1 TITLE PAGE



Clinical Study Protocol

Study Protocol Number:	E7090-J081-101
Study Protocol Title:	A Phase 1 Study of E7090 in Subjects with Solid Tumor
Sponsor:	Eisai Co., Ltd.
Sponsor's Investigational Product Name:	E7090
Indication:	Solid tumor
Phase:	Phase 1
Approval Date:	V1.0 1 August 2014 V2.0 4 September 2014 V3.0 13 November 2014 V4.0 29 January 2016 V5.0 4 April 2016 V6.0 22 April 2016 V7.0 3 July 2017 V8.0 25 October 2017 V9.0 13 July 2018
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7090

Name of Active Ingredient:
5-({2-[({4-[1-(2-Hydroxyethyl)piperidin-4-yl]phenyl}carbonyl)amino]pyridin-4-yl}oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide butanedioate (2:3)

Study Protocol Title
A phase 1 study of E7090 in subjects with solid tumor

Site(s)
Study region (Country): Japan
Study sites: 1 site in Part 1, about 14 to 17 sites in Part 2 (planned)

Study Period and Phase of Development
FPI: November 2014
LPI: September 2018 (planned)
Phase 1

Objectives

Primary objective

- To investigate the tolerability and safety of E7090 in patients with solid tumors

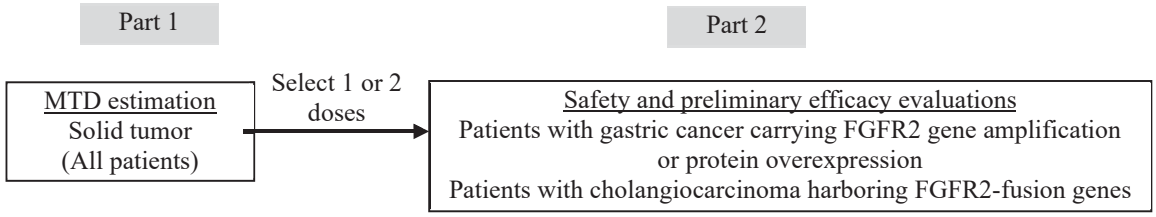
Secondary objectives

- To estimate the maximum tolerated dose (MTD) of E7090 (only in Part 1)
- To assess the pharmacokinetics (PK) of E7090
- To estimate the recommended dose for subsequent phase studies
- To preliminarily evaluate the antitumor activity of E7090

Exploratory objectives

- To investigate the pharmacodynamic (PD) markers and pharmacogenomics (PGx) of E7090
- To investigate the PK, PD markers, and PGx relationship for E7090
- To assess overall survival (OS) and progression-free survival (PFS) with E7090 treatment (only in Part 2)
- To analyze plasma and urinary metabolites of E7090

Study Design
This is a phase 1 study of E7090 in patients with solid tumors, consisting of 2 parts (Part 1 and Part 2). In Part 1, patients with solid tumors receiving E7090 will be evaluated for dose-limiting toxicities (DLTs) to estimate its MTD. Part 2 will include patients with gastric cancer carrying the FGFR2 gene amplification or FGFR2 protein overexpression and patients with cholangiocarcinoma harboring FGFR2-fusion genes among patients with solid tumors. E7090 will be administered at 1 or 2 doses selected from among the doses studied in Part 1 to evaluate its tolerability and safety in detail and its efficacy preliminarily. On the basis of the results from Part 1 and Part 2, the recommended dose for subsequent phase studies will be estimated. The dose for Part 2 will be determined through discussion among the investigator, the sponsor, the medical expert, and if necessary, the Data and Safety Monitoring Advisor.



Study Design Overview

(1) Part 1: Part 1 will include patients with solid tumors and will consist of a pretreatment period, a treatment period, and a follow-up period. The pretreatment period involves informed consent, screening test, subject registration, and baseline assessment. The treatment period consists of Cycle 0, and Cycle 1 and subsequent cycles. Cycle 0 is 7 days long, and Cycle 1 and subsequent cycles are 28 days long. In Cycle 0, subjects will take a single dose of E7090 at the dose for each dose group on Day 1 for PK evaluation. In Cycle 1 and subsequent cycles, subjects will take E7090 at the dose for each dose group once daily continuously until any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met. The follow-up period involves the early discontinuation procedures and final observation.

Method of subject's dose assignment

Dose assignment will be performed using a modified toxicity probability interval (mTPI) design. According to an established target DLT rate of 25% for this study, 3 toxicity probability intervals are defined as 20% to 30% (proper dosing), 0% to 20% (underdosing), and 30% to 100% (overdosing). In accordance with the rules of the mTPI design based on these intervals, each subject will be assigned a dose of E7090. The decision rules for all dose assignment will be calculated in advance on the basis of the mTPI design, presented as the "Decision Rules for Dose Assignment" below.

Decision Rules for Dose Assignment

		Number of subjects treated at each dose				
		2	4	6	8	10
Number of subjects with DLT	0	E	E	E	E	E
	1	D [a]	S	S	E	E
	2	D, U	D	S	S [b]	S
	3		D, U	D	S	S [b]
	4		D, U	D, U	D, U	S
	5			D, U	D, U	D, U

E = Escalate to the next higher dose, S = Stay at the current dose, D = De-escalate to the next lower dose, U = The current dose is unacceptably toxic (ie, Do not re-register any subject in this dose)
Target DLT rate and its corresponding interval, 25%, 20% to 30%; Cohort size, 2 subjects
Rules for the number of subjects per dose being above 10 are omitted.
a: Extra subjects may be added for the initial dose.
b: Early termination of registration may be considered.

Two subjects will be registered at each dose level. In a new dose group, the safety of the first subject should be evaluated before enrollment of the second and subsequent subjects. On the basis of the number of subjects with DLT at each dose level, assignment of the next dose will be determined according to the Decision Rules for Dose Assignment. If DLT develops in 1 of the 2 subjects at the initial dose level, however, extra subjects may be added through discussion

among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Any subject not evaluable for DLT (eg, a subject discontinuing the study during Cycle 1 for reasons other than the development of DLT) should be replaced at the dose level for the subject. Under the mTPI design, subject registration will be closed when the DLT rate at the initial dose is much higher than the target DLT rate (25%) or when the prespecified maximum sample size (approximately 20 subjects) is reached. However, the maximum sample size will be adjusted as required. For a particular dose, subject registration may be closed early if a subsequent subject is highly likely to be allocated to the dose. The mTPI design is described in the "Statistical Methods."

Method of determining the dose for the next dose group

The dose for the next dose group will be determined according to the degree of toxicities (adverse events possibly related to E7090) observed in subjects in the immediately preceding dose group during Cycle 0 and Cycle 1 (see the table below). The dose for the next dose group will be escalated by 100% if all toxicities observed in the immediately preceding dose group during Cycle 0 and Cycle 1 are Grade 1 or lower. If a Grade 2 toxicity is observed in 1 subject, the next dose will be escalated by 50%. If Grade 2 toxicities are observed in 2 subjects or if Grade 3 or higher toxicities are observed in 1 or more subjects, the next dose will be escalated by 33%.

When a dose is escalated or de-escalated by 1 dose level according to the mTPI design, if there is a higher or lower dose level evaluated previously, subjects will be added to the immediately preceding dose level evaluated previously, instead of following the "Method of Determining the Dose for the Next Dose Group" shown below. In addition, an intermediate dose may be added, if necessary, on the basis of the safety or PK of the previously evaluated dose. The addition of a new dose level will be determined through discussion among the investigator, the sponsor, the medical expert, and if necessary, the Data and Safety Monitoring Advisor.

Method of Determining the Dose for the Next Dose Group

Dose escalation for the next dose group (%)	Toxicities observed during Cycle 0 and Cycle 1 [(a)]
100	Grade ≤1 toxicity only
50	Grade 2 toxicity in 1 subject
33	Grade 2 toxicity in 2 subjects or Grade ≥3 toxicity in ≥1 subject

(a) Excluding clinically insignificant events such as laboratory abnormalities requiring no treatment

Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group (including changes in the assignment of a dose and the percentage of dose escalation).

(2) Part 2: Part 2 will include patients with solid tumors, consisting of the following cohorts:

Gastric cancer cohort: Patients with gastric cancer carrying an amplified FGFR2 gene or overexpressed FGFR2 protein (including patients with gastroesophageal junction cancer diagnosed as adenocarcinoma)

Cholangiocarcinoma cohort: Patients with cholangiocarcinoma harboring FGFR2-fusion genes

Part 2 will consist of a pretreatment period, a treatment period, and a follow-up period.

The pretreatment period consists of Screening 1, Screening 2, and baseline assessment. In Screening 1, each subject will be examined for FGFR genetic abnormalities in the tumor, and in Screening 2, each subject will be examined for the other eligibility criteria. Separate written informed consent will be obtained before the start of Screening 1 and Screening 2. Screening 1 will include gastric cancer patients with documented FGFR2 gene amplification and cholangiocarcinoma patients with documented FGFR2-fusion genes. In addition, Screening 1 will also include any gastric cancer patient with an unknown FGFR2 amplification status who has an archived tumor sample available for the confirmation of FGFR2 protein expression. No biopsy should be performed at Screening 1.

In Screening 1, the following will be confirmed:

- For patients with the documented genetic abnormalities mentioned above, the documents necessary for genetic testing will be submitted to the sponsor to confirm the presence of genetic abnormalities.
- For gastric cancer patients with unknown genetic abnormalities who have an archived tumor sample available for the confirmation of the FGFR2 protein expression mentioned above, the archived tumor sample will be sent to the central laboratory to confirm the presence of FGFR2 protein overexpression with immunohistochemical staining.

Patients considered eligible according to either of the criteria above are eligible to enter into Screening 2.

Because no biopsy is permitted in Screening 1, adverse advents will be collected only after informed consent for Screening 2 is obtained. Patients meeting all of the inclusion criteria and not meeting any of the exclusion criteria in Screening 2 will be considered eligible for treatment, and study treatment will be started after baseline assessment. In Screening 2, a biopsy will be performed in all patients, other than those who have only a tumor lesion not amenable to biopsy for safety reasons. The treatment period will consist of 28-day treatment cycles, and patients will take the study drug once daily continuously until any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met. The follow-up period will involve the early discontinuation procedures and the final observation.

Number of Subjects

Part 1

20 subjects (planned)

Part 2

15 to 20 subjects (planned) (10 with gastric cancer and 5 to 10 with cholangiocarcinoma)

Inclusion Criteria (for both Part 1 and Part 2)

(1) Patients providing voluntary written consent for the participation in this study

(2) Patients who have been given a sufficient explanation of the requirements in this study and are willing and able to follow them

(3) Patients aged ≥20 years at the time of informed consent

(4) Patients with a histological or cytological diagnosis of solid tumor

(5) Patients who have not responded to standard treatment or for whom no other appropriate treatment is available

(6) Patients with adequate major organ function

1) Hemoglobin ≥9.0 g/dL (≥8.0 g/dL in Part 2)
2) Neutrophil count ≥1.5 × 10^3/μL
3) Platelet count ≥10 × 10^4/μL
4) Total bilirubin ≤1.5 times the institutional upper limit of normal (ULN)
5) AST and ALT ≤3.0 times the ULN (≤5.0 times the ULN in the presence of intrahepatic bile duct cancer or liver metastases)
6) Serum creatinine ≤1.5 times the ULN

(7) Corrected serum calcium ≤ ULN

Corrected serum calcium = serum calcium (mg/dL) + (4 − serum albumin [g/dL]) × 0.8

(to be corrected only for subjects with a serum albumin <4 g/dL)

(8) Blood phosphate ≤ ULN

(9) Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1

(10) Patients expected to survive for 3 months or longer after registration (Part 1) or the start of study treatment (Part 2)

(11) Patients with the following time intervals between prior therapy and study treatment in this study:

1) Anticancer therapy
   (a) Other investigational products, antibody therapy: ≥4 weeks (≥5 half-lives are acceptable for other investigational products with a known half-life)
   (b) Anticancer agents (excluding small molecule targeted drugs), surgical therapy, radiation therapy: ≥3 weeks
   (c) Endocrine therapy, immunotherapy, small molecule targeted drugs: ≥2 weeks
2) Supportive therapy
   (a) Blood transfusions, blood products, hematopoietic factor products including granulocyte colony-stimulating factor (G-CSF) products: ≥2 weeks

(12) Women of childbearing potential must have practiced contraception since 28 days before registration (Part 1) or 28 days before the start of study treatment (Part 2), and must agree to use medically effective contraception (eg, the subject is using intrauterine devices,* condoms with spermicide,* contraceptive implants,** or oral contraceptives;* or the subject's male partner is confirmed to have no sperm after vasectomy)[Note] throughout the study period (for 30 days after the final study drug administration). Any subject practicing contraception by abstinence must agree to practice contraception with condoms with spermicide during the study period and for 30 days after the final study drug administration. Women of childbearing potential using any oral contraceptive are to use the oral contraceptive at a fixed dose for at least 4 weeks before study drug administration and continue to use the same oral contraceptive during the study period and for 30 days after the final study drug administration.
All women will be considered to have childbearing potential, except for postmenopausal women (being amenorrheic for at least 12 consecutive months without suspected causes including age) and women undergoing sterilization (bilateral tubal ligation at least 1 month before study treatment, hysterectomy, or bilateral oophorectomy at least 1 month before study treatment).

Note: Whether the drug/medical device has been approved or authorized in Japan (*, yes; **, no)

(13) Male participants or their female partners meeting the criteria above (when the partner is a woman with no childbearing potential or will use medically effective contraception throughout the study period and for 30 days after final study drug administration)

Inclusion Criteria (for Part 2 only)

(14) Patients whose solid tumors have been confirmed to meet either of the following in Screening 1:
   1) Patients with gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2 protein (including patients with gastroesophageal junction cancer diagnosed as adenocarcinoma)
   2) Patients with cholangiocarcinoma harboring FGFR2-fusion genes

(15) Patients with a target lesion that can be evaluated according to RECIST 1.1

(16) Patients meeting both of the following criteria 1) and 2) concerning tumor sample submission:
   1) Patients agreeing to submit any tumor sample collected in the past
   2) Patients agreeing to submit any biopsy sample in Screening 2 (excluding those who have only a tumor lesion not amenable to biopsy for safety reasons)

Exclusion Criteria

(1) Patients with a brain metastasis accompanied by clinical symptoms or requiring treatment

(2) Patients with any of the following clinically significant cardiovascular disorders:
   1) New York Heart Association (NYHA) Grade III or higher cardiac disease (Appendix 1)
   2) Unstable angina pectoris or myocardial infarction within 6 months before enrollment in this study (Part 1) or within 6 months before the start of study treatment (Part 2)
   3) QTc >480 msec (Fridericia method)
   4) Arrhythmia requiring treatment

(3) Patients with serious systemic infection requiring treatment including bacterial infection and fungal infection

(4) Patients with a positive test result for human immunodeficiency virus (HIV)

(5) Patients with celomic fluid retention requiring drainage

(6) Patients with any of the following previous or concurrent corneal or retinal diseases:
   1) Grade ≥2 corneal disorder
   2) Active macular disease (eg, age-related macular degeneration, central serous chorioretinopathy)

(7) Patients in whom the adverse effects of prior treatment have not recovered to Grade 1 or lower, except for alopecia and Grade 2 peripheral neuropathy

(8) Patients with active malignancy within 36 months before the start of study treatment (excluding the primary disease, and carcinomas in situ such as completely treated melanoma in situ, basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and early-stage large bowel cancer)

(9) Patients with prior therapy targeting FGFR2

(10) Patients who are using any CYP3A inhibitor or inducer (Appendix 2) and will require it during study treatment (there must be a time interval of ≥7 days between the final dose of these drugs and the start of study treatment)

(11) Patients known to be intolerant to any of the ingredients of the study drug (or excipients)

(12) Patients unable to take drugs orally or with malabsorption syndrome (patients undergoing gastrectomy may be enrolled)

(13) Patients with mental or physical disorders, such as alcoholism and drug dependence, considered to preclude the participation in this study in the opinion of the investigator or subinvestigator

(14) Pregnant or breastfeeding patients (breastfeeding patients may not be enrolled even if they discontinue breastfeeding)

(15) Any others considered ineligible for the participation in this study in the opinion of the investigator or subinvestigator

Study Treatment

E7090 will be administered orally once daily. Study drug consists of 1, 1.5, 5, 20, and 60 mg capsules (Part 1) and 35 mg tablets (Part 2). The initial dose in Part 1 will be 1 mg and the starting dose in Part 2 will be 140 mg.

Administration schedule

(1) Part 1

1) Cycle 0 (for 7 days)
A single dose of E7090 at the dose for each group will be administered on Day 1 to evaluate its PK following single administration. Subjects will take a single dose of E7090 in the fasting state on waking after an at least 10-hour overnight fast. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water.

2) Cycle 1 and subsequent cycles (for 28 days each)
Subjects will start Cycle 1 between the 8th and 10th days after administration in Cycle 0 and take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, and will not eat anything for 1 hour after administration. On the 8th day of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.

(2) Part 2

Subjects will take E7090 at least 2 hours after breakfast and will not eat anything for 1 hour after administration. On Day 1 and Day 8 of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.

Methods of dose interruption and reduction

(1) Part 1

1) Cycle 1

(a) If a DLT is observed

Study treatment will be interrupted immediately. When the investigator or subinvestigator considers it possible to continue the study, study treatment may be restarted at a 1-level dose reduction once the toxicity resolves to Grade 0 to 1 or baseline.

(b) If no DLT is observed

Study treatment will not be interrupted until a DLT is observed. However, when the investigator or subinvestigator considers interruption clinically necessary, study treatment may be interrupted and restarted at the same dose as appropriate. No dose reduction will be permitted.

2) Cycle 2 and subsequent cycles

If any E7090-related toxicity is observed, the following criteria for dose interruption/reduction should be followed.

