permitted	To prohibit surgery or biopsy of target lesions
6.1. Study Drug Administered, Up-titration Guidelines; 6.6.1.1 Guidelines for the Management of Elevated Phosphate Levels, Table 5 and Table 6	Values for grading of hyperphosphatemia have been revised throughout the protocol to include 2 decimals, for consistency with the case report form (CRF), and instructions for rounding the second decimal point were deleted.	To ensure consistency between the protocol and CRF guidelines, harmonize rounding of phosphate values
6.6.1.2. Guidelines for the Management of Dry Mouth and Mucositis ,Table 7, Table 8, 6.6.1.3 Guidelines for the Management of Dry Skin and Skin Toxicity, Table 9; 6.6.1.4. Guidelines for the Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia), Table 11	Updated toxicity guidelines for general prophylaxis; updated guidance for management of oral mucositis and nail discoloration	To improve adherence to and consistency in management of adverse events, as oral mucositis and nail toxicity were commonly observed adverse events in the study so far, and for consistency with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines

Section Number and Name	Description of Change	Brief Rationale
6.6.1.4. Guidelines for the Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia), Table 10	Deleted "Hyperphosphatemia" from the table title .	To align with table content
8.1. Screening Phase	Added that Full-study informed consent form (ICF) and Molecular Eligibility ICF may be combined or collected at the same time	To allow sites to combine Full-study ICF and Molecular Eligibility ICF for subjects entering with local NGS results or consent on the ICFs at the same time
8.2.1.2. Radiographic Assessment (previously Radiographic Images Assessment)	Added that imaging should be performed as scheduled irrespective of study drug interruption (previously not delayed due to delays in cycle starts or extension of cycle intervals); added that the End-of-Treatment Visit should occur after discontinuation of treatment (previously disease progression)	To align with study design
8.3.2. Vital Signs	Removed the specification for methods of temperature assessment	Minor revision
8.3.3. Electrocardiograms	Clarified that ECG assessments for on-study visits are required, and are to be conducted postdose if possible	To clarify ECG assessments for on-study visits are required
8.3.5 Ophthalmologic Examination	Added that Optical Coherence Tomography (OCT) **and fluorescein angiography images** should be stored in the subject's records if performed, and to contact the sponsor when only a PDF imaging is available	To clarify ophthalmologic images storage
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents; 8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Removed the following: "or before the start of subsequent cancer therapy, whichever is longer,"	Standardization across erdafitinib (monotherapy) protocols
8.4.6. Disease-relate Events Not Qualifying as Adverse Event; Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, Procedures	Updated protocol template language replaced by existing protocol text	To align with updated company protocol template language
8.4.7 Adverse Events of Special Interest; 10.4 Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, Special Reporting Situations	Deleted special reporting of Grade 1 and Grade 2 corneal and retinal abnormalities	Unlike Grade 1 and Grade 2 corneal and retinal abnormalities, Grade 3 and higher central serous retinopathy events are potentially medically significant events and should be reported as serious adverse events
Synopsis; 4.2.3. Patient-reported Outcomes Research; 8.7. Patient-reported Outcomes; 9.4.6. Medical Resource Utilization and Patient-reported Outcomes Analyses	Text specifying hypothesis testing, treatment group comparisons, and time to events analyses were deleted	To delete nonapplicable text for PRO analyses