Criteria for Dose Interruption/Reduction

E7090-related toxicity [a]	Management	Dose after restart
Grade 1 or tolerable Grade 2 [b]	Continue study treatment	No change
Intolerable Grade 2 [b] or Grade 3	Interrupt treatment until the toxicity resolves to Grade 0 to 1 or baseline [c]	Same dose or 1-level dose reduction
Grade 4 [d]	Discontinue study treatment	NA

a: Laboratory abnormalities not requiring treatment will be excluded.
b: The tolerability of Grade 2 will be determined by the investigator or subinvestigator.
c: When the investigator or subinvestigator considers interruption clinically acceptable, study treatment may be restarted also when the toxicity resolves to tolerable Grade 2.
d: Any laboratory abnormality considered non-life-threatening will be excluded and managed as a Grade 3 event.

(2) Part 2

If any E7090-related toxicity or hyperphosphatemia is observed, the "Criteria for Dose Interruption/Reduction" and the "Criteria for Dose Interruption/Reduction Based on Hyperphosphatemia," respectively, should be followed. If study treatment is continued after the dose reduction, the dose will be reduced step-by-step to 105 mg, 70 mg, and then 35 mg.

Criteria for Dose Interruption/Reduction

Toxicity [a]	Criteria	Management
Hematological	Grade 3 toxicity is observed.	Interrupt treatment until the toxicity resolves to Grade 2 or lower and restart at the same dose as that before interruption
	Grade 4 toxicity is observed.	Interrupt treatment until the toxicity resolves to Grade 2 or lower and restart at a 1-level dose reduction
Non-hematological	Intolerable Grade 2 [b] or Grade 3 toxicity is observed.	Interrupt treatment until the toxicity resolves to Grade 1 or baseline and restart at a 1-level dose reduction
	Grade 4 [c] toxicity is observed.	Discontinue treatment [d]

a: Laboratory abnormalities not requiring treatment will be excluded.
b: The tolerability of Grade 2 will be determined by the investigator or subinvestigator.
c: Any laboratory abnormality considered non-life-threatening by the investigator or subinvestigator will be managed as a Grade 3 event instead of a Grade 4 event.
d: If study treatment is considered clinically beneficial to the subject by the investigator or subinvestigator, treatment may be interrupted until the toxicity resolves to Grade 1 or baseline and restarted at a 1-level dose reduction.

Criteria for Dose Interruption/Reduction Based on Hyperphosphatemia

Criteria	Management
Serum phosphate level is ≥5.5 mg/dL and ≤7.0 mg/dL.	Start treatment of hyperphosphatemia.
Despite appropriate treatment of hyperphosphatemia,[a] serum phosphate levels ≥7.1 and ≤9.0 mg/dL last for ≥2 weeks,[b] or serum phosphate levels are ≥9.1 mg/dL.	Interrupt treatment until serum phosphate levels decrease to ≤7.0 mg/dL and restart treatment at a 1-level dose reduction.

a: This refers to treatments, such as diet therapy and hyperphosphatemia drugs, considered appropriate by the investigator or subinvestigator.

b: Any subject with a serum phosphate level of ≥7.1 mg/dL should visit the study site 1 week later and undergo measurement of serum phosphate levels for the evaluation of hyperphosphatemia.

Duration of Treatment

Treatment with E7090 will be continued until any of the following discontinuation criteria is met.

Discontinuation Criteria for Individual Subjects

(1) Subject's refusal to continue study participation or withdrawal of consent
(2) Major inclusion/exclusion criteria violation after registration (Part 1) or enrollment (Part 2)
(3) Difficulty in continuing the study due to an adverse event in the opinion of the investigator or subinvestigator
(4) Subject's pregnancy
(5) Disease progression (except when the investigator or subinvestigator considers study treatment clinically beneficial to the subject)
(6) Dose reduction to <1 mg (Part 1) or 35 mg (Part 2) required due to an adverse drug reaction
(7) Other cases where the investigator or subinvestigator considers study discontinuation appropriate

Concomitant Drug/Therapy

Prohibited concomitant drugs/therapies

(1) Cycle 0 and Cycle 1 (Part 1 only)
    1) Treatments, changes in dosage, and changes in drugs to prevent DLT occurrence
(2) From the time of registration (Part 1) or the start of study treatment (Part 2) to the time of the discontinuation of study treatment
    1) Treatments for malignant tumors other than E7090 (eg, surgical therapy, chemotherapy, endocrine therapy, palliative radiotherapy, or immunotherapy) except for drugs for bone lesions (eg, bisphosphonates, anti-RANKL monoclonal antibodies) that have been used since before the registration in this study (Part 1) or the start of study treatment (Part 2)
    2) Drugs that inhibit or induce CYP3A (see Appendix 2 for relevant drugs)
    3) Other investigational products

Assessments

(1) Efficacy assessments

Tumor assessment (target lesion, non-target lesion, presence/absence of new lesions) will be performed using RECIST 1.1. Tumor markers will also be determined. Survival follow-up will be terminated 2 years after the last subject's registration (Part 2).

(2) Pharmacokinetic (PK) assessments

Blood and urine samples will be collected to determine plasma and urine E7090 concentrations. In addition, plasma and urine E7090 metabolites will be analyzed in an exploratory manner.

(3) PD and PGx assessments

[Part 1]

1) Blood

Blood samples will be collected to determine the following biomarkers (but not limited to):

(a) FGF23
(b) 1,25-(OH)2-Vitamin D
(c) CCI [redacted]
(d) Angiogenesis markers (eg, VEGF, FGF)
(e) Circulating tumor DNA

2) Archived tumor

If available, an archived tumor sample (optional) will be obtained to determine the following biomarkers (but not limited to):

(a) FGFR

3) Biopsied tumor

At screening and on the 15th day of Cycle 1 (optional), biopsy tumor samples will be collected to determine the following biomarkers:

(a) FGFR

(b) Phosphorylated FGFR

(c) ERK

(d) Phosphorylated ERK

[Part 2]

1) Blood

Blood samples will be collected to determine the following biomarkers (but not limited to):

(a) FGF23

(b) 1,25-(OH)2-Vitamin D

(c) CCI

(d) Angiogenesis markers (eg, VEGF, FGF)

(e) Circulating tumor DNA

2) Archived tumor

If any sample collected in the past is available, an archived tumor sample should be submitted (mandatory).

3) Biopsied tumor

Except for subjects who have only a tumor lesion not amenable to biopsy for safety reasons, samples obtained from the biopsy performed in Screening 2 must be submitted (mandatory). In addition, samples obtained from the biopsy performed on the 15th day of Cycle 1 will be submitted (optional).

For 2) and 3) above, immunohistochemical staining or comprehensive genomic analysis will be performed to evaluate their correlation with the efficacy of E7090. In addition, samples will be archived for the development of diagnostic agents.

(4) Safety assessments

Safety will be assessed through monitoring and recording of all adverse events and serious adverse events. Laboratory tests, vital signs, 12-lead ECGs, ECOG-PS, physical findings, and ophthalmologic examination will be evaluated at prespecified time points.

In addition, DLTs will be assessed to determine the MTD. The nature, frequency, and severity of adverse events will be evaluated, and the severity of adverse events will be graded using the CTCAE v4.03. DLTs will be defined as the following events occurring during Cycle 0 and Cycle 1 considered to be possibly related to E7090. DLTs will be determined through discussion among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary.

1) DLT criteria

(a) Febrile neutropenia, or Grade 4 neutropenia persisting for ≥7 days

(b) Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia requiring platelet transfusions

(c) Grade ≥3 non-hematological toxicity, except for the following:
   a) Clinically insignificant laboratory abnormalities
   b) Toxicity that can be controlled to Grade ≤2 by best supportive care

(d) Potentially clinically significant, new radiographic mineralization in the soft tissue, kidneys, intestines, heart, lungs, or other organs

(e) Hyperphosphatemia meeting either of the following:
   a) Serum phosphate level >7 mg/dL persisting for ≥7 days despite best treatment
   b) Serum phosphate level >9 mg/dL despite best treatment

(f) Treatment interruption for ≥8 days during Cycle 0 and Cycle 1 required by possibly E7090-related toxicity, except for treatment interruption for ≥8 days for reasons other than toxicity. In this case, the subject will be removed from the DLT evaluation and replaced by a new subject.

2) Determination of the MTD

The MTD of E7090 will be determined using the mTPI design. At the end of Part 1, the MTD will be selected as a dose with the smallest difference from the target DLT rate of 25% according to the posterior distribution of the DLT rate for each dose.

Bioanalytical Methods

E7090 concentrations in plasma and urine and PD markers in blood will be determined using a validated method of measurement.

Statistical Methods

Statistical design concerning the modified toxicity probability interval method in Part 1:

The MTD of E7090 will be determined using the mTPI design. The mTPI design uses a beta/binomial hierarchical model in a Bayesian statistical framework to calculate the posterior probabilities of 3 intervals that reflect the relative distance between the target DLT rate of 25% and the DLT rate for each dose level.

The decision rules for finding doses are based on the calculation of the unit probability mass (UPM) of the 3 intervals corresponding to 0% to 20% (underdosing), 20% to 30% (proper dosing), and 30% to 100% (overdosing) in terms of toxicity. The UPM of each interval is defined as the probability of the interval divided by the length of the interval, and the interval with the largest UPM indicates the decision on the next dose level to be assigned: dose escalation (E), staying at the current dose (S), and dose de-escalation (D).

These dose assignment rules minimize the posterior expected loss in the Bayes' rule when equal prior expected losses are used for E, S, and D in a decision-theoretic framework. The decision rules for all dose assignment will be calculated in advance, as presented in Table 1.

The MTD will be determined when the posterior probability of the DLT rate at the initial dose exceeding 25% exceeds 95% (ie, an unacceptable DLT rate exceeding the target DLT rate) or when a prespecified maximum sample size of approximately 20 subjects is reached. However, the maximum sample size will be adjusted as necessary according to the actual number of dose levels to be evaluated and the number of subjects evaluable for DLT. In addition, if the Bayesian predictive probability of being S when another 10 subjects are added to a dose level is 80% or higher (ie, if it is highly likely that subsequent registered subjects will also be assigned to the dose level), subject registration may be closed early to determine the MTD.

The MTD will be defined as the dose with the smallest difference between the target DLT rate of 25% and an estimated DLT rate at each dose among all the evaluated doses for which the posterior probability of the DLT rate exceeding 25% is 95% or lower. The isotonically transformed posterior mean under a beta posterior distribution with non-informative beta prior distribution Beta (0.005,

0.005) will be used to determine the estimated DLT rate at each dose. The pooled-adjacent-violators algorithm (PAVA) will be used to maintain the monotonic increase of the DLT rate with increasing dose level.

Efficacy endpoints

The efficacy endpoints to be calculated will include the best overall response (BOR) according to RECIST 1.1, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and percent changes from baseline in the sum of the diameters of target lesions (when appropriate). BOR includes complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE), where SD must to be achieved beyond 7 weeks after the first dose. In this study, CR and PR will require no confirmation based on the next response evaluation beyond 4 weeks. ORR is defined as the proportion of subjects with a BOR of CR or PR. DCR is defined as the proportion of subjects with a BOR of CR, PR, or SD. PFS is defined as the time from the date of the first dose to the date of the first event (disease progression or death due to any cause, whichever comes first). OS is defined as the time from the date of the first dose to the date of death due to any cause.

Tolerability/Safety endpoints

The tolerability endpoint will include DLTs. The safety endpoints will include adverse events, laboratory tests, vital signs, weight, 12-lead ECG, ECOG-PS, and ophthalmologic examination.

PK endpoints

Blood and urine samples will be collected for PK analysis to determine E7090 concentrations in plasma and urine. Metabolites of E7090 in plasma and urine will be analyzed in an exploratory manner.

PD and PGx endpoints

The PD and PGx endpoints will include measurements of biomarkers (in blood and tumor tissue) and their percent changes. Of these, the PGx endpoints refer to measurements of circulating tumor DNA in blood and measurements of genetic mutations in biopsied tumor tissues.

Analysis sets

The DLT analysis set is the group of subjects completing treatment with E7090 in Cycle 0 and Cycle 1 with a compliance rate of ≥75% and evaluated for DLT and subjects experiencing DLT in Cycle 0 or Cycle 1 in Part 1. This analysis set will be used to estimate the MTD in Part 1.

The safety analysis set is the group of subjects receiving at least 1 dose of E7090.

The efficacy analysis set is the group of subjects receiving at least 1 dose of E7090 with at least 1 tumor assessment at baseline and after administration. This analysis set will be used for the interim assessment in Part 2.

The PK analysis set is the group of subjects receiving at least 1 dose of E7090 with data from which at least 1 PK parameter can be calculated.

The PD and PGx analysis set is the group of subjects receiving at least 1 dose of E7090 with at least 1 PD or PGx data.

Efficacy analyses

Part 1: Efficacy analyses will be performed using the efficacy analysis set. On the basis of tumor assessments according to RECIST 1.1, the BOR will be summarized for each group and overall. In subjects with non-target lesions only, a BOR of non-CR/non-PD will be categorized into SD.

Part 2: Analysis results will be summarized for each cohort and overall. In addition to the analyses similar to those for Part 1, ORR, DCR, and their exact two-sided 95% confidence intervals will be calculated. PFS and OS will also be summarized and plotted over time using the Kaplan-Meier method. When appropriate, a waterfall plot will be created for the percent change from baseline in the sum of the diameters of target lesions at the time of maximum tumor reduction after administration.

Pharmacokinetic analyses

The PK analysis set will be used to summarize E7090 plasma concentrations and PK parameters and perform other PK analyses. A non-compartmental analysis of plasma and urine E7090 concentrations will be performed to calculate PK parameters including C_{max}, t_{max}, AUC, and renal clearance. Detailed methods and results of the exploratory metabolite analysis will be provided in a separately prepared analysis plan and report, and its results will not be included in the clinical study report.

PD and PGx analyses

PD and PGx analyses will be performed using the PD and PGx analysis set. Measurements of biomarkers (in blood and tumor tissue) and their percent changes will be evaluated visually with the use of figures and tables. If necessary, correlations of measurements of biomarkers and their percentage changes with the efficacy and safety of E7090 will be analyzed, or various exploratory analyses will be performed. Results of other comprehensive analyses will not be included in the clinical study report.

Tolerability/Safety analyses

DLT analyses will be performed using the DLT analysis set. The number and percentage of subjects with DLTs will be summarized. DLTs will also be summarized by type. Other safety analyses will be performed using the safety analysis set. The number and percentage of subjects with treatment-emergent adverse events and serious adverse events will be summarized by system organ class (SOC) and preferred term (PT). Summary statistics will be used to summarize the results of laboratory tests, vital signs, weight, 12-lead ECG, ECOG-PS, and ophthalmologic examination as well as their changes from baseline.

Interim Analyses

No interim analysis taking into consideration adjustment for type I and II errors will be performed in this study.

In the gastric cancer cohort in Part 2, an interim efficacy evaluation will be performed, and if no responder is observed in 5 evaluable subjects, the cohort may discontinue further enrollment. The duration of follow-up of subjects with continuous SD will be determined through discussion with the sponsor.

This criterion is based on the posterior distribution of Bayesian statistics. When a non-informative beta prior distribution Beta (1,1) is used, the discontinuation criterion corresponds to the case where the probability of ORR being 40% or higher is less than 10% in the posterior distribution of the 5 subjects at the time of evaluation. In cases other than the number of evaluable subjects established as the discontinuation criterion, if necessary, it will be acceptable to consider interim evaluations and discontinuation of enrollment based on the posterior distribution and criteria described above.

The ORR threshold of 40% has been established as a beneficial effect size, taking the mechanism of action of E7090 into consideration.

Sample Size Rationale

The primary objective of this study is to evaluate the tolerability and safety of E7090. The sample size for Part 1 has been set to approximately 20 subjects, assuming the number of dose levels to be evaluated of 9 and a cohort size of 2 on the basis of the recommended sample size to reach the MTR in the mTPI design. When deemed necessary, the sample size may be adjusted, depending on the actual number of dose levels to be evaluated and the number of evaluable subjects for DLT.

The sample size for Part 2 has been set to approximately 10 subjects or 5 to 10 subjects per cohort, considering its feasibility, to allow further safety evaluation and the preliminary antitumor effect evaluation.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ALP	alkaline phosphatase
ALT	alanine aminotransferase (GPT)
AST	aspartate aminotransferase (GOT)
AUC	area under the plasma concentration-time curve
BUN	blood urea nitrogen
CL	total clearance
C_{max}	maximum observed concentration
CR	complete response
CRM	Continual Reassessment Method
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CYP/CYP3A4	cytochrome P450/cytochrome P450 3A4
DCR	disease control rate
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FGF/FGFR	fibroblast growth factor/fibroblast growth factor receptor
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
γ-GTP	gamma glutamyl transferase
HBs	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
JCOG	Japan Clinical Oncology Group
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval

Abbreviation	Term
NA	not applicable
NE	not evaluable
NGS	next-generation sequencing
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAVA	pooled-adjacent-violators algorithm
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PGx	pharmacogenomics
PR	partial response
PS	performance status
PT	preferred term
QT	QT interval
RECIST	Response Evaluation Criteria in Solid Tumor
RT-PCR	real-time polymerase chain reaction
SD	stable disease
SOC	system organ class
SOP	standard operating procedures
$t_{1/2}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment emergent markedly abnormal laboratory values
t_{max}	time at which the highest drug concentration occurs
TNM classification	tumor, nodes, metastasis classification
ULN	upper limit of normal
UPM	unit probability mass
V_Z	volume of distribution at terminal phase
WHO	United Nations World Health Organization

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documented study approval from the IRB/IEC chairman must be sent to the head of the medical institution with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) via the head of the medical institution in accordance with GCP. The sponsor will submit, depending on local regulations, periodic reports and inform the investigator and the IRB/IEC via the head of the medical institution of any reportable adverse events (AEs) per GCP and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC and the sponsor via the head of the medical institution with a brief report of the outcome of the study.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects
- GCP
- Standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960)

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject (or the subject's guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the

subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed (at the Screening). No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the investigator, subinvestigator (study coordinator, as necessary). The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The ICF for genetic testing will be prepared separately from that for study participation, and genetic testing will be conducted in subjects who have consented to the testing. In Part 1, genetic testing involving the use of blood samples is required and subjects who do not consent to such testing cannot be included in this clinical study, whereas those who do not consent to genetic testing of tumor samples can still be eligible for this study. In Part 2, genetic testing involving the use of blood and tumor samples are required (tumor samples will not be obtained from subjects who cannot submit an archived tumor sample collected in the past or who are not amenable to biopsy).

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor). Part 1 will be conducted at 1 medical institution in Japan, and Part 2 will be conducted at approximately 14 to 17 medical institutions (planned) in Japan.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in Appendix 3.

7 INTRODUCTION

7.1 Fibroblast Growth Factor Receptor

Fibroblast growth factor receptors (FGFR) are transmembrane tyrosine kinase receptors consisting of 4 types: FGFR-1, -2, -3, and -4. There are 18 FGFs known as ligands involved in FGF/FGFR signaling. It is known that binding of FGF to FGFR activates numerous pathways involved in cellular functions such as cellular proliferation and survival via the MAP kinase pathway (RAS/RAF/MEK/ERK pathways) and PI3K/AKT pathway (Haugsten EM, et al., 2010) (Turner N, Grose R, 2010) (Dieci MV, et al., 2013).

In cancer cells, not only signal activation is induced by increased expression of FGF/FGFR or by supply of FGF by peritumoral tissues, but also constant downstream signaling activation is triggered by various FGFR gene abnormalities such as translocations, point mutations, and gene amplifications. Accordingly, associated tumorigenicity, increased metastasis/invasiveness, and drug resistance have been reported (Haugsten EM, et al., 2010) (Turner N, Grose R, 2010) (Dieci MV, et al., 2013).

Analyses of clinical samples have revealed FGFR gene abnormalities or FGF/FGFR overexpression in various types of cancers including lung cancer, breast cancer, endometrial cancer, gastric cancer, and bladder cancer (Haugsten EM, et al., 2010) (Turner N, Grose R, 2010) (Dieci MV, et al., 2013), some of which have been associated with prognosis or drug resistance (Kim HR, et al., 2013) (Jung EJ, et al., 2012) (Byron SA-, et al., 2012). Also in vascular endothelial cells, it has been reported that FGF/FGFR signaling is a major angiogenesis signaling pathway like VEGF/KDR and PDGF/PDGFR signaling pathways, and it has been suggested that FGF/FGFR signaling is involved in the investment in the resistance to VEGF/KDR inhibitors (Casanovas O, et al., 2005).

These findings indicate that FGFR inhibitors are expected to have direct effects on tumors with activated FGFR signaling and antiangiogenic effects on tumor blood vessels.

7.2 E7090

E7090, an oral FGFR kinase inhibitor developed at Eisai Tsukuba Research Laboratories, selectively inhibits FGFR-1, -2, and -3. Its excellent antitumor effects on a variety of human cancer cell lines with FGFR abnormalities (eg, gene translocation, point mutation, amplification) observed in nonclinical pharmacology studies indicate a promising efficacy in cancer patients, especially those with FGFR abnormalities.

7.3 Nonclinical Studies of E7090

7.3.1 Pharmacodynamics

[Primary Pharmacodynamic Studies]

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7.3.2 Pharmacokinetics and Drug Metabolism

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7.3.3 Toxicology

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7.4 Clinical Experience

As of 28 March 2017, 24 patients (2 each in the 1, 2, 4, 8, 16, and 30 mg groups and 3 each in the 60, 100, 140, and 180 mg groups) have been enrolled in Part 1 of this study. Commonly reported adverse events (≥20% across the groups) included hyperphosphatemia (37.5%); increased blood creatinine and nausea (33.3% each); diarrhea (29.2%); increased ALT and fatigue (25.0% each); and constipation, increased lipase, pyrexia, and tumor pain

(20.8% each). Reported Grade ≥3 adverse events included increased ALT (2 subjects in the 180 mg group), increased AST (1 subject in the 180 mg group), decreased appetite (1 subject in the 180 mg group), decreased neutrophil count (1 subject in the 180 mg group), vomiting (1 subject in the 180 mg group), and decreased lymphocyte count (1 subject in the 60 mg group), all of which were Grade 3 in severity. DLTs (Grade 3 increased AST and increased ALT) occurred in 1 subject in the 180 mg group. Three serious adverse events were reported in 2 subjects in the 8 mg group (cancer pain and dyspnea each in 1 subject) and 1 subject in the 30 mg group (pyrexia), all of which were assessed as unrelated to study treatment. No adverse events led to death or treatment discontinuation.

7.5 Study Rationale

This study is a phase 1 study of E7090 designed to investigate the pharmacological profile of E7090 when administered to humans for the first time. The study consists of Part 1 and Part 2.

7.5.1 Rationale for the Study Design

7.5.1.1 Referenced Guidelines and Guidances

This study was designed with reference to "Guidelines for Clinical Evaluation Methods of Anticancer Drugs" (PFSB/ELD Notification No. 1101001 dated 1 November 2005), ICH S9 "Guidelines for Nonclinical Evaluation Methods of Anticancer Drugs" (PFSB/ELD Notification No. 0604-1 dated 4 June 2010), "Guidance for Establishing Safety in First-in-Human Studies During Drug Development" (PFSB/ELD Notification No. 0402-1 dated 2 April 2012), and "Technical Guidance on In Vitro Companion Diagnostics and Corresponding Therapeutic Products" (Administrative Notice dated 26 December 2013).

7.5.1.2 Rationale for the Initial Dose for Part 1

The initial dose of E7090 for this study was established with reference to ICH S9 "Guidelines for Nonclinical Evaluation Methods of Anticancer Drugs" (PFSB/ELD Notification No. 0604-1 dated 4 June 2010). This guideline states that for many small-molecule drugs, their initial dose should be usually set at 1/10 the severely toxic dose (STD 10; toxicity associated with lethality, life-threatening toxicities, or irreversible toxicities) in 10% of rodent test animals, or at 1/6 the highest non-severely toxic dose (HNSTD) in the case where non-rodents are the most appropriate test species.



CCI [redacted]

Taking subject safety into consideration, the dose of 1.46 mg calculated on the basis of the toxicity study in rats (more susceptible to toxicity) has been selected to set the initial dose at 1 mg, which is below 1.46 mg.

7.5.1.3 Rationale for the Starting Dose for Part 2

On the basis of the data from Part 1, the starting dose for Part 2 has been set at 140 mg. In Part 1, patients were enrolled in the following order: 1 mg (n = 2), 2 mg (n = 2), 4 mg (n = 2), 8 mg (n = 2), 16 mg (n = 2), 30 mg (n = 2), 60 mg (n = 3), 100 mg (n = 3), 180 mg (n = 3), and 140 mg (n = 3). Because a DLT was observed in 1 subject in the 180-mg cohort (Grade 3 increased AST/ALT) and no DLT was observed in the 140-mg cohort, 140 mg has been selected as the recommended dose for Part 2.

7.5.1.4 Rationale for Once-Daily Dosing

Physiological PK models were used to estimate the PK profile of E7090 in humans. CCI [redacted] elimination half-life following oral dose was estimated to be 27 to 48 hours. Given that administration once daily was considered to be adequate to maintain the plasma concentration of E7090, a once-daily dosing schedule was selected.

7.5.1.5 Rationale for Targeting Patients with Solid Tumors in Part 1

Part 1 will include patients with solid tumors. As described in Section 7.3.1 "Primary Pharmacodynamic," E7090 is expected to be effective particular in patients with FGF/FGFR gene abnormalities because it showed its effects on cell lines where FGF/FGFR signaling is constantly active. It has been reported that FGF/FGFR signaling is a major angiogenesis signaling pathway like VEGF/KDR and PDGF/PDGFR signaling pathways, and it has been suggested that FGF/FGFR signaling is involved in the investment in the resistance to VEGF/KDR inhibitors (Casanovas O, et al., 2005). It is therefore considered that E7090 is also expected to be effective in patients without FGF/FGFR abnormalities. The "Technical Guidance on In Vitro Companion Diagnostics and Corresponding Therapeutic Products" (Administrative Notice dated 26 December 2013) states, "It is important to establish a drug development strategy that reflects the need to evaluate negative patients at an earlier stage. For instance, both biomarker-positive and negative patients should be evaluated earlier phase clinical studies such as exploratory dose-response studies." Therefore, although E7090 is expected to be effective particularly for patients with FGF/FGFR abnormalities, it has been

determined that Part 1 will include patients with solid tumors with or without FGF/FGFR abnormalities.

7.5.1.6 Rationale for the Use of the mTPI Design in Part 1

In Part 1, the MTD will be determined by assigning doses to subjects according to a modified toxicity probability interval (mTPI) design. Unlike the commonly used 3 + 3 design, the mTPI design, a Bayes-based adaptive assignment method, enables the true MTD corresponding to the target DLT rate to be selected more precisely on the basis of a statistical rationale (Ji Y, et al., 2013). Similarly, many articles have reported that the continual reassessment method (CRM), a well-known Bayes-based adaptive assignment method, and its extended design enable more precise selection of the MTD than the 3 + 3 design and have superior operating characteristics (Thall PF, Lee SJ, 2003) (Iasonos A, et al., 2008) (Le Tourneau C, et al., 2009). Before the start of a study, however, these designs based on complicated dose-response models require careful configuration of prior information to obtain desired operating characteristics or establishment of a structure to allow the treating physician to know the dose to be allocated to the next subject in a timely manner (Ji Y, et al., 2010). Although these designs have recently been used in an increasing number of cases because of improved environments to implement them through the availability of free software, the simpler 3 + 3 design is still preferred frequently and these designs are not used widely despite their superior operating characteristics (Ji Y, et al., 2013).

On the other hand, the mTPI design can be used easily like the 3 + 3 design because it requires no complicated dose-response models, and has been reported to have operating characteristics that are non-inferior to those of the CRM through simulations (Ji Y, et al., 2010). In addition, the mTPI design is safer for subjects than the CRM because it can averagely minimize the proportion of subjects experiencing DLTs during a study and the number of subjects allocated to a toxic dose that may exceed the target DLT rate (Ji Y, et al., 2010). The mTPI design was also presented at the 2013 ASCO Pre-Annual Meeting Seminar, and cases using the design have been reported in recent years (Ji Y, et al., 2013).

It has thus been determined that the mTPI design will be used for subject's dose assignment in Part 1.

7.5.1.7 Rationale for Determining the Dose for the Next Dose Group

In phase 1 studies of an anticancer drug, it is considered important to minimize the number of subjects treated in the group receiving the low dose in which biological activity cannot be expected, and to escalate the dose while safety is considered carefully in the group receiving the high dose for which toxicities are expected to develop (Simon R, et al., 1997). In this study, taking these requirements into account, it has been determined that in low-dose groups, subjects will take a 100% escalated dose when they have Grade ≤1 toxicities only, and in high-dose groups, subjects will take a 50% or 33% escalated dose after a toxicity is observed, depending on the severity of the toxicity, while sufficient attention is paid to the development of toxicities. This escalation method ensures subject safety and meets ethical considerations because the percentage of dose escalation can be determined according to the severity of toxicities observed in each dose group.

7.5.1.8 Rationale for Including Patients with Gastric Cancer Carrying an Amplified FGFR2 Gene or an Overexpressed FGFR2 Protein and Patients with Cholangiocarcinoma Harboring FGFR2-Fusion Genes in Part 2

Given that responses were achieved in patients with gastric cancer carrying an amplified FGFR2 gene in Part 1 of this study, gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2 protein is expected to be a promising target for E7090.

In addition, a Japanese research group recently identified an in-frame fusion transcript (FGFR2 fusion gene) involving FGFR2 and other genes (BICC1 gene or AHCYL1 gene) in cholangiocarcinoma (Arai Y1, et al., 2014), suggesting that it may be a promising target for FGFR inhibitors. Therefore, cholangiocarcinoma harboring FGFR2-fusion genes is expected to be a promising target for E7090.

7.5.1.9 Rationale for Selecting 1 or 2 Doses from among the Part 1 Doses in Part 2

The objective of this design is to select a dose that can maintain adequate efficacy with low toxicity as the recommended dose for subsequent phase studies. For many small-molecule kinase inhibitors to date, although the MTD determined in phase 1 studies were selected as their recommended dose for subsequent phase studies (Hidalgo M, et al., 2001) (Strumberg D, et al., 2005), recent years have seen some subjects in whom the development of adverse drug reactions (ADRs) specific to small-molecule kinase inhibitors, such as hand-and-foot syndrome, precluded continuation of study treatment (Lacouture ME, et al., 2008) (Manchen E, et al., 2011). It is therefore considered important to pursue regimens that allow long-term administration to patients in the future development of small-molecule kinase inhibitors. In this design, when 2 doses are selected for Part 2, and if the efficacy of the drug is considered to be maintained with the lower dose of them, it will be possible to select the lower dose as the recommended dose.

7.5.2 Methods of Evaluating Adverse Drug Reactions Expected from Nonclinical Toxicity Studies

Mineralization associated with hyperphosphatemia and thinning of the corneal epithelium were observed in the non-clinical toxicity studies. These changes were considered attributable to FGFR kinase inhibition by E7090 as its pharmacological action. Given that hyperphosphatemia and corneal abnormalities have also been seen in clinical studies of similar drugs, special attention needs to be paid to these toxicities in this study.

[Evaluation of mineralization]

Since mineralization is induced by the deposition of phosphate combined with calcium in the blood, it is important to evaluate and control serum phosphate levels. In this study, it is stipulated that serum phosphate levels must be measured at study visits and that high phosphate levels will be managed in accordance with the criteria for dose interruption/reduction shown in Table 6. In addition, it is stipulated that necessary tests (eg, X-ray) will be performed if any clinical symptoms suggestive of mineralization are observed.

[Evaluation of thinning of the corneal epithelium]

Serious corneal thinning could greatly reduce the patient's QOL, therefore requiring special attention. In Part 1, the dose-escalation part of this study, to rigorously evaluate the effect of E7090 on the eyes, the ophthalmologist at each study site participated in the study as a subinvestigator and performed the following tests on prespecified evaluation days: visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and anterior segment optical coherence tomography (OCT) to evaluate the corneal epithelium.

In Part 1, prespecified tests have revealed no significant thinning of the corneal epithelium, but Grade 1 retinal adverse events were observed. In Part 2, taking these findings into consideration, anterior segment OCT will be replaced by posterior segment OCT to evaluate the retina. More specifically, visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and posterior segment OCT to evaluate the retina will be performed on prespecified evaluation days in Part 2.

8 STUDY OBJECTIVES

8.1 Primary Objective

To investigate the tolerability and safety of E7090 in subjects with solid tumors

8.2 Secondary Objectives

(1) To estimate the maximum tolerated dose (MTD) of E7090 (only in Part 1)

(2) To assess the pharmacokinetics (PK) of E7090

(3) To estimate the recommended dose for subsequent phase studies

(4) To preliminarily evaluate the antitumor activity of E7090

8.3 Exploratory Objectives

(1) To investigate the pharmacodynamic (PD) markers and pharmacogenomics (PGx) of E7090

(2) To investigate the PK, PD markers, and PGx relationship for E7090

(3) To assess overall survival (OS) and progression-free survival (PFS) with E7090 treatment (only in Part 2)

(4) To analyze plasma and urinary metabolites of E7090

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a dose-escalation, open-label study in patients with solid tumors who have not responded to standard treatment or for whom no other appropriate treatment is available, which consists of 2 parts (Part 1 and Part 2). The study design overview is shown in Figure 1. In Part 1, patients with solid tumors receiving E7090 will be evaluated for dose-limiting toxicities (DLTs) to estimate its MTD. In Part 2, E7090 will be evaluated for its tolerability and safety in detail and its efficacy preliminarily in patients with gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2 protein and patients with cholangiocarcinoma harboring FGFR2-fusion genes. Part 2 will include patients with solid tumors, consisting of a gastric cancer cohort and a cholangiocarcinoma cohort. In Part 2, after evaluation of the safety, efficacy, and PK/PD data obtained in Part 1, 1 or 2 doses will be selected from among the doses studied in Part 1 to expand the study population. On the basis of the results from Part 1 and Part 2, the recommended dose for future studies will be estimated. The dose for Part 2 will be determined through discussion among the investigator, the sponsor, the medical expert, and if necessary, the Data and Safety Monitoring Advisor.

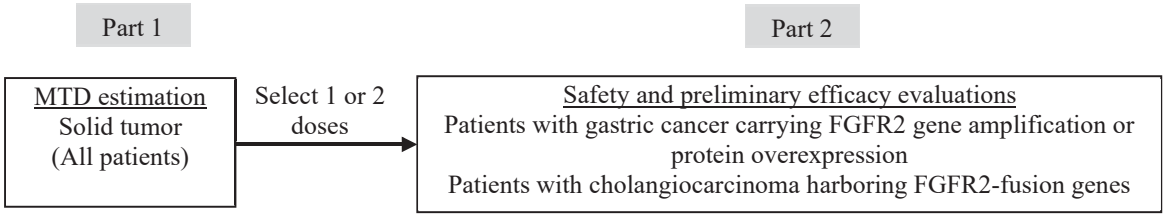


Figure 1 Study Design Overview

9.1.1 Part 1

The study design for Part 1 is outlined in Figure 2. Part 1 will consist of a pretreatment period, a treatment period, and a follow-up period.