Section Number and Name	Description of Change	Brief Rationale
9.4.3.1. Primary Analysis; 9.4.3.2. Final Analysis; 9.5 Interim Analysis, Figure 4	Efficacy analysis plan updated for the primary analysis to be conducted 6 months after enrollment of 240 subjects; text reorganized for clarity; final analysis information added; deleted final analysis graphic from Figure 4	To clarify timing of primary analysis and plan for final analysis
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents	Added for parathyroid hormone assessments may be performed within 3 days prior to D1 of each cycle	To clarify visit window
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents	Edited the table header for Cycle 1 Day 1 to: C1:-3 days to D1	To remove reference to Day 0
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents (footnotes)	Clarified that the 30-day screening visit window starts with the first planned study procedure **other than the tissue biopsy and informed consent**	To clarify screening visit window
1.4. Schedule of Activities for Adolescents	Edited the table header for Day 7 to specify visit assessment only on Cycles 1 and 2 (+ 2 days)	To clarify Day 7 assessment cycles for adolescents
1.4. Schedule of Activities for Adolescents	Specified in header that Day 7 assessments apply to Cycle 1 and Cycle 2 only	To clarify Day 7 assessments for adolescent subjects
10.9 Appendix 9 Amsler Grid	Updated the Amsler grid	To use updated Amsler grid
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents; 8.1.1.1. Molecular Eligibility Screening Period; 10.12 Appendix 12 Guidance on Study Conduct During a National Disaster	Added National Disaster appendix (appendix is cross-referenced in a footnote to the Schedules of Activities) Added guidance for remote consent as applicable per local guidance	To provide instructions to be followed during a national disaster
1.3. Schedule of Activities for Adults; 1.4. Schedule of Activities for Adolescents (footnotes)	Added footnote to allow patient reported outcome (PRO) measures to be conducted using Interview Mode, if necessary.	To allow PRO assessment using Interview Mode
Title page and footer	Updated confidentiality information added	To update information
Throughout the protocol	Removed the numbering from the References and using only parenthetical referencing	To align with updated company protocol template
Throughout the protocol	The term “patient” was changed to “subject” as appropriate	Minor errors were noted
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (15 August 2019)

The overall reason for this amendment: To add a mutation to the list of excluded mutations and gene fusions for subjects with non-small cell lung cancer (NSCLC) and add the actual List of Target Fibroblast Growth Factor Receptor (FGFR) Mutations to the protocol as requested by the United States Food and Drug Administration (FDA).

Applicable Section(s)	Description of Change(s)
Rationale: To add BRAF V600E to the list of excluded pathogenic somatic mutations or gene fusions for subjects with NSCLC as requested by the FDA.	
5.2. Exclusion Criteria (Number 3)	The above-mentioned mutation was added to Exclusion Criterion 3 (now numbered 3.1).
Rationale: To add the actual List of Target Fibroblast FGFR Mutations as requested by the FDA.	
1.2. Schema (Figure 1 Footnote "d"); 4.1. Overall Design (Figure 2 Footnote "a"); 4.2.1. Cohort Design; 5.1. Inclusion Criteria (Number 2); 9.3.1. Broad Panel Cohort; 10.11. Appendix 11: List of Target FGFR Mutations	The location of the List of Target FGFR Mutations (required for inclusion in the Broad Panel Cohort) has been changed from the Laboratory Manual to Appendix 11 in Section 10.11; this change has been noted in the sections listed to the left (ie, under "Applicable Sections").
Figure 1 (footnote e); Figure 2 (footnote b); 4.2.1. Cohort Design; 5.1. Inclusion Criteria (Number 2)	Clarification has been added that FGFR gene fusions must have an intact FGFR kinase domain.

Rationale: Updated the instruction regarding strong CYP3A4 and CYP2C9 inhibitors for consistency with the Investigators Brochure.

6.5.3. Precautions for Concomitant Medications; 10.10. Appendix 10: Drugs Classified as . . .	In Section 6.5.3 (first bullet), the text regarding the change in erdafitinib exposure with strong CYP3A4/2C9 inhibitors was replaced with the following text: "For this reason, strong CYP3A4 and CYP2C9 inhibitors should be used with caution. Consider alternative therapies that are not strong inhibitors of CYP2C9 or CYP3A4 during treatment with erdafitinib. If co-administration of a strong inhibitor of CYP2C9 or CYP3A4 is unavailable, 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." The appendix heading was updated and strong in vivo inhibitors of CYP3A4/2C9 were added to Appendix 10.

Rationale: The Amsler Grid Tests was added at Cycle 3 Day 1 (C3D1) and is now consistent with the Adolescent Schedule of Activities.

1.3. Schedule of Activities for Adults . . .	The Amsler Grid Test was added at C3D1.

Rationale: Simplified the exclusion criterion regarding hepatitis.

5.2. Exclusion Criteria (Number 13)	Revised Exclusion Criterion 13 (now 13.1) to state: "Evidence of active hepatitis B or C infection (for example, subjects with history of hepatitis C infection but normal hepatitis C virus polymerase chain reaction test and subjects with hepatitis B with positive HBsAg antibody are allowed)." The previous text was "Known active Hepatitis B or C infection (unless polymerase chain reaction [(PCR] negative [according to local laboratory range] on all available tests for the past 6 months)."

Rationale: Added the Chronic Kidney Disease in Children (CKiD) Schwartz Formula for estimation of creatinine clearance in adolescents, as it is deemed more accurate than adult formulas.

5.1. Inclusion Criteria (Number 9c); 10.7. Appendix 7	Added the CKiD Schwartz Formula to Inclusion Criterion 9 for estimation of creatinine clearance in adolescents. The CKiD Schwartz Formula with reference was added to Appendix 7. The Appendix 7 title was revised accordingly and new subheaders were added to distinguish between the adult and adolescent formulas.

Rationale: Assessment of additional hormones that play a role in childhood growth were added to the list of clinical laboratory tests for adolescent subjects.	
1.4. Schedule of Activities: Adolescents . . .; 4.2.4. Study-specific Ethical Design Considerations; 8. Study Assessments and Procedures; 10.2. Appendix 10.2	The following clinical laboratory tests were added to the Schedule of Activities for Adolescents: thyroid stimulation hormone (TSH), total triiodothyronine (T3), and free thyroxine (T4). These tests were added at screening and Day 1 of every odd-numbered cycle, and at end of treatment (these tests were mentioned in Appendix 2 in Section 10.2 of the original protocol). Insulin-like growth factor 1 (IGF-1) was added at screening and at the time of the DEXA scan. The abbreviations for these tests were added to the abbreviation list at the end of this table. Also, IGF-1 was added to Appendix 2 in Section 10.2. The blood volume for adolescents was updated in Sections 4.2.4 and 8, ie, the blood volume was changed from approximately 280 mL to 275 mL over 6 cycles.
Rationale: The sample size calculation has been adjusted (ie, the power).	
9.2. Sample Size Determination	The sample size calculation has been adjusted as follows: The sample size of 200 response-evaluable subjects for the Broad Panel Cohort is selected based on extensive simulations with various Bayesian hierarchical model designs to achieve approximately 80% (previously 85%) power to select 80% tumor histologies (eg, ≥12 of 15 [previously 8 of 10] tumor histologies) for the final analysis if the true ORR is 35% for each tumor histology.
Rationale: Clarified the timing of some of the Patient Report Outcome (PRO) assessments, ie, the Patient Global Impression of Change (PGIC), the EORTC-QLQ-C30, and the EQ-5D-5L. In addition, the order in which the PRO assessments should be conducted was clarified.	
1.3. Schedule of Activities: For Adults . . .; 1.4. Schedule of Activities: For Adolescents . . .; 8.7. Patient Reported Outcomes	Timepoints for assessment of PGIC have been limited to Cycle 2 Day 1, and the EoT Visit. Also, in the table "NOTES" for the EORTC-QLQ-C30 and EQ-5D-5L for these schedules, it was added that these assessments may be conducted by telephone during the Follow-up Phase and that during this phase the assessment is conducted until the start of subsequent anticancer therapy. In addition, the order in which the PRO assessments should be conducted was clarified, ie, Patient Global Impression of Symptom Severity (PGIS), PGIC, EORTC-QLQ-C30, and EQ-5D-5L.