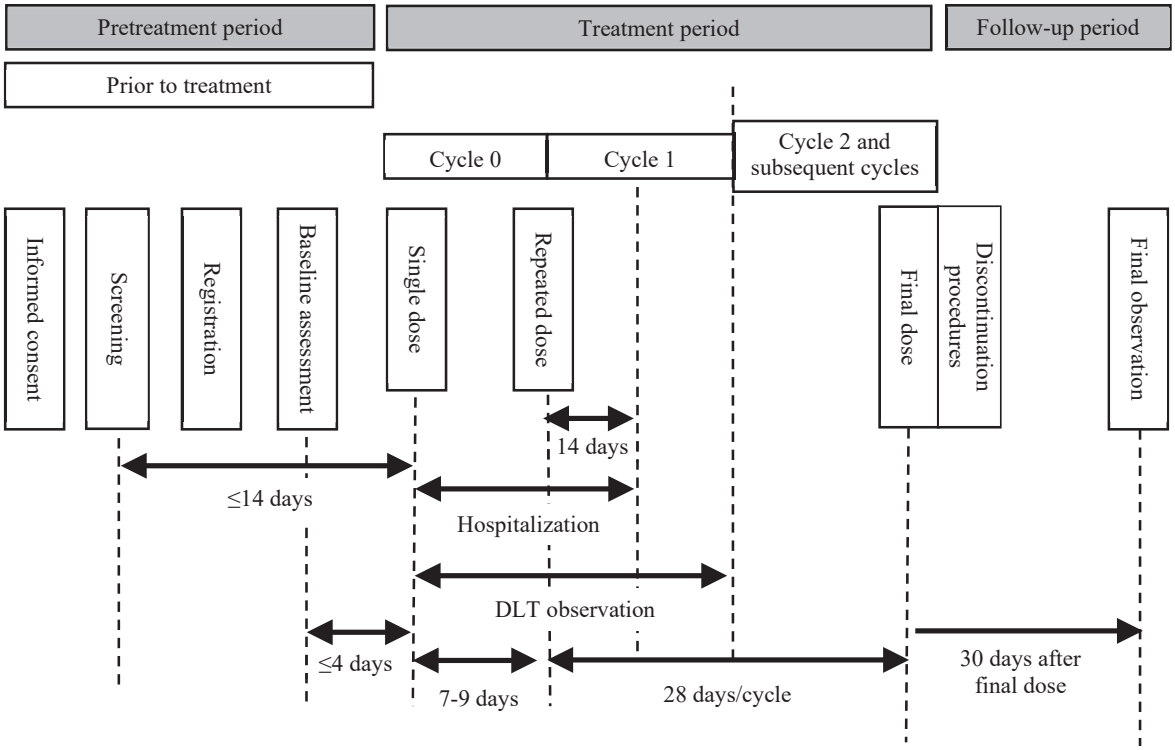


Figure 2 Outline of Study Design for Part 1

9.1.1.1 Pretreatment Period

The pretreatment period will involve informed consent, screening, subject registration, and baseline assessment. Prior to any study-related investigation or assessment, written informed consent will be obtained from each subject after giving an adequate explanation about the details of this study. At screening, it will be confirmed that each subject meets all of the inclusion criteria and none of the exclusion criteria. Screening will occur within 14 days prior to the first dose of study treatment. Subjects confirmed to be eligible by screening will be registered and undergo baseline assessment within 4 days prior to the first dose of study treatment.

9.1.1.2 Treatment Period

The treatment period will consist of Cycle 0, Cycle 1, Cycle 2, and subsequent cycles.

In Cycle 0, subjects will take a single dose of E7090 at the dose for each dose group on Day 1 for PK evaluation.

In Cycle 1 and subsequent cycles, each consisting of 28 days, subjects will take repeated doses. Subjects will be hospitalized from Day 1 of Cycle 0 to the morning of Day 15 of

Cycle 1. The investigator or subinvestigator will carefully evaluate the results of the physical examination performed on Day 15 of Cycle 1 and all test results to determine from a medical standpoint whether each subject can be managed on an outpatient basis. If continued hospitalization is considered necessary from the aspect of subject safety, hospitalization will be continued after Day 15 of Cycle 1. In Cycle 0 and Cycle 1, DLTs will be monitored and evaluated. Treatment may be continued unless any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met.

9.1.1.3 Follow-up Period

The follow-up period will involve the early discontinuation procedures and final observation. If any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met, study treatment will be discontinued and the early discontinuation procedures will be performed within 7 days after study discontinuation. In addition, the final observation will be performed within 30 days (+7 days) after the final dose of study treatment.

9.1.2 Part 2

The study design for Part 2 is outlined in Figure 3. Part 2 will consist of a pretreatment period, a treatment period, and a follow-up period.

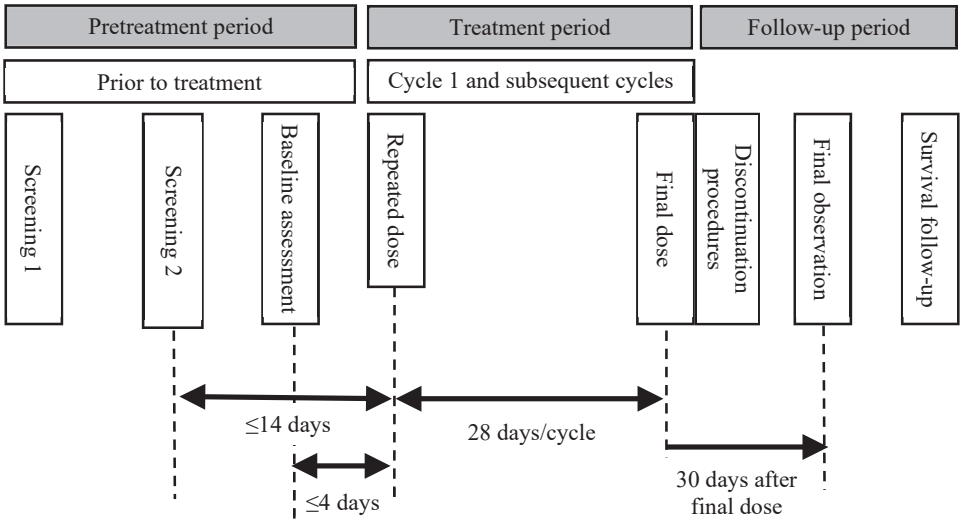


Figure 3 Outline of Study Design for Part 2

Part 2 will include patients with solid tumors, consisting of the following cohorts:

- Gastric cancer cohort: Patients with gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2 protein (including patients with gastroesophageal junction cancer diagnosed as adenocarcinoma)

- Cholangiocarcinoma cohort: Patients with cholangiocarcinoma harboring FGFR2-fusion genes

For any cohort for which no more patient enrollment is anticipated, enrollment may be discontinued before completion of enrollment of the planned sample size.

9.1.2.1 Pretreatment Period

The pretreatment period will consist of Screening 1, Screening 2, and baseline assessment. In Screening 1, each subject will be examined for FGFR genetic abnormalities in the tumor, and in Screening 2, each subject will be examined for the other eligibility criteria. Separate written informed consent will be obtained before the start of Screening 1 and Screening 2.

Screening 1 will include gastric cancer patients with documented FGFR2 gene amplification and cholangiocarcinoma patients with documented FGFR2-fusion genes. In addition, Screening 1 will also include any gastric cancer patient with unknown FGFR2 amplification status who has an archived tumor sample available for the confirmation of FGFR2 protein expression. No biopsy should be performed at Screening 1.

In Screening 1, the following will be confirmed:

- For patients with the documented genetic abnormalities mentioned above, the documents necessary for genetic testing will be submitted to the sponsor to confirm the presence of genetic abnormalities.
- For gastric cancer patients with unknown genetic abnormalities who have an archived tumor sample available for confirmation of the FGFR2 protein expression mentioned above, the archived tumor sample will be sent to the central laboratory to confirm the presence of FGFR2 protein overexpression with immunohistochemical staining.

Patients considered eligible according to either of the criteria above are eligible to enter into Screening 2.

Because no biopsy is permitted in Screening 1, adverse advents will be collected after informed consent for Screening 2 is obtained. Patients meeting all of the inclusion criteria and none of the exclusion criteria in Screening 2 will be considered eligible for treatment, and study treatment will be started after baseline assessment. In Screening 2, a biopsy will be performed in all patients, other than those who have only a tumor lesion not amenable to biopsy for safety reasons. Screening 2 will occur within 14 days prior to the first dose of study treatment. Subjects confirmed to be eligible by screening will be registered and undergo baseline assessment within 4 days prior to the first dose of study treatment.

9.1.2.2 Treatment Period

The treatment period will consist of 28-day treatment cycles. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.

9.1.2.3 Follow-up Period

The follow-up period will involve the early discontinuation procedures and final observation. If any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met, study treatment will be discontinued and the early discontinuation procedures will be performed within 7 days after study discontinuation. In addition, final observation will be performed within 30 days (+7 days) after the final dose of study treatment. Subjects will be followed for survival every 12 weeks (±2 weeks) from the time of study treatment discontinuation. When necessary, follow-up survival may be performed at unspecified time points.

9.2 Discussion of Study Design, Including Choice of Control Groups

No control group will be established in this study. The rationale for the design of this study is described in Section 7.5.1 “Rationale for the Study Design.”

9.3 Selection of Study Population

Approximately 20 subjects will be enrolled in Part 1. Approximately 10 subjects with gastric cancer confirmed to carry an amplified FGFR2 gene or an overexpressed FGFR2 protein and approximately 5 to 10 subjects with cholangiocarcinoma confirmed to harbor FGFR2-fusion genes will be enrolled in Part 2. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to take the study drug.

9.3.1 Inclusion Criteria

For both Part 1 and Part 2

(1) Patients providing voluntary written consent for the participation in this study

(2) Patients who have been given a sufficient explanation of the requirements in this study and are willing and able to follow them

(3) Patients aged ≥20 years at the time of informed consent

(4) Patients with a histological or cytological diagnosis of solid tumor

(5) Patients who have not responded to standard treatment or for whom no other appropriate treatment is available

(6) Patients with adequate major organ function

1) Hemoglobin ≥9.0 g/dL (≥8.0 g/dL in Part 2)

2) Neutrophil count $\geq 1.5 \times 10^3/\mu L$

3) Platelet count $\geq 10 \times 10^4/\mu L$

4) Total bilirubin ≤1.5 times the institutional upper limit of normal (ULN)

5) AST and ALT ≤3.0 times the ULN (≤5.0 times the ULN in the presence of intrahepatic bile duct cancer or liver metastases)

6) Serum creatinine ≤1.5 times the ULN

(7) Corrected serum calcium ≤ ULN

Corrected serum calcium = serum calcium (mg/dL) + (4 − serum albumin [g/dL]) × 0.8 (to be corrected only for subjects with a serum albumin <4 g/dL)

(8) Blood phosphate ≤ ULN

(9) Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1

(10) Patients expected to survive for 3 months or longer after registration (Part 1) or the start of study treatment (Part 2)

(11) Patients with the following time intervals between prior therapy and study treatment in this study:

1) Anticancer therapy

(a) Other investigational products, antibody therapy: ≥4 weeks (≥5 half-lives are acceptable for other investigational products with a known half-life)

(b) Anticancer agents (excluding small molecule targeted drugs), surgical therapy, radiation therapy: ≥3 weeks

(c) Endocrine therapy, immunotherapy, small molecule targeted drugs: ≥2 weeks

2) Supportive therapy

(a) Blood transfusions, blood products, hematopoietic factor products including granulocyte colony-stimulating factor (G-CSF) products: ≥2 weeks

(12) Women of childbearing potential must have practiced contraception since 28 days before registration (Part 1) or 28 days before the start of study treatment (Part 2), and must agree to use medically effective contraception (eg, the subject is using intrauterine devices,* condoms with spermicide,* contraceptive implants,** or oral contraceptives;* or the subject's male partner is confirmed to have no sperm after vasectomy)[Note] throughout the study period (for 30 days after the final study drug administration). Any subject practicing contraception by abstinence must agree to practice contraception with condoms with spermicide during the study period and for 30 days after the final study drug administration. Women of childbearing potential using any oral contraceptive are to use the oral contraceptive at a fixed dose for at least

4 weeks before study drug administration and continue to use the same oral contraceptive during the study period and for 30 days after the final study drug administration.

All women will be considered to be of childbearing potential unless they are postmenopausal women (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

Note: Whether the drug/medical device has been approved or authorized in Japan (*, yes; **, no)

(13) Male participants or their female partners meeting the criteria above (when the partner is a woman with no childbearing potential or will use medically effective contraception throughout the study period and for 30 days after final study drug administration)

For Part 2 only

(14) Patients whose solid tumors have been confirmed to meet either of the following in Screening 1:

1) Patients with gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2 protein (including patients with gastroesophageal junction cancer diagnosed as adenocarcinoma)

2) Patients with cholangiocarcinoma harboring FGFR2-fusion genes

(15) Patients with a target lesion that can be evaluated according to RECIST 1.1

(16) Patients meeting both of the following criteria 1) and 2) concerning tumor sample submission:

1) Patients agreeing to submit any tumor sample collected in the past

2) Patients agreeing to submit any biopsy sample in Screening 2 (excluding those who have only a tumor lesion not amenable to biopsy for safety reasons)

9.3.2 Exclusion Criteria

(1) Patients with a brain metastasis accompanied by clinical symptoms or requiring treatment

(2) Patients with any of the following clinically significant cardiovascular disorders:

1) New York Heart Association (NYHA) Grade III or higher cardiac disease (Appendix 1)

2) Unstable angina pectoris or myocardial infarction within 6 months before enrollment in this study (Part 1) or within 6 months before the start of study treatment (Part 2)

3) QTc >480 msec (Fridericia method)

4) Arrhythmia requiring treatment

(3) Patients with serious systemic infection requiring treatment including bacterial infection and fungal infection

(4) Patients with a positive test result for human immunodeficiency virus (HIV)

(5) Patients with celomic fluid retention requiring drainage

(6) Patients with any of the following previous or concurrent corneal or retinal diseases:

1) Grade ≥2 corneal disorder

2) Active macular disease (eg, age-related macular degeneration, central serous chorioretinopathy)

(7) Patients in whom the adverse effects of prior treatment have not recovered to Grade 1 or lower, except for alopecia and Grade 2 peripheral neuropathy

(8) Patients with active malignancy within 36 months before the start of study treatment (excluding the primary disease, and carcinomas in situ such as completely treated melanoma in situ, basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and early-stage large bowel cancer)

(9) Patients with prior therapy targeting FGFR2

(10) Patients who are using any CYP3A inhibitor or inducer (Appendix 2) and will require it during study treatment (there must be a time interval of ≥7 days between the final dose of these drugs and the start of study treatment)

(11) Patients known to be intolerant to any of the ingredients of the study drug (or excipients)

(12) Patients unable to take drugs orally or with malabsorption syndrome (patients undergoing gastrectomy may be enrolled)

(13) Patients with mental or physical disorders, such as alcoholism and drug dependence, considered to preclude the participation in this study in the opinion of the investigator or subinvestigator

(14) Pregnant or breastfeeding patients (breastfeeding patients may not be enrolled even if they discontinue breastfeeding)

(15) Any others considered ineligible for the participation in this study in the opinion of the investigator or subinvestigator

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator or subinvestigator may discontinue treatment for a subject undergoing study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment but agrees to continue study-related procedures, specified assessments at the time of study treatment completion will be performed, protocol-specified information will be collected, and survival follow-up (Part 2 only) will be performed (unless the subject withdraws consent). The investigator or subinvestigator should confirm whether the subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up. If a subject withdraws consent, the date will be documented in the source documents. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study treatment should be recorded in the case report form (CRF). In addition, the date of the last dose of study treatment will be recorded in the CRF.

9.3.3.1 Discontinuation Criteria for Individual Subjects

Treatment with E7090 will be continued until any of the following discontinuation criteria is met:

(1) Subject's refusal to continue study participation or withdrawal of consent

(2) Major inclusion/exclusion criteria violation after registration (Part 1) or enrollment (Part 2)

(3) Difficulty in continuing the study due to an adverse event in the opinion of the investigator or subinvestigator

(4) Subject's pregnancy

(5) Disease progression (except when the investigator or subinvestigator considers study treatment clinically beneficial to the subject)

(6) Dose reduction to <1 mg (Part 1) or 35 mg (Part 2) required due to an adverse drug reaction

(7) Other cases where the investigator or subinvestigator considers study discontinuation appropriate

9.4 Treatment

The study drug for this study is E7090 in the following formulations, 1, 1.5, 5, 20, and 60 mg capsules (Part 1) and 35 mg tablets (Part 2), which will be administered orally once daily.

However, the dosage regimen may be modified if a different dosage regimen (eg, twice daily) is shown to be more appropriate on the basis of efficacy, safety, or PK evaluations. A change in the dosage regimen will be determined through discussion among the investigator, the sponsor, the medical expert, and the Data and Safety Monitoring Advisor.

9.4.1 Treatment Administered (Part 1)

9.4.1.1 Initial Dose

The initial dose will be 1 mg once daily. The rationale for selecting this initial dose is described in Section 7.5.1.2 “Rationale for the Initial Dose for Part 1.”

9.4.1.2 Administration Schedule

(1) Cycle 0

A single dose of E7090 at the dose for each group will be administered on Day 1 to evaluate its PK following single administration. Subjects will take a single dose of E7090 in the fasting state on waking after an at least 10-hour overnight fast. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water.

(2) Cycle 1 (28 days)

Subjects will start Cycle 1 between the 8th and 10th days after administration in Cycle 0 and take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, without eating anything for 1 hour after administration. For PK evaluation, subjects will be instructed not to take E7090 on the morning of each visit day. On Day 8 of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water.

(3) Cycle 2 and subsequent cycles (28 days each)

Subjects will take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, without eating anything for 1 hour after administration. For PK evaluation, subjects will be instructed not to take E7090 on the morning of Day 1 of each cycle.

Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.

Precautions for administration

(1) If vomiting occurs after dosing, the subject will be considered to have taken the study drug and will not be given the study drug again.

(2) It is clear that E7090 is metabolized by CYP3A4. Since it is known that grapefruit and Saint John's wort (Hypericum perforatum) inhibit or induce CYP3A, subjects will be instructed to avoid consuming grapefruit, its juice, or foods containing Saint John's wort (Hypericum perforatum).

(3) Subjects will be instructed to document whether they took the study drug and when they took it in the dosing diary.

(4) Since it is currently unknown whether E7090 may cause phototoxicity, subjects will be instructed to avoid long-term sunlight exposure.

9.4.1.3 Method of Subject's Dose Assignment

Dose assignment will be performed using a modified toxicity probability interval (mTPI) design. According to an established target DLT rate of 25% for this study, 3 toxicity probability intervals are defined as 20% to 30% (proper dosing), 0% to 20% (underdosing), and 30% to 100% (overdosing). In accordance with the rules of the mTPI design based on these intervals, each subject will be assigned a dose of E7090. The decision rules for all dose assignment will be calculated in advance on the basis of the mTPI design, presented as the "Decision Rules for Dose Assignment" below (Table 1) (see Appendix 4 for details).

Table 1 Decision Rules for Dose Assignment

		Number of subjects treated at each dose				
		2	4	6	8	10
Number of subjects with DLT	0	E	E	E	E	E
	1	D [a]	S	S	E	E
	2	D, U	D	S	S [b]	S
	3		D, U	D	S	S [b]
	4		D, U	D, U	D, U	S
	5			D, U	D, U	D, U

E = Escalate to the next higher dose, **S** = Stay at the current dose, **D** = De-escalate to the next lower dose, **U** = The current dose is unacceptably toxic (ie, Do not re-register any subject in this dose)

Target DLT rate and its corresponding interval, 25%, 20% to 30%; Cohort size, 2 subjects

Rules for the number of subjects per dose being above 10 are omitted.

a: Extra subjects may be added for the initial dose.

b: Early termination of registration may be considered.

Two subjects will be registered at each dose level. In a new dose group, the safety of the first subject should be evaluated before enrollment of the second and subsequent subjects. On the basis of the number of subjects with DLT at each dose level, assignment of the next dose will be determined according to Table 1. If DLT develops in 1 of the 2 subjects at the initial dose level, however, extra subjects may be added through discussion among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Any subject not evaluable for DLT (eg, a subject

discontinuing the study during Cycle 1 for reasons other than the development of DLT) should be replaced at the dose level for the subject. Under the mTPI design, subject registration will be closed when the DLT rate at the initial dose is much higher than the target DLT rate (25%) or when the prespecified maximum sample size (approximately 20 subjects) is reached. However, the maximum sample size will be adjusted as required. For a particular dose, subject registration may be closed early if a subsequent subject is highly likely to be allocated to the dose. The mTPI design is described in Section 9.7.4 "Other Statistical/Analytical Issues." Figure 4 shows the process for subject's dose assignment based on Table 1.

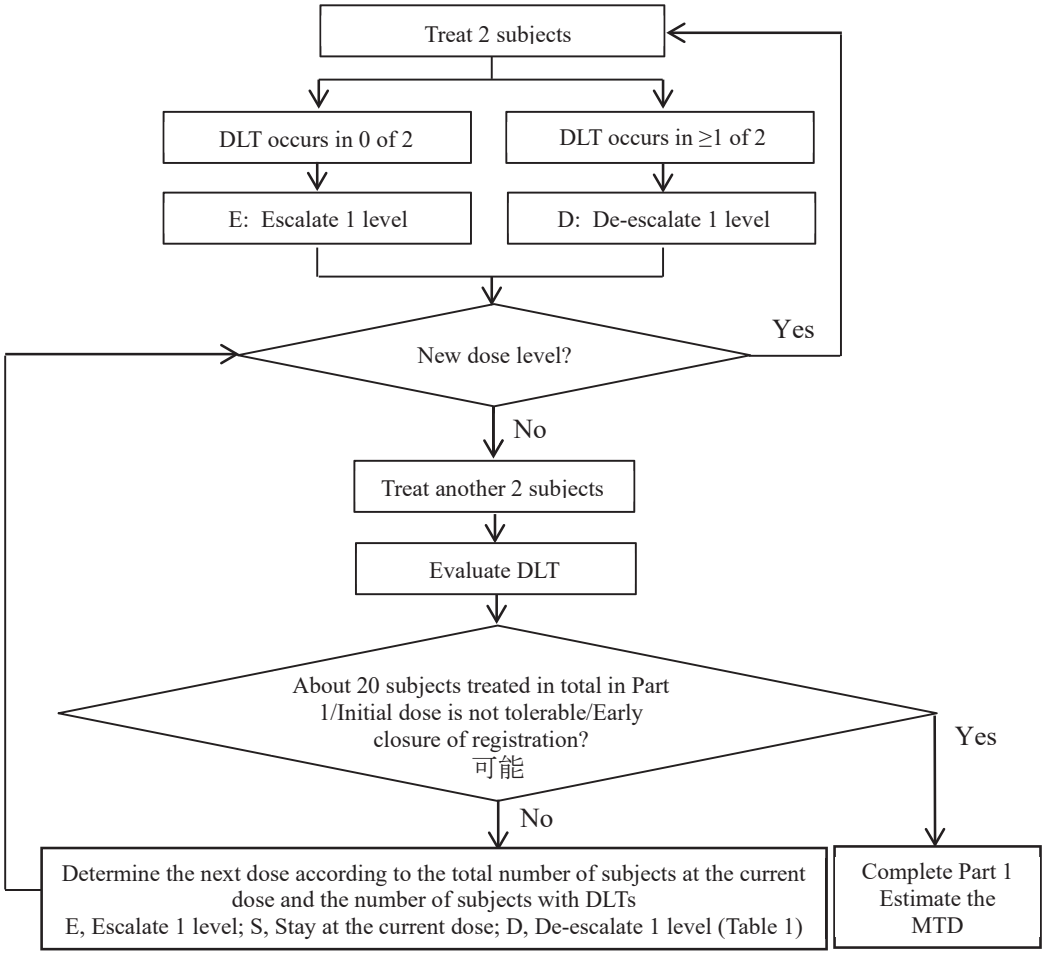


Figure 4 Process for Subject's Dose Assignment

9.4.1.4 Method of Determining the Dose for the Next Dose Group

The dose for the next dose group will be determined according to the degree of toxicities (adverse events possibly related to E7090) observed in subjects in the immediately preceding

dose group during Cycle 0 and Cycle 1. The dose for the next dose group will be escalated by 100% if all toxicities observed in the immediately preceding dose group during Cycle 0 and Cycle 1 are Grade 1 or lower. If a Grade 2 toxicity is observed in 1 subject, the next dose will be escalated by 50%. If Grade 2 toxicities are observed in 2 subjects or if Grade 3 or higher toxicities are observed in 1 or more subjects, the next dose will be escalated by 33% (Table 2).

When a dose is escalated or de-escalated by 1 dose level according to the mTPI design, if there is a higher or lower dose level evaluated previously, subjects will be added to the immediately preceding dose level evaluated previously, instead of following Table 2. In addition, an intermediate dose may be added, if necessary, on the basis of the safety or PK of the previously evaluated dose. The addition of a new dose level will be determined through discussion among the investigator, the sponsor, the medical expert, and if necessary, the Data and Safety Monitoring Advisor.

Table 2 Method of Determining the Dose for the Next Dose Group

Dose escalation for the next dose group (%)	Toxicities observed during Cycle 0 and Cycle 1 [(a)]
100	Grade ≤1 toxicity only
50	Grade 2 toxicity in 1 subject
33	Grade 2 toxicity in 2 subjects or Grade ≥3 toxicity in ≥1 subject

(a) Excluding clinically insignificant events such as laboratory abnormalities requiring no treatment

Since theoretical values calculated using the above method of determining the dose may become fractions that cannot be formulated with the capsule potencies (1, 1.5, 5, 20, and 60 mg) used in this study, the actual dose will be determined by correcting theoretical values according to the rules (1) to (3) below. Table 3 shows some examples of dose corrections.

(1) Round off the 3rd digit of a calculated theoretical value (to obtain a rounded off value).

(2) Examine whether the rounded off value can be formulated with the capsule potencies. When it is possible, use the rounded off value as the actual dose.

(3) When it is not possible, use the dose closest to and not exceeding the rounded off value among the doses that can be formulated with the capsule potencies as the actual dose.

Table 3 Examples of Dose Corrections

	Theoretical value	Round off value obtained by rounding off the 3rd digit	Actual dose
Case A	3.99 mg	4.0 mg	4.0 mg
Case B	6.65 mg	6.7 mg	6.5 mg

Case A: The value calculated by rounding off the 3rd digit of the theoretical value of 3.99 mg is 4.0 mg.
The actual dose will be 4.0 mg because it can be formulated with a 1-mg capsule.

Case B: The value calculated by rounding off the 3rd digit of the theoretical value of 6.65 mg is 6.7 mg.
It is not possible to formulate 6.7 mg with the capsules used in this study. The actual dose will be 6.5 mg because 6.5 mg (1.5-mg and 5-mg capsules) is the dose closest to and not exceeding 6.7 mg among the doses that can be formulated with the capsules used in this study.

If treatment compliance is expected to be markedly decreased due to an increased number of capsules to be taken to meet the dose required by the rules above, it is acceptable to select a lower dose through discussion between the investigator and the sponsor.

9.4.1.5 Examples of Dose Assignment and Dose Escalation

On the basis of Section 9.4.1.3 “Method of Subject’s Dose Assignment” and Section 9.4.1.4 “Method of Determining the Dose for the Next Dose Group,” a hypothetical example of dose assignment and dose escalation is shown in Figure 5.

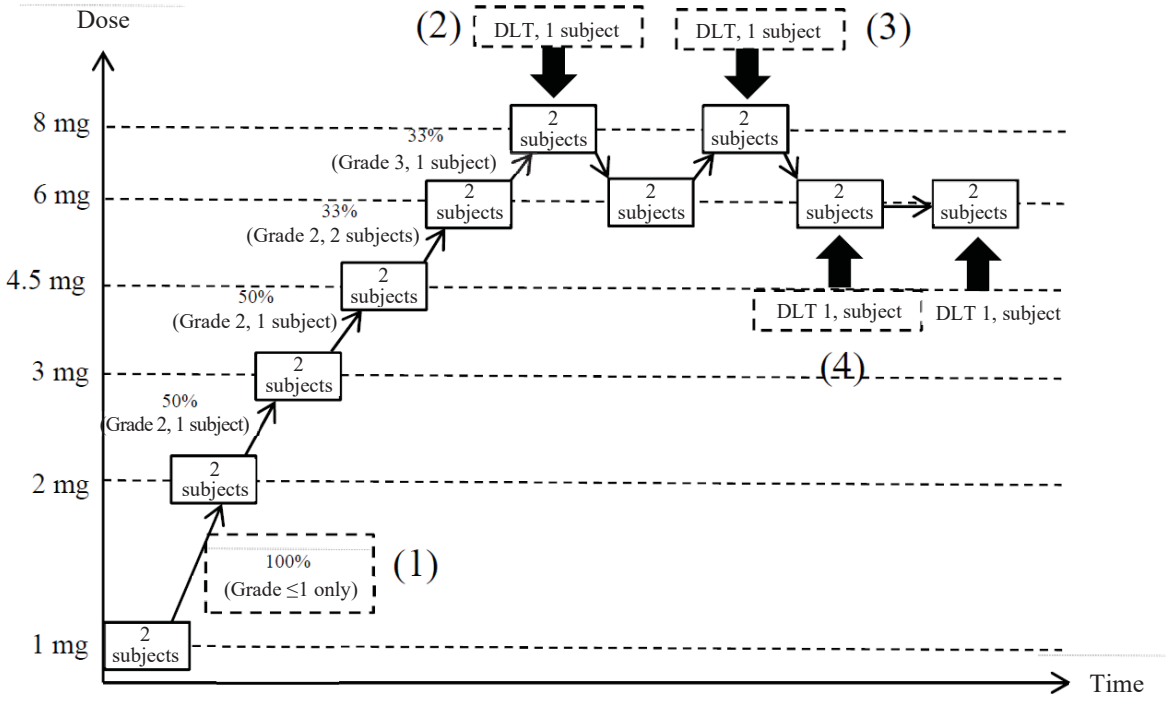


Figure 5 Example of Dose Assignment and Dose Escalation

(1) If only Grade ≤1 ADRs occur in the 2 subjects in the 1 mg group in Cycle 0 and Cycle 1, the next dose will be 100% escalated to 2 mg according to the method of determining the dose for the next dose group (Table 2). The doses after 2 mg will also be escalated according to the severity of ADRs occurring in Cycle 0 and Cycle 1, as shown in Figure 5.

(2) Any DLT in 1 of the 2 subjects in the 8 mg group would correspond to "D (de-escalation to the next lower dose)" according to the method of subject's dose assignment (Table 1). Therefore, the dose will be de-escalated to the already evaluated next lower dose of 6 mg.

(3) The 8 mg group will have a total of 4 subjects. Any DLT in 2 of the 4 subjects in the 8 mg group would correspond to "D (de-escalation to the next lower dose)" according to the subject's dose assignment (Table 1). Therefore, the dose will be de-escalated to the already evaluated next lower dose of 6 mg.

(4) Any DLT in 1 of the 6 subjects in the 6 mg group would correspond to "S (stay at current dose)" according to subject's dose assignment (Table 1). Therefore, new subjects will be added to the same dose level (6 mg group).

9.4.1.6 Determination of Transition to the Next Dose Group

Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert according to Section 9.4.1.3 "Method of Subject's Dose Assignment" and Section 9.4.1.4 "Method of Determining the Dose for the Next Dose Group." At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group (including changes in the assignment of a dose and the percentage of dose escalation).

9.4.1.7 Definition of Dose-Limiting Toxicity (DLT)

DLTs will be assessed to determine the MTD. The nature, frequency, and severity of adverse events will be evaluated, and the severity of adverse events will be graded using the CTCAE v4.03. DLTs will be defined as the following events occurring during Cycle 0 and Cycle 1 considered to be possibly related to E7090. DLTs will be determined through discussion among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary.

DLT criteria

(1) Febrile neutropenia, or Grade 4 neutropenia persisting for ≥7 days

(2) Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia requiring platelet transfusions

(3) Grade ≥3 non-hematological toxicity, except for the following:

a) Clinically insignificant laboratory abnormalities

b) Toxicity that can be controlled to Grade ≤2 by best supportive care

(4) Potentially clinically significant, new radiographic mineralization in the soft tissue, kidneys, intestines, heart, lungs, or other organs

(5) Hyperphosphatemia meeting either of the following:

a) Serum phosphate level >7 mg/dL persisting for ≥7 days despite best treatment

b) Serum phosphate level >9 mg/dL despite best treatment

(6) Treatment interruption for ≥8 days during Cycle 0 and Cycle 1 required by possibly E7090-related toxicity, except for treatment interruption for ≥8 days for reasons other than toxicity. In this case, the subject will be removed from the DLT evaluation and replaced by a new subject.

Considerations in determining the DLT

(1) If Grade 4 neutropenia or a serum phosphate level exceeding 7 mg/dL is observed, additional hematology or blood biochemistry will be performed so as to confirm the duration of the toxicity.

(2) If no additional test can be performed by Day 8 after the day when Grade 4 neutropenia or a serum phosphate level exceeding 7 mg/dL is first observed (ie, Day 1), handling of the adverse event and determination of the DLT will be determined through discussion among the investigator, sponsor, and medical advisors. In this case, advice may be obtained from the Data and Safety Monitoring Advisor as necessary.

9.4.1.8 Criteria for Dose Interruption/Reduction

(1) Cycle 1

1) If a DLT is observed
Study treatment will be interrupted immediately. When the investigator or subinvestigator considers it possible to continue the study, study treatment may be restarted at a 1-level dose reduction once the toxicity resolves to Grade 0 to 1 or baseline.

2) If no DLT is observed
Study treatment will not be interrupted until a DLT is observed. However, when the investigator or subinvestigator considers interruption clinically necessary, study treatment may be interrupted and restarted at the same dose as appropriate. No dose reduction will be permitted.

(2) Cycle 2 and subsequent cycles

If any E7090-related toxicity is observed, treatment will be interrupted or the dose will be reduced according to the criteria shown in Table 4.

Table 4 Criteria for Dose Interruption/Reduction (Part 1)

E7090-related toxicity [a]	Management	Dose after restart
Grade 1 or tolerable Grade 2 [b]	Continue study treatment	No change
Intolerable Grade 2 [b] or Grade 3	Interrupt treatment until the toxicity resolves to Grade 0 to 1 or baseline [c]	Same dose or 1-level dose reduction
Grade 4 [d]	Discontinue study treatment	NA

a: Laboratory abnormalities not requiring treatment will be excluded.
b: The tolerability of Grade 2 will be determined by the investigator or subinvestigator.
c: When the investigator or subinvestigator considers interruption clinically acceptable, study treatment may be restarted also when the toxicity resolves to tolerable Grade 2.
d: Any laboratory abnormality considered non-life-threatening will be excluded and managed as a Grade 3 event.

Up to 2 dose reductions due to toxicity will be permitted. At the first dose reduction, the dose will be de-escalated to the dose of the next lower dose group. At the second dose reduction, the dose will be de-escalated to the dose of the second lower dose group. The sponsor should be consulted for more than 2 dose reductions. The study will be discontinued if the dose needs to be reduced below 1 mg. No dose escalation should be performed in the same subject.

9.4.2 Treatment Administered (Part 2)

9.4.2.1 Starting Dose

E7090 will be administered orally at 140 mg once daily. If any E7090-related toxicity is observed, treatment will be interrupted or the dose will be reduced according to the criteria shown in 9.4.2.3

9.4.2.2 Administration Schedule

Subjects will take E7090 at least 2 hours after breakfast, and will not eat anything for 1 hour after administration. On Day 1 and Day 8 of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. For PK evaluation, subjects will be instructed not to take E7090 on the morning of Day 1 of Cycle 2 and subsequent cycles. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.

Precautions for administration

(1) If vomiting occurs after dosing, the subject will be considered to have taken the study drug and will not be given the study drug again.

(2) It is clear that E7090 is metabolized by CYP3A4. Since it is known that grapefruit and Saint John's wort (Hypericum perforatum) inhibit or induce CYP3A, subjects will be instructed to avoid consuming grapefruit, its juice, or foods containing Saint John's wort (Hypericum perforatum).

(3) Since it is currently unknown whether E7090 may cause phototoxicity, subjects will be instructed to avoid long-term sunlight exposure.

9.4.2.3 Criteria for Dose Interruption/Reduction

If any E7090-related toxicity or hyperphosphatemia is observed, the criteria in Table 5 and Table 6, respectively, should be followed. If study treatment is continued after the dose reduction, the dose will be reduced step-by-step to 105 mg, 70 mg, and then 35 mg.

To ensure subject safety, study treatment should be restarted as soon as possible if treatment is interrupted due to events not stipulated in Table 5 or Table 6.