Rationale: Highlighted the need to submit tumor tissue and clarified the use of tissue samples when local FGFR testing is utilized. Additional instruction regarding molecular testing was provided in Section 8.1.1.1.	
1.3. Schedule of Activities: For Adults . . .; 1.4. Schedule of Activities: For Adolescents . . .; 8.1.1.1. Molecular Eligibility Screening Period; Figure 3	In the "Local FGFR results . . . " row of each Schedule of Activities, the section bullet was revised to state: "Tumor tissue must be submitted.* See 'Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostic Development'. Also, the last sentence was revised to state: "*If tissue is not available [this phrase was removed here 'for central confirmation'], please contact the sponsor prior to proceeding with full-study screening." Small edits were made to the Adolescent Schedule of Activities so that that row is identical to the adult entry. Cross-reference to Tumor Tissue for Molecular Eligibility, Biomarker Research, and/or Companion Diagnostic Development was added to the NOTE for the row "Central Molecular Eligibility Testing from Tissue". In the Schedules of Activities, the row title "Tumor tissue for biomarker research" was lengthened by adding "for molecular eligibility…and/or companion diagnostics development". The original text was replaced with the following: "Tumor tissue must be submitted.* Samples will be used for any or all of the following purposes: molecular eligibility for study eligibility (Central Screening); biomarker research; diagnostic development; central confirmation of local FGFR testing results (if applicable). This row is newly added to Section 1.4. *If tissue is not available, please contact the sponsor prior to proceeding with full-study screening". In Section 8.1.1.1, the first sentence of Part 2a has been revised to 1) include biomarker research, 2) add (where applicable), and 3) remove timing of submission. The first sentence now states: "If a subject is enrolled based on local testing, a tissue sample must be submitted for: retrospective confirmation of FGFR[a] status (where applicable); diagnostic development; biomarker research." The remaining portion of Section "a" was added as a footnote at the bottom of the page. The first 2 changes were added to Figure 3 in this section.
Rationale: Clarified the timing of the cerebrospinal fluid (CSF) PK and plasma PK samples at the time of a routine CSF procedure.	
1.3. Schedule of Activities: For Adults . . .; 1.4. Schedule of Activities: For Adolescents . . .; 8.5. Pharmacokinetics	It was noted in the referenced sections to the left that CSF PK and plasma PK samples will be conducted during the Treatment Phase at the time of a routine CSF procedure (they were previously shown on the Schedule of activities during this timeframe, but instruction has been added in text.)
Rationale: Slightly revised the laboratory values indicative of bone marrow function in Inclusion Criterion 9 to align more closely with Inclusion Criterion 7, ie, Grade 2 absolute neutrophil count (ANC) and hemoglobin include the value 1,000/mm^3 and 8.0 g/dL, respectively, and Grade 1 platelet count includes the value 75,000/mm^3.	
5.1. Inclusion Criteria (Number 9a)	For Inclusion Criterion 9, revised the inclusion limits for these laboratory tests as follows (the ">" sign was replaced by the "≥" sign: - Absolute neutrophil count (ANC) ≥1,000/mm^3 - Platelet count ≥75,000/mm^3 - Hemoglobin ≥8.0 g/dL

Rationale: Clarified the timing of the urine or serum β-hCG pregnancy test at screening and thereafter.	
1.3. Schedule of Activities: For Adults . . .; 1.4. Schedule of Activities: For Adolescents . . .; 10.2. Appendix 2, Clinical Laboratory Tests	Clarified the timing of the pregnancy test at screening on the Schedule of Activities by adding that the test may be done at C1D1 prior to the first dose. Also, in Section 10.2, clarified that additional serum or urine pregnancy tests will be performed on Day 1 of every cycle (starting with C2D1); the information in parentheses was added.
Rationale: Clarified the meaning of "permanently sterile" in the inclusion criterion regarding contraception per the protocol template.	
5.1. Inclusion Criteria	The above clarification was added to Inclusion Criterion 12 (now 12.1), ie, "[for the purpose of this study]" was added to this criterion so that it now states: "For females of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile [for the purpose of this study]. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy):".
Rationale: Corrected wording of Exclusion Criterion 11 to remove mention of triplicate measurement, which makes this criterion now consistent with the Schedule of Activities	
5.2. Exclusion Criteria (Number 11)	Removed the mention of triplicate measurement (not required) for assessment of QTc prolongation.
Rationale: Use of the Bazett formula for assessment of QTc prolongation in adolescent subjects is allowed.	
5.2. Exclusion Criteria (Number 11); 8.3.3. Electrocardiogram; 9.4.7. Safety Analyses (Electrocardiogram)	Optional use of the Bazett formula was added for determination of QTc prolongation in adolescent subjects was added.
Rationale: Clarified when Tanner Staging is discontinued. The Tanner Staging chart was removed to simplify the protocol, as it is deemed a routine assessment.	
1.4. Schedule of Activities: For Adolescents . . .; 8.3.1. Physical Examinations; 10.11. Appendix 11, Sexual Maturity Rating . . .	Noted that Tanner Staging is discontinued when a subject turns 18 years of age. As mentioned above, the Tanner Staging chart was removed from Section 10.11.