Table 5 Criteria for Dose Interruption/Reduction (Part 2)

Toxicity [a]	Criteria	Management
Hematological	Grade 3 toxicity is observed.	Interrupt treatment until the toxicity resolves to Grade 2 or lower and restart at the same dose as that before interruption
	Grade 4 toxicity is observed.	Interrupt treatment until the toxicity resolves to Grade 2 or lower and restart at a 1-level dose reduction
Non-hematological	Intolerable Grade 2 [b] or Grade 3 toxicity is observed.	Interrupt treatment until the toxicity resolves to Grade 1 or baseline and restart at a 1-level dose reduction
	Grade 4 [c] toxicity is observed.	Discontinue treatment [d]

a: Laboratory abnormalities not requiring treatment will be excluded.
b: The tolerability of Grade 2 will be determined by the investigator or subinvestigator.
c: Any laboratory abnormality considered non-life-threatening by the investigator or subinvestigator will be managed as a Grade 3 event instead of a Grade 4 event.
d: If study treatment is considered clinically beneficial to the subject by the investigator or subinvestigator, treatment may be interrupted until the toxicity resolves to Grade 1 or baseline and restarted at a 1-level dose reduction.

Table 6 Criteria for Dose Interruption/Reduction Based on Hyperphosphatemia (Part 2)

Criteria	Management
Serum phosphate level is ≥5.5 mg/dL and ≤7.0 mg/dL.	Start treatment of hyperphosphatemia.
Despite appropriate treatment of hyperphosphatemia,[a] serum phosphate levels ≥7.1 and ≤9.0 mg/dL last for ≥2 weeks,[b] or serum phosphate levels are ≥9.1 mg/dL.	Interrupt treatment until serum phosphate levels decrease to ≤7.0 mg/dL and restart treatment at a 1-level dose reduction.

a: This refers to treatments, such as diet therapy and hyperphosphatemia drugs, considered appropriate by the investigator or subinvestigator.

b: Any subject with a serum phosphate level of ≥7.1 mg/dL should visit the study site 1 week later and undergo measurement of serum phosphate levels for the evaluation of hyperphosphatemia.

9.4.3 Estimation of the Recommended Dose for Subsequent Phase Studies

The recommended dose for subsequent phase studies will be estimated considering an overall discussion of efficacy, safety, and PK data and changes in PD markers in Part 1 and Part 2. For example, if 2 doses are selected in Part 2 and the lower dose is effective in some subjects, this lower dose may be selected as the recommended subsequent phase dose, provided that the dose appears to be useful as an anticancer agent on the basis of the balance between its efficacy and safety. In this case, safety data not only from Cycle 1 but also from Cycle 2 and subsequent cycles will be considered. The recommended subsequent phase dose will be estimated through discussion among the investigator, the sponsor, the medical expert, and if necessary, the Data and Safety Monitoring Advisor.

9.4.4 Identity of Investigational Product

The study drug will be supplied by the sponsor in labeled containers.

9.4.4.1 Chemical Name and Structural Formula of E7090

Test drug code: E7090

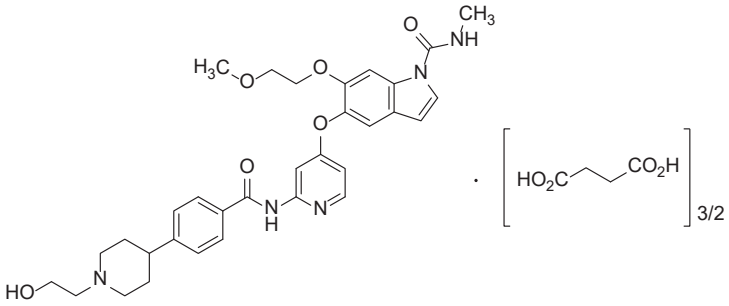
Generic name: To be determined

Chemical name: 5-({2-[({4-[1-(2-Hydroxyethyl)piperidin-4-yl]phenyl}carbonyl)amino]pyridin-4-yl}oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide butanedioate (2:3)

Molecular formula: $C_{32}H_{37}N_5O_6 \cdot 3/2C_4H_6O_4$

Molecular weight: 764.81

Structural formula:



9.4.4.2 Comparator Drug

Not applicable.

9.4.4.3 Labeling for Study Drug

The following information has to be provided. Detailed information on labeling and packaging is provided in Appendix 5.

- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.4.4 Storage Conditions

The study drug will be stored in accordance with the specified storage conditions. The study drug manager (or designee) will monitor the temperature at the storage location to ensure that the study drug is maintained within an established temperature range. The study drug manager (or designee) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be recorded by using a temperature data acquisition system, automatic recording device, or by manual means at each medical institution.

9.4.5 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to take E7090. There is no randomization in this study. The subject registration procedure is shown in Figure 6 (Part 1) and Figure 7 (Part 2).

[Part 1]

(1) The investigator, subinvestigator, or clinical study collaborator will assign a sponsor-specified subject ID number to each patient providing written informed consent for study participation and document this information in the Subject Screening Log.

(2) The investigator or subinvestigator will screen each patient and determine his/her eligibility based on the inclusion/exclusion criteria. The investigator, subinvestigator, or clinical study collaborator will document the result of eligibility determination in the Subject Screening Log.

(3) On the basis of the screening result and patient characteristics of each patient determined to be eligible, the investigator, subinvestigator, or clinical study collaborator will enter necessary information in the Subject Registration Form (Appendix 6) and send the form via fax to the Subject Registration Center.

(4) The Subject Registration Center will check the eligibility of each patient on the basis of the Subject Registration Form sent by fax. When determining a patient to be ineligible, the Subject Registration Center will enter the reason for ineligibility in the Notice of Ineligibility and send the notice by fax to the investigator, subinvestigator, or clinical study collaborator. The investigator or subinvestigator will confirm the reason for ineligibility and will not administer the study drug to the patient.

(5) If the Subject Registration Form has any defect (eg, omissions), the Subject Registration Center will inquire the defect of the investigator, subinvestigator, or clinical study collaborator.

(6) When determining a patient to be eligible, the Subject Registration Center will enter his/her subject ID number, date of confirmation of registration, and dose to be administered in the Registration Confirmation Form and send the form by fax to the investigator, subinvestigator, or clinical study collaborator, and the sponsor (subject registration).

(7) The investigator, subinvestigator, or clinical study collaborator will confirm the information entered in the Registration Confirmation Form.

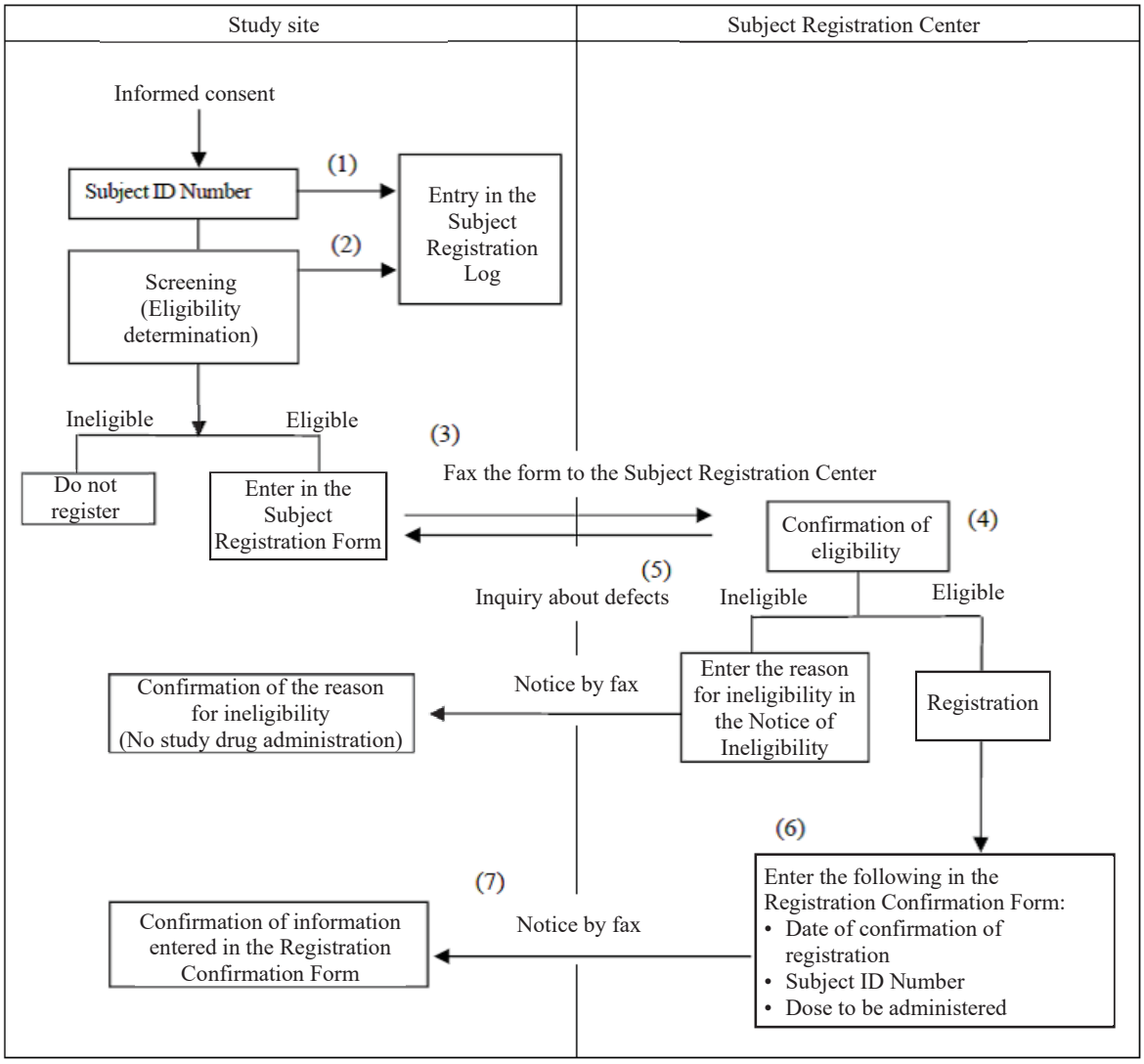


Figure 6 Subject Registration Procedure (Part 1)

[Part 2]

(1) The investigator, subinvestigator, or clinical study collaborator will assign a sponsor-specified subject ID number to each patient providing written informed consent for Screening 1 and document this information in the Subject Screening Log.

(2) For a patient known to have FGF/FGFR genetic abnormality, the investigator, subinvestigator, or clinical study collaborator will submit necessary documents about the genetic abnormality to the sponsor. The sponsor will check the documents about the genetic abnormality and notify the investigator, subinvestigator, or clinical study collaborator of the patient's eligibility/ineligibility by e-mail or fax.

(3) If it is not known whether a gastric cancer patient has a FGF/FGFR genetic abnormality, the investigator, subinvestigator, or clinical study collaborator will submit an archived sample to the central laboratory. The central laboratory will report the result of genetic abnormality test to the sponsor and the study site. The patient will be determined to be eligible for Screening 1 if the test result is positive and ineligible for Screening 1 if the test result is negative.

(4) The investigator, subinvestigator, or clinical study collaborator will enter the result of the patient's eligibility for Screening 1 in the Subject Screening Log, and patients who are determined to be eligible will go to the procedure for Screening 2.

(5) The investigator or subinvestigator will screen the patient providing written informed consent for Screening 2 and determine his/her eligibility according to the inclusion/exclusion criteria. The investigator, subinvestigator, or clinical study collaborator will document the result of eligibility determination in the Subject Screening Log.

(6) After the investigator and the subinvestigator determine the eligibility of the patient through the screening test, the investigator, subinvestigator, or clinical study collaborator will promptly document the eligibility/ineligibility determined by the screening test, the planned start date of study treatment (when the patient is eligible), and the planned date of baseline assessment (when the baseline assessment is performed separately) in the Subject Eligibility Confirmation Form (Appendix 6: Part 2) and notify the sponsor by e-mail or fax.

(7) The investigator or subinvestigator will check the result of the baseline assessment against the inclusion/exclusion criteria to determine the eligibility of the patient again, and document the result of eligibility determination in the Subject Screening Log. After confirmation of his/her eligibility, the patient will start study treatment.

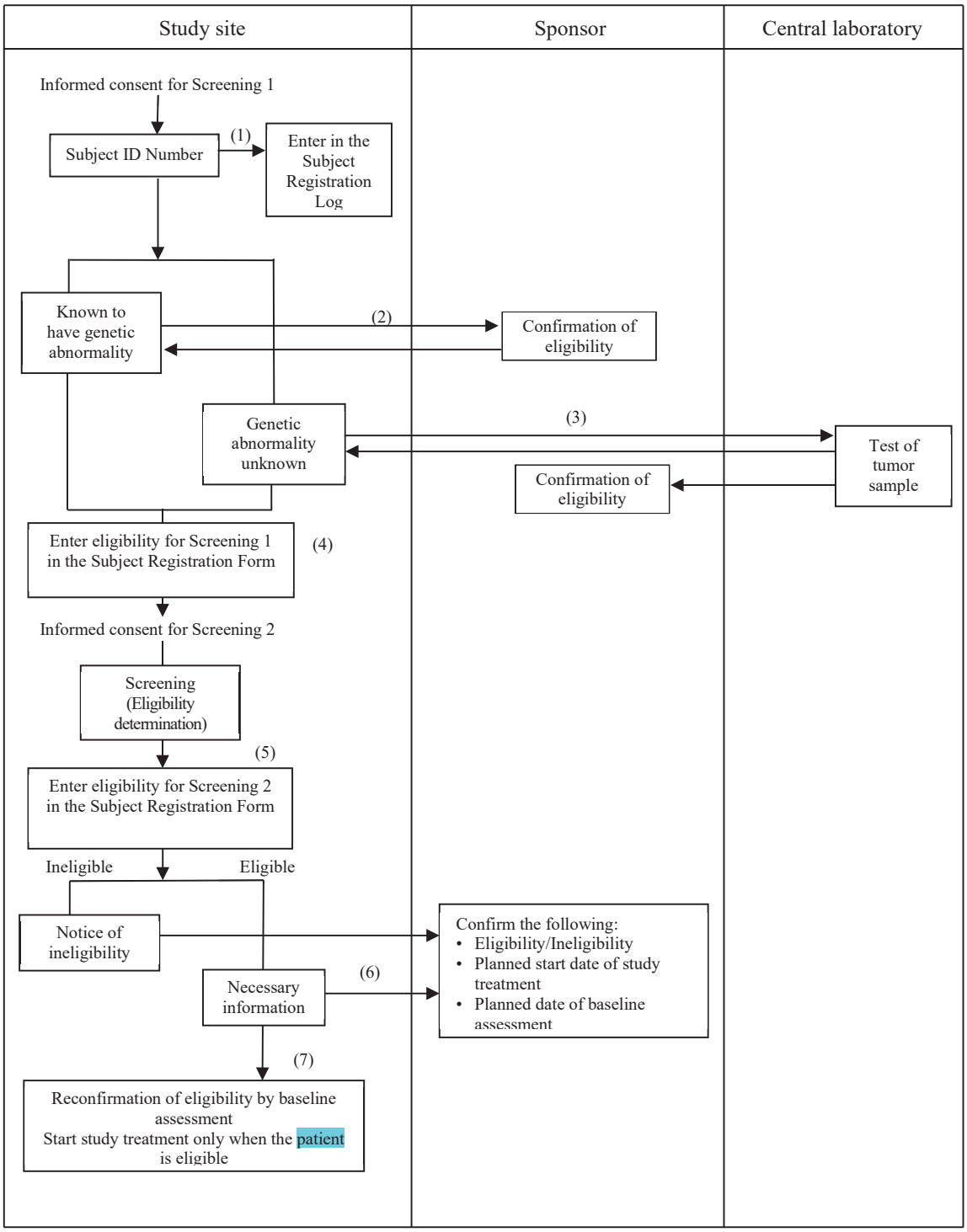


Figure 7 Subject Enrollment Procedure (Part 2)

9.4.6 Selection of Doses in the Study

The appropriateness of selection of the doses for Part 1 and Part 2 of this study is justified in Section 7.5.1 “Rationale for the Study Design,” Section 7.5.1.2 “Rationale for the Initial Dose for Part 1,” and Section 7.5.1.3 “Rationale for the Starting Dose for Part 2.”

9.4.7 Selection and Timing of Dose for Each Subject

The selection and timing of dose for each subject is described in Section 9.4 “Treatment.”

9.4.8 Blinding

The study will not be blinded.

9.4.9 Prior and Concomitant Therapy

All concomitant therapies used after the time of informed consent (after the time of informed consent for Screening 2 in Part 2) until the date of final observation will be recorded in the CRF. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded, except for medications used for non-treatment purposes (eg, contrast agents, test agents, antiseptic agents, fluids used for drug preparations or flushes).

9.4.9.1 Drug-Drug Interactions

CYP3A4 has been identified as the major enzyme that metabolizes E7090 in non-clinical studies. See Appendix 2 for CYP3A inhibitors or inducers.

9.4.9.2 Prohibited Concomitant Therapies and Drugs

The following concomitant therapies and drugs will be prohibited.

(1) Cycle 0 and Cycle 1 (Part 1 only)

1) Treatments, changes in dosage, and changes in drugs to prevent DLT occurrence

(2) From the time of registration (Part 1) or the start of study treatment (Part 2) to the time of the discontinuation of study treatment

1) Treatments for malignant tumors other than E7090 (eg, surgical therapy, chemotherapy, endocrine therapy, palliative radiotherapy, or immunotherapy) except for drugs for bone lesions (eg, bisphosphonates, anti-RANKL monoclonal antibodies) that have been used since before the registration in this study (Part 1) or the start of study treatment (Part 2)

2) Drugs that inhibit or induce CYP3A (see Appendix 2 for relevant drugs)

3) Other investigational products

9.4.10 Treatment Compliance

The investigator, subinvestigator, or clinical study collaborator will check and keep records of treatment compliance for each subject during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.11 Drug Supplies and Accountability

The study drug manager or designee will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) by following the sponsor's instructions for handling of study drugs and adhering to GCP guidelines as well as other requirements.

Under no circumstances will the investigator or subinvestigator allow the study drug to be used for purposes other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The study drug manager or designee must maintain an accurate and timely record of the following: the number of study drugs received, the number of study drugs dispensed to subjects, the number of study drugs dispensed to subjects but not used (unused study drug-1), the number of study drugs shipped to the medical institution but not dispensed to subjects (unused study drug-2), and the number of study drugs returned to the sponsor (sum of unused study drug-1 and unused study drug-2); where applicable, destruction of reconciled study drugs at the medical institution should also be recorded. These records include, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drug dispensing/return reconciliation log for each subject, (c) study drug accountability log, (d) documentation of return of study drugs, and (e) logs of any destruction of study drugs that occurs at the medical institution.

The study drugs and inventory records must be made available, upon request, for inspection by the study monitor or a representative of the health authority during site visits. Upon completion of drug accountability and after the receipt/return documentation of the study drugs have been submitted to the sponsor, the study drug manager or designee will return all unused study drugs (including empty boxes) to the sponsor. Such study drugs will be collected by the monitor directly and returned to the sponsor's designated depot.

Study drug accountability will be reviewed by the monitor over the duration of the study such as during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demographic Assessments

The investigator, subinvestigator, or clinical study collaborator will assess each patient providing written informed consent for necessary information to confirm the inclusion and exclusion criteria, and document this information in the Subject Registration Form (Part 1)

and the Subject Eligibility Confirmation Form (Part 2). The investigator, subinvestigator, or clinical study collaborator will also assess each patient providing written informed consent for the following subject demography information, and document the information in the CRF. For any information already assessed during the confirmation of the inclusion and exclusion criteria, the investigator, subinvestigator, or clinical study collaborator may enter the data entered in the Subject Registration Form (Part 1) and the Subject Eligibility Confirmation Form (Part 2) in the CRF, instead of assessing such information again.

(1) Subject ID Number

(2) Date of signed written informed consent

(3) Sex

(4) Ethnicity

(5) Race

(6) Date of birth

9.5.1.2 Pretreatment Assessments

9.5.1.2.1 Medical History, Current Medical Conditions, Prior Treatment

Medical history (including surgical history) and current medical conditions will be assessed at the screening visit. All medical history considered by the investigator or subinvestigator to affect the safety, efficacy, and PK evaluations and all current medical conditions confirmed at the screening visit will be recorded in the CRF. For prior treatment, the following information will be assessed:

(1) Initial diagnosis (site of the primary lesion, date of diagnosis, method of diagnosis [histology/cytology], histologic type, staging classification specific to each carcinoma, and corresponding stage [eg, TNM classification])

(2) Prior treatment for the primary disease

    1) Surgical therapy (date of surgery, site of surgery)

    2) Radiation therapy (site of radiation, date of last radiation)

    3) Anticancer therapy (drug name, best overall response [BOR] for each regimen, total dose when necessary, dates of the first and last doses)

    4) Other therapies (therapy name, dates of the first and last procedures)

9.5.1.2.2 Other Pretreatment Assessments Specific to the Study or Target Disease

(1) For subjects with tumors harboring FGF/FGFR genetic abnormality (Part 1) and all subjects entering Screening 2 (Part 2), the following information will be recorded in the CRF:

1) Type of FGF/FGFR genetic abnormality (translocation, point mutation, amplification, other)

2) Diagnostic method for FGF/FGFR genetic abnormality (FISH, immunostaining, RT-PCR, NGS, other)

3) Site of the sample tested for FGF/FGFR genetic abnormality and date of the sample collected

4) Date of FGF/FGFR genetic abnormality test

5) Status of FGF/FGFR protein expression

(2) Use of contact lenses at the screening visit will be assessed and documented in the CRF.

9.5.1.3 Efficacy Assessments

Tumor evaluation in this study will be performed by the treating physician according to RECIST 1.1 (Appendix 7). Antitumor effects will be assessed on the basis of images taken under the same conditions as those at the screening visit with the use of appropriate equipment such as CT or MRI. Assessments at the screening visit will include overall tumor site assessment (presence or absence of target lesions [tumor lesions and lymph node lesions], presence or absence of non-target lesions), target lesion assessment (site, tumor diameter, assessment date, measurement method), and non-target lesion assessment (site, assessment, assessment date, diagnostic method). Results of these assessments will be documented in the CRF. After the screening visit, target lesions, non-target lesions, new lesions (presence or absence of lesions, site, date of development, diagnostic method), and overall response will be assessed, and results of these assessments will be documented in the CRF.

Third-party assessments of antitumor effects or safety may be performed as necessary. In such cases, the investigator, subinvestigator, or clinical study collaborator will provide image data via electronic media to the sponsor if requested.

9.5.1.3.1 Assessment of Tumor Lesions

Chest X-rays will not be used to assess target lesions.

Assessment methods for each site are as follows:

- Head: CT or MRI

- Chest: CT
- Abdomen: CT or MRI
- Pelvis: CT or MRI
- Other sites: CT, MRI, or other method
- Visible or palpable clinical lesions: Clinical evaluation

(1) CT or MRI

CT or MRI will be performed with contrast, except in subjects not amenable to oral/intravenous contrast agents (due to allergy or renal dysfunction). In subjects not amenable to contrast agents, a plain CT scan without contrast will be performed. In subjects not amenable to intravenous contrast agents, CT with oral contrast may be considered, and for the abdominal or pelvic region, MRI with intravenous gadolinium may be considered.

Low-dose CT images from positron emission tomography with CT (PET/CT), CT images for attenuation correction, or ultrasonography will not be used to assess tumors. When a skin lesion is recorded in a color digital photo, a millimeter scale ruler and a label describing the subject ID number and the date should be included in the photo. Measurements should be performed with calipers.

1) At screening

- The head, chest, abdomen, pelvis, and sites of known or suspected lesions will be assessed.
- Any data obtained before informed consent, as long as obtained within 28 days before the start of study treatment, may be used.

2) In Cycle 2 and subsequent cycles

- The chest, abdomen, pelvis, tumor sites present at the time of screening, and any other sites of newly suspected lesions will be assessed.

(2) Clinical evaluation

It is recommended that any lesion allowing visual inspection should be assessed using a color photo that contains a ruler to allow assessment of its size. For any palpable lesion, its size will be assessed by clinical examination and the results will be recorded in source documents.

Tumor lesion assessment will be performed at the time of screening, every 8 weeks starting from Day 1 of Cycle 1 (Day 1 of each odd-numbered cycle [±7 days]), and at the time of discontinuation (+7 days). Assessments may be added as clinically required. Any data obtained within 28 days before discontinuation may be used as data at the time of discontinuation.

9.5.1.3.2 Tumor Markers

The investigator or subinvestigator will identify any tumor markers considered to be appropriate for the primary disease from among CEA, CA19-9, CA72-4, STN, and other tumor markers. Examples of tumor markers are listed in Table 7. The investigator or subinvestigator will assess identified tumor markers according to the schedules in Table 13 and Table 14 and document assessment results in the CRF. Tumor marker assessment will be performed at the time of screening, every 8 weeks starting from Day 1 of Cycle 1 (Day 1 of each odd-numbered cycle [±7 days]), and at the time of discontinuation (+7 days). Assessments may be added as clinically required. Any data obtained within 28 days before discontinuation may be used as data at the time of discontinuation.

Table 7 Examples of Tumor Markers

Tumor	Serum tumor markers [a]
Breast cancer	CEA, CA15-3, ST-439
Large bowel cancer, gastric cancer	CEA
Pancreas cancer	CA19-9
Prostate cancer	PSA, PAP
Hepatocellular carcinoma	AFP, PIVKA-II
Ovarian cancer	CA125
Testicular cancer	AFP, hCG, LDH
Trophoblastic tumor	hCG
Lung cancer (small cell)	NSE, ProGRP
Neuroblastoma	Vanillylmandelic acid (VMA), catecholamine, neuron-specific enolase (NSE)
Thyroid cancer	Thyroglobulin, calcitonin
Carcinoid tumor	5-HIAA

a: Recommended serum tumor markers. Not all markers are listed. If there is any other marker known to be useful in individual subjects, it is desirable to use the marker.

9.5.1.3.3 Survival Follow-up

Subjects will be followed for survival every 12 weeks (±2 weeks) from the time of study treatment discontinuation. Follow-up is to be continued until the confirmation of death. For any antitumor therapy, which is known as of the assessment to be provided for the subject after completion of study treatment, its start date and end date will be recorded. Survival follow-up will be terminated 2 years after the last subject's registration (Part 2).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

9.5.1.4.1 Pharmacokinetic Assessments

(1) Plasma concentration measurement

Blood samples will be collected at the time points shown in Table 8 (Part 1) and

Table 9 (Part 2), and the plasma concentrations of E7090 and its active metabolite, E7090-M2, will be determined using a validated LC-MS/MS method. In Part 1, remaining samples from the unchanged E7090 measurement will be used for exploratory metabolite analyses. See Appendix 8 for a description of collection, handling, and shipping procedures of the samples. Regarding sampling time points, the actual time of blood sampling will be documented in the CRF.

Table 8 Blood Sampling Schedule for PK Evaluation (Part 1)

Cycle	Sampling day	Sampling time point	Allowable sampling time interval	Blood sampling volume
Cycle 0	Day 1	Predose	Within −60 minutes	2 mL at each time point
		30 minutes postdose	Within ±10 minutes	
		1 hour postdose	Within ±10 minutes	
		2 hours postdose	Within ±10 minutes	
		3 hours postdose	Within ±10 minutes	
		5 hours postdose	Within ±10 minutes	
		10 hours postdose	Within ±30 minutes	
	Day 2	24 hours postdose	Within ±60 minutes	
	Day 3	48 hours postdose	Within ±60 minutes	
	Day 4	72 hours postdose	Within ±60 minutes	
Cycle 1	Day 1	Predose	Within −60 minutes	
	Day 3	Predose	Within −60 minutes	
	Day 8	Predose	Within −60 minutes	
		30 minutes postdose	Within ±10 minutes	
		1 hour postdose	Within ±10 minutes	
		2 hours postdose	Within ±10 minutes	
		3 hours postdose	Within ±10 minutes	
		5 hours postdose	Within ±10 minutes	
		10 hours postdose	Within ±30 minutes	
	Day 9	Predose	Within −60 minutes	
	Day 15	Predose	Within −60 minutes	
	Day 22	Predose	Within −60 minutes	

Cycle 2 and subsequent cycles	Day 1	Predose	Within −60 minutes	

Table 9 Blood Sampling Schedule for PK Evaluation (Part 2)

Cycle	Sampling day	Sampling time point	Allowable sampling time interval	Blood sampling volume
Cycle 1	Day 1	Predose	Within −60 minutes	2 mL at each time point
		30 minutes postdose	Within ±10 minutes	
		1 hour postdose	Within ±10 minutes	
		2 hours postdose	Within ±10 minutes	
		3 hours postdose	Within ±10 minutes	
		5 hours postdose	Within ±10 minutes	
		10 hours postdose	Within ±30 minutes	
		24 hours postdose (Predose on Day 2)	Within −60 minutes	
	Day 8	Predose	Within −60 minutes	
		30 minutes postdose	Within ±10 minutes	
		1 hour postdose	Within ±10 minutes	
		2 hours postdose	Within ±10 minutes	
		3 hours postdose	Within ±10 minutes	
		5 hours postdose	Within ±10 minutes	
		10 hours postdose	Within ±30 minutes	
		24 hours postdose (Predose on Day 9)	Within −60 minutes	
	Day 15	Predose	Within −60 minutes	
Cycle 2 and subsequent cycles	Day 1	Predose	Within −60 minutes	

(2) Urinary concentration measurement

Urinary PK measurements will be performed in Part 1 only. On Day 8 of Cycle 1 in Part 1, a 24-hour urine collection will be performed to determine the urinary concentration of unchanged E7090. In addition, remaining samples will be used for exploratory metabolite analyses. The start time of urine collection (at study drug administration), end time of urine collection, urine volume, and amount of ethanol added will be recorded in the CRF. See Appendix 8 for a description of collection, handling, and shipping procedures of the samples.

9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood, archived tumor, and biopsied tumor samples will be obtained for PD and PGx assessments. The following measurements may be increased as necessary, depending on new findings or progress of science. These measurements will be obtained to understand the

pharmacological response of E7090, identify biomarkers useful in predicting treatment effects, and develop diagnostic agents.

[Part 1]

(1) In blood samples

Blood samples will be collected according to the procedures and methods shown in Table 10 to determine blood biomarkers. For sampling time points, the actual time of blood sampling will be recorded in the CRF. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples.

The following measurements will be determined:

1) FGF23

2) 1,25-(OH)2-Vitamin D

3) CCI

4) Angiogenesis markers (eg, VEGF, FGF)

5) Circulating tumor DNA

Table 10 Blood Sampling Schedule for PD and PGx Evaluations (Part 1)

Cycle	Sampling day	Sampling time point	Allowable sampling time interval	Sampling volume	Measurement
At baseline	Within 4 days after start of treatment			15 mL	5)
Cycle 0	Day 1	Predose	Within −60 minutes	7 mL	1) to 4)
		3 hours postdose	Within ±10 minutes	7 mL	
		5 hours postdose	Within ±10 minutes	7 mL	
		10 hours postdose	Within ±30 minutes	7 mL	
	Day 2	24 hours postdose	Within ±60 minutes	7 mL	
	Day 3	48 hours postdose	Within ±60 minutes	7 mL	
	Day 4	72 hours postdose	Within ±60 minutes	7 mL	
Cycle 1	Day 1	Predose	Within −60 minutes	7 mL	
	Day 3	Predose	Within −60 minutes	7 mL	
	Day 8	Predose	Within −60 minutes	7 mL	
	Day 15	Predose	Within −60 minutes	7 mL	

Odd-numbered cycles (Cycle 3 and subsequent cycles)	Day 1	Predose	Within −60 minutes	10 mL	5)

(2) In archived tumor samples

If available, archived tumor samples will be evaluated for FGFR protein expression by immunohistochemical staining. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples. If known, the date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF.

(3) In biopsied tumor samples

Tumor biopsies will be collected at screening and on Day 15 of Cycle 1 to determine protein expression of the following factors by immunohistochemical staining. Tumor biopsies should be taken from the same organ whenever possible. The actual time of sample collection will be recorded in the CRF. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples. The date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF.

(a) FGFR

(b) Phosphorylated FGFR

(c) ERK

(d) Phosphorylated ERK

[Part 2]

(1) In blood samples

Blood samples will be collected according to the procedures and methods shown in Table 11 to determine blood biomarkers. For sampling time points, the actual time of blood sampling will be recorded in the CRF. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples.

The following measurements will be determined:

1) FGF23

2) 1,25-(OH)2-Vitamin D

3) CCI [redacted]

4) Angiogenesis markers (eg, VEGF, FGF)

5) Circulating tumor DNA

Table 11 Blood Sampling Schedule for PD and PGx Evaluations (Part 2)

Cycle	Sampling day	Sampling time point	Allowable sampling time interval	Sampling volume	Measurement
At baseline	Within 4 days after start of treatment			15 mL	5)
Cycle 1	Day 1	Predose	Within −60 minutes	7 mL	1) to 4)
	Day 8	Predose	Within −60 minutes	7 mL	
	Day 15	Predose	Within −60 minutes	7 mL	
Odd-numbered cycles (Cycle 3 and subsequent cycles)	Day 1	Predose	Within −60 minutes	10 mL	5)

(2) In archived tumor samples

If any sample collected in the past is available, an archived tumor sample should be submitted (mandatory). If known, the date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF.

(3) In biopsied tumor samples

Except for subjects who have only a tumor lesion not amenable to biopsy for safety reasons, samples obtained from the biopsy performed in Screening 2 must be submitted (mandatory). Any reason for infeasible biopsy will be recorded in source documents. The date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF. In addition, a biopsy tumor sample will be collected on Day 15 of Cycle 1 (optional). Tumor biopsies should be taken from the same organ whenever possible. The actual time of sample collection will be recorded in the CRF. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples. The date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF.

For (2) and (3) above, immunohistochemical staining or comprehensive genomic analysis will be performed to evaluate their correlation with the efficacy of E7090. In addition, samples will be archived for the development of diagnostic agents (see Appendix 9 for details).

9.5.1.5 Safety Assessments

Safety assessments will consist of the following:

All adverse events including serious and nonserious events (changes in CTCAE v4.03 grades [for both increasing and decreasing severity]), DLTs (Part 1 only), laboratory tests

(hematology, blood chemistry, and urinalysis), vital signs, ECGs, ECOG-PS, ophthalmological examinations, and physical examinations.

9.5.1.5.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E7090.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (For Part 2, events observed after informed consent for Screening 2 will be assessed)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in a change in treatment or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

It is the responsibility of the investigator and subinvestigator to review all laboratory findings in all subjects and determine if they constitute an AE.

The investigator or subinvestigator should determine whether a laboratory result, abnormal or not, should be classified as an AE if it:

- Leads to discontinuation of study treatment
- Leads to withholding (interruption) of study treatment until some test result becomes clear
- Requires a medical intervention (eg, potassium supplement for hypokalemia)
- Leads to any out-of-range laboratory value (the investigator or subinvestigator will determine whether the laboratory result meets any of the definitions of AEs considering the subject’s current or previous medical condition)
- Is considered by the investigator or subinvestigator to be an AE (excluding values related to lymphocyte, albumin, cholesterol, and glucose) because of its clinically significant

changes: worsening by ≥2 grades of CTCAE v 4.03 compared to baseline and further worsening by ≥2 grades

All AEs observed during the study (for Part 2, after informed consent for Screening 2) will be recorded in the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the informed consent form (for Part 2, after informed consent for Screening 2) through the last visit (30 days after the last dose of study treatment). If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, the final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent.

With regard to serious adverse events (SAEs), events occurring by the time of final observation should be collected. For a screening failure due to the development of an AE, the name and seriousness of the AE will be recorded in the CRF.

Any laboratory abnormality considered to constitute an AE should be recorded in the CRF. Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator or subinvestigator considers as an AE should be recorded in the CRF.

Disease progression will not be treated as an AE. If any unfavorable changes associated with disease progression (eg, worsening pain, pleural effusion) are observed, these changes will be recorded as AEs.