Rationale: Minor errors, editorial issues, or changes for clarity/consistency were noted and corrected.	
1.3. Schedule of Activities: For Adults . . .; 1.4. Schedule of Activities: For Adolescents . . .; 2.2.3. Fibroblast Growth Factor . . . 6.6.1.6. Guidelines . . . ; 8.2.1.1 RECIST and RANO… 8.2.1.2. Radiographic Images Assessment; 8.2.2. Continuation of Treatment…; 8.3.7. Bone-related Assessments (Adolescents); 8.6. Biomarkers; 8.7. Patient Report Outcomes; 9.4.4. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic… 10.6. Appendix 6; 11. References	On the Schedule of Activities, added a row for the Investigator RECIST or RANO Assessment (abbreviations added to table lists), and added subheaders for "Patient Reported Outcome Assessments", and "PK and Biomarker Assessments". Added that the visit window that applies to C2 also applies to C3, by addition "C3" to the table header. On the Adult Schedule of Activities after the text "Fresh tumor biopsy . . . " added "(Paired biopsies)" as this fresh tumor biopsy is referred to as such in the body of the protocol; the biomarker section (Section 8.6) was referenced. Aligned footnote d in Section 1.3 and footnote e in Section 1.4 with scheduled timepoints in the Schedule of Activities. Requirements for radiographic assessments were clarified in Section 1.4, Section 8.2.1.2, and Section 8.3.7. Text in Section 8.2.1.1 revised to indicate that RANO criteria will be used to assess response to treatment for subjects with primary CNS tumors. Corrected the Phase 2 Study noted in Section 8.6 to JNJ42756493BLC2001 (deleted JNJ42756493EDI1001). Removed small amount of text in strike-out font in Section 6.6.1.6. In Section 8.2.2, a sentence was added noting ECOG, Karnofsky, Lansky performance score comparison chart is provided in Section 10.6. Text reordered and references added for the EORTC-QLQ-C30 in Section 8.7; citations were added to the reference list in Section 11. The heading in Section 9.4.4 was updated. Clarification added to Appendix 6 indicating the ages at which the Karnofsky and Lansky scales are used. In the reference list, added mention of CGI to Reference 17, revised access date for Reference 28, and added References 25, 31, and 34. The genomic databases were referenced in Section 2.2.3.

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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 intervention, 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: *electronic signature appended at the end of the protocol* Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD PPD	23-Feb-2023 13:22:35 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

A Phase 2 Study of Erdafitinib in Subjects with Advanced Solid Tumors and FGFR Gene Alterations

Protocol 42756493CAN2002; Phase 2

JNJ-42756493 (erdafitinib)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: 2019-002113-19

Status: Approved
Date: 08 June 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-83679, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL 42756493CAN2002 (EDMS-ERI-179740920)

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

COVID-19 APPENDIX

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 and for molecular eligibility screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-42756493 (erdafitinib) Clinical Protocol 42756493CAN2002

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 intervention, 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: _____
(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. 4
Status: Approved, Date: 08 June 2020