All AEs must be followed until the last visit (30 days after the last dose of study treatment) or resolution, whichever comes first. If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, the final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent. All SAEs must be followed until resolution or, if resolution is unlikely, until stabilization, although follow-up may be terminated on the basis of the medical judgment of the investigator or subinvestigator.

Every effort must be made by the investigator or subinvestigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

The severity of AEs will be graded on a 5-point scale according to CTCAE v4.03 and recorded in the CRF (changes in CTCAE v4.03 grades [for both increasing and decreasing severity]).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

Not related: A causal relationship between the study drug and the AE is not a reasonable possibility.

Related: A causal relationship between the study drug and the AE is a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error (see Section 9.5.4.2 and Section 9.5.4.3). These events associated with special situations are to be captured using the SAE procedures but are to be considered as

SAEs only if they meet one of the above criteria. All AEs associated with special situations (excluding normal births) are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 Laboratory Measurements

Clinical laboratory tests to be performed, including hematology, blood chemistry, and urinalysis, are summarized in Table 12. The Schedule of Procedures/Assessments (Table 13 and Table 14) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 12 Clinical Laboratory Tests

Category	Parameters
Hematology	RBC count, hemoglobin, hematocrit, platelets, WBC count, and WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood chemistry	
Liver function tests	ALP, AST, ALT, γ-GTP, total bilirubin, direct bilirubin
Renal function tests	BUN, creatinine
Other	Blood glucose, albumin, cholesterol, triglycerides, phosphorus, LDH, total protein, uric acid, lipase, amylase, Na, K, Cl, Ca, CRP
Blood coagulation tests	Activated partial thromboplastin time (aPTT)
Urinalysis	pH, protein, glucose, ketone bodies, occult blood
Virus tests (screening only)	HBs antigen, HCV antibodies, HIV antibodies

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded in the CRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.5.2), the investigator must fax or email the SAE report to the sponsor using the SAE form (see Section 9.5.4.1 “Reporting of Serious Adverse Events”). In addition, test results for any AEs determined through laboratory tests performed during nonprotocol-required visits will also be recorded in the CRF.

[Monitoring of serum phosphorus levels]

Nonclinical toxicity studies have reported mineralization associated with hyperphosphatemia, which are considered attributable to the inhibition of FGFR kinase, the pharmacological action of E7090. Given that similar events have also been observed in clinical studies of similar drugs, attention needs to be paid to such toxicities in this study. If high serum phosphorus levels are observed, the criteria for dose interruption/reduction shown in Table 6 should be followed. In addition, any necessary test (eg, X-ray) should be performed if any clinical symptom suggestive of mineralization is observed.

9.5.1.5.4 Vital Signs, Weight, and Height Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [°C], weight [kg], height [cm] [screening only]) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14) by a validated method. Blood pressure and pulse will be measured with the subject at rest and sitting.

9.5.1.5.5 Physical Examinations

Physical examinations will be performed at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Physical examinations will include the head, eyes, ears, nose, throat, neck, chest (include the heart and lungs), abdomen, four limbs, skin, and a neurological examination. Results of physical examinations will be documented in the medical records at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded in the CRF.

9.5.1.5.6 Electrocardiograms

Electrocardiograms will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Standardized 12-lead ECG recordings will be used. Electrocardiogram parameters (heart rate, PR interval, QRS interval, QRS axis, QT interval, RR interval) will be recorded in the CRF. In addition, ECG findings (normal, abnormal not clinically significant, abnormal clinically significant) will also be recorded.

An ECG abnormality may meet the criteria of an AE as described in this protocol (Section 9.5.1.5.1). In these instances, the AE corresponding to the ECG abnormality will be recorded in the CRF.

For ECG abnormalities meeting the criteria of an SAE (see Section 9.5.1.5.2), the investigator must fax or email the SAE report (including the ECG report) to the sponsor using SAE form (see Section 9.5.4.1 “Reporting of Serious Adverse Events”).

9.5.1.5.7 Ophthalmological Examinations

Ophthalmological examinations will be performed at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Examinations in Part 1 will include visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and anterior segment optical coherence tomography (OCT) to evaluate the corneal epithelium. Corneal epithelial thickness will be measured by anterior segment OCT and recorded in the CRF. Examinations in Part 2 will include visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and posterior segment OCT to evaluate the retina.

9.5.1.5.8 ECOG-PS

ECOG-PS will be assessed according to Appendix 10 at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14).

9.5.1.5.9 Pregnancy Test

Serum or urine hCG tests will be performed in females of childbearing potential at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14).

9.5.1.5.10 Transcutaneous Arterial Oxygen Saturation Measurement

Arterial oxygen saturation will be measured with a pulse oximeter at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14).

9.5.1.6 Compliance with Study Treatment

The investigator, subinvestigator, or clinical study collaborator will instruct subjects on the proper administration of the study drug. Compliance with study treatment (date of administration, dose administered, time of administration [only on the previous day and the day of PK evaluation shown in Table 8], reason for any change) will be assessed and recorded in the CRF.

9.5.1.7 Concomitant Drugs and Therapies

The investigator, subinvestigator, or clinical study collaborator will instruct subjects to comply with the stipulations on prohibited concomitant treatments in Section 9.4.9.2 “Prohibited Concomitant Therapies and Drugs,” and investigate concomitant treatment according to the following.

(1) Concomitant drugs

At each visit, all drugs used from the time of written informed consent (for Part 2, informed consent for Screening 2) through the end of the last observation period will be investigated, and the information listed below will be recorded in the CRF. If the subject is treated at another department or hospital, the treating physician will be interviewed if necessary. If it is necessary to start a new anticancer agent immediately due to deterioration of the subject’s

condition, final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent.

Drug name, route of administration, reason for use, start date of treatment, and end date of treatment (date when the treatment is completed or “continued treatment after the last visit”)

For drugs used to treat hyperphosphatemia or Grade 3 ADRs, the dosage regimen as well as the information above will be recorded in the CRF.

(2) Concomitant therapies

At each visit, all therapies provided from the time of written informed consent (for Part 2, informed consent for Screening 2) through the end of the last observation period will be investigated, and the information listed below will be recorded in the CRF. If the subject is treated at another department or hospital, the treating physician will be interviewed if necessary.

Therapy name, reason for therapy, start date of therapy, and end date of therapy (date when the therapy is completed or “continued therapy after the last visit”)

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments in Part 1

Schedule of procedures/assessments in Part 1 and Part 2 is shown in Table 13 and Table 14, respectively.

Table 13 Schedule of Procedures/Assessments in Part 1

Phase	Pretreatment				Treatment											Follow-up	
Period	IC	Screening	Registration	Baseline [d]	Cycle 0		Cycle 1					Cycle 2 and subsequent cycles				Discontinuation	Final observation [v]
Day		Within 14 days predose		Within 4 days predose	1	2	1 [i]	3	8 (±1)	15 (±1)	22 (±1)	1 (±3) [a]	8 [o] (±3)	15 (±3)	22 [o] (±3)	(+7)	30 days after last dose (+7)
Informed consent	X																
Registration			X														
Inclusion/exclusion criteria		X															
Subject demographics Prior treatment Previous/current condition		X															
Height, viral test		X [b]															
Weight		X		X			X [j]		X	X	X	X		X		X [t]	
Vital signs Transcutaneous arterial oxygen saturation		X		X	X [e]	X [f]	X [j]		X	X	X	X	X	X	X	X [t]	X
Physical examination		X		X			X [j]		X	X	X	X	X	X	X	X [t]	X
ECOG-PS		X		X			X [j]					X				X [t]	
12-lead ECG		X			X [e]		X [j]		X		X	X		X [o]		X [t]	
Urinalysis		X		X			X [j]		X	X	X	X	X	X	X	X [t]	X
Hematology Blood chemistry Blood coagulation		X		X		X [f]	X [j]	X [w]	X	X	X	X	X	X	X	X [t]	X
Ophthalmology		X								X		X [p]				X [t]	X
Pregnancy (if applicable)		X															X
Tumor evaluation Tumor markers		X [c]					X [q]									X [u]	
PK (blood)					X [g]		X [j]	X [j]	X [k]	X [j]	X [j]	X [j]					
PK (urine)									X [l]								
PD markers and PGx (blood)				X	X [h]		X [j]	X [j]	X [j]	X [j]		X [r]					
Archived tumor [a]	X [s]																
Biopsied tumor [a]		X								X [m]							
E7090 administration					X		←	—	—	—	—	—	—	—	→		
Adverse events	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant drugs/therapies	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

a) To be performed only when consent is obtained.
b) Any available viral test data obtained within 6 months before the start of study treatment may be used as screening data.
c) Any data obtained within 28 days before the start of study treatment may be used (any data obtained before informed consent may also be used).
d) For assessments performed at both screening and baseline, if screening assessment is performed within 4 days after the start of study treatment, baseline assessment may be omitted.
e) To be performed 2 to 4 hours postdose.
f) To be performed 24 hours (±60 minutes) postdose.
g) To be performed predose and 0.5, 1, 2, 3, 5, 10, 24, 48, and 72 hours postdose.
h) To be performed predose and 3, 5, 10, 24, 48, and 72 hours postdose.
i) Cycle 1 will be started between Day 8 and Day 10 after administration in Cycle 0.
j) To be performed predose.
k) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours postdose.
l) A 24-hour urine collection will be performed.
m) To be performed within ±2 days.
n) To be performed within +3 days only in Cycle 2.
o) In Cycle 3 and subsequent cycles, the test/observation may be omitted only if the investigator or subinvestigator considers that the safety of the subject is ensured.
p) To be performed on Day 1 of Cycle 2. To be performed every 8 weeks (on Day 1 [±3 days] of even-numbered cycles) thereafter.
q) Tumor evaluation and tumor marker assessment will be performed every 8 weeks (on Day 1 [±7 days] of odd-numbered cycles) after Day 1 of Cycle 1, and more frequently if clinically indicated.
r) To be performed in odd-numbered cycles after Cycle 3.
s) To be obtained during the study period whenever possible.
t) Any available data obtained within 7 days before discontinuation may be used as data at discontinuation.
u) Any available data obtained within 28 days before discontinuation may be used as data at discontinuation.
v) If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, the final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent.
w) Only blood chemistry (blood phosphorus level) will be performed.

Table 14 Schedule of Procedures/Assessments in Part 2

Phase	Pretreatment				Treatment								Follow-up	
Period	Screening 1	Screening 2		Baseline [c]	Cycle 1				Cycle 2 and subsequent cycles				Discontinuation	Final observation [r]
Day			Within 14 days before dose	Within 4 days before dose	1	8 (±2)	15 (±2)	22 (±2)	1 (±3)	8 [l] (±3)	15 (±3)	22 [l] (±3)	(+7)	30 days after last dose (+7)
Consent for tumor test	X													
Consent for study		X												
Inclusion/exclusion criteria			X											
Subject demographics	X													
Prior treatment Previous/current condition			X											
Height, viral test			X [b]											
Weight			X	X		X	X	X	X		X		X [p]	
Vital signs Transcutaneous arterial oxygen saturation			X	X		X	X	X	X	X	X	X	X [p]	X
Physical examination			X	X		X	X	X	X	X	X	X	X [p]	X
ECOG-PS			X	X					X				X [p]	
12-lead ECG			X			X		X	X		X [l]		X [p]	
Urinalysis			X	X		X	X	X	X	X	X	X	X [p]	X
Hematology Blood chemistry Blood coagulation			X	X		X	X	X	X	X	X	X	X [p]	X
Ophthalmology			X [c]				X [i]		X [m]				X [p]	X
Pregnancy (if applicable)			X											X
Tumor evaluation Tumor markers			X [c]		X [j]								X [q]	
PK (blood)					X [f]	X [h]	X [g]		X [g]					
PD markers and PGx (blood)				X	X [g]	X [g]	X [g]		X [n]					
Archived tumor	X [a]	X [o]												
Biopsied tumor			X [d]				X [k]							
E7090 administration					◄	―	―	―	―	―	―	►		
Adverse events		◄	―	―	―	―	―	―	―	―	―	―	―	►
Concomitant drugs/therapies		◄	―	―	―	―	―	―	―	―	―	―	―	►
Survival follow-up														X [s]

a) Only in gastric cancer patients with available samples to allow confirmation of FGFR2 protein expression at the time of informed consent for Screening 1. Patients in whom the presence of FGFR2 gene amplification is unknown but the presence of FGFR2 protein overexpression is confirmed by central laboratory may enter Screening 2.
b) Any available viral test data obtained within 6 months before the start of study treatment may be used as screening data.
c) Any data obtained within 28 days before the start of study treatment may be used (any data obtained before informed consent may also be used).
d) Excluding patients with only a tumor lesion not amenable to biopsy for safety reasons.
e) For assessments performed at both screening and baseline, if screening assessment is performed within 4 days after the start of study treatment, baseline assessment may be omitted.
f) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours (predose on Day 2) postdose.
g) To be performed predose.
h) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours (predose on Day 9) postdose on Day 8. PK evaluation may be performed within +1 or +2 days (not −2 or −1 days).
i) To be performed within ±3 days.
j) Tumor evaluation and tumor marker assessment will be performed every 8 weeks (on Day 1 [±7 days] of odd-numbered cycles) after Day 1 of Cycle 1, and more frequently if clinically indicated.
k) Only in patients providing consent (optional).
l) In Cycle 3 and subsequent cycles, test/observation may be omitted only if the investigator or subinvestigator considers the subject safe. However, if the blood phosphorus level is ≥7.1 mg/dL on Day 1 or Day 15, blood phosphorus levels should be measured to evaluate hyperphosphatemia.
m) To be performed on Day 1 (±3 days) of Cycle 2. To be performed every 8 weeks (on Day 1 [±3 days] of even-numbered cycles) thereafter.
n) To be performed in odd-numbered cycles after Cycle 3.
o) To be obtained during the study period whenever possible.
p) Any available data obtained within 7 days before discontinuation may be used as data at discontinuation.
q) Any available data obtained within 28 days before discontinuation may be used as data at discontinuation.
r) If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, the final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent.
s) To be performed every 12 weeks (±2 weeks) after the time of discontinuation of study treatment.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of solid cancers.

The tolerability and safety assessments to be performed in this study, including vital signs, ECGs, ECOG-PS, ophthalmology, physical examinations, laboratory tests (hematology, blood chemistry, urinalysis), and AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event. However, any event resulting in death or life-threatening event should be reported immediately by telephone before completing an SAE form and reported to the sponsor within 1 business day using an SAE form (Appendix 11 or Uniform Format 12).

All SAEs, regardless of causality assessment, occurring through the last visit must be collected. All SAEs must be followed to resolution, or, if resolution is unlikely, to stabilization. Although SAEs are followed to resolution, or, if resolution is unlikely, to stabilization, follow-up may be terminated on the basis of the medical judgment of the investigator or subinvestigator. Any SAE judged by the investigator or subinvestigator to be possibly related to the study treatment (or any protocol-required procedure) should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in Appendix 3.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any relevant follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the relevant follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported, regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion should be considered to be an SAE and reported in the same time frame and format as all other SAEs (see Section 9.5.4.1 “Reporting of Serious Adverse Events”).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the information. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in Appendix 3. The Pregnancy Report Form (Appendix 12) must be used for reporting. The investigator must follow all pregnancies to outcome, and it must be reported to the sponsor using the Pregnancy Outcome Form (Appendix 13) as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated with Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug (including the use by subjects themselves) outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject

All AEs associated with overdose, misuse, abuse, or medication errors should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators, the head of the medical institution and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described in Reporting of Serious Adverse Events (Section 9.5.4.1).

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 13 and Table 14).

The investigator or subinvestigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up whenever possible by mail, phone, or other means.

For a subject who discontinues early from the study, 1 of the primary reasons for study discontinuation will be recorded in the CRF. In addition to the primary reason, the subject may indicate 1 or more secondary reasons for discontinuation.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs. As defined by GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from Eisai, except to those relevant parties designated by the sponsor or representatives of appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed after the study is completed and the database is locked. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of this study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 Primary Endpoints

- DLT (Part 1)
- Safety endpoints (AEs, laboratory tests, vital signs, weight, 12-lead ECG, ECOG-PS, ophthalmology)

9.7.1.1.2 Secondary Endpoints

- PK parameters
- Efficacy endpoints (best overall response [BOR], objective response rate [ORR], disease control rate [DCR], percent change from baseline in the sum of the diameters of tumor target lesions [if appropriate])

9.7.1.1.3 Exploratory Endpoints

- PD markers
- PGx
- Efficacy endpoints (progression-free survival [PFS], overall survival [OS])

9.7.1.2 Definitions of Analysis Sets

The DLT analysis set is the group of subjects completing treatment with E7090 in Cycle 0 and Cycle 1 with a compliance rate of ≥75% and evaluated for DLT and subjects experiencing DLT in Cycle 0 or Cycle 1 in Part 1. This analysis set will be used to estimate the MTD in Part 1.

The safety analysis set is the group of subjects receiving at least 1 dose of E7090.

The efficacy analysis set is the group of subjects receiving at least 1 dose of E7090 with at least 1 tumor assessment at baseline and after administration. This analysis set will be used for the interim assessment in Part 2.

The PK analysis set is the group of subjects receiving at least 1 dose of E7090 with data from which at least 1 PK parameter can be calculated.

The PD and PGx analysis set is the group of subjects receiving at least 1 dose of E7090 with at least 1 PD or PGx data.

The inclusion/exclusion of each analysis set will be summarized for each group in Part 1, for each cohort in Part 2, for the combined groups in each part, and for all study groups combined.

9.7.1.3 Subject Disposition

Subjects providing informed consent, registered subjects, screening failures, and reasons for screen failure will be presented. Subjects treated, subjects not treated, subjects completing the study, subjects discontinuing the study, and reasons for study discontinuation will be presented. Similarly, subjects completing study treatment, reasons for treatment completion, subjects discontinuing study treatment, and reasons for treatment discontinuation will be presented.

In this study, subjects completing the study will be defined as those completing DLT assessment appropriately in Part 1 and those completing the early discontinuation procedures or final observation in Part 2. Subjects completing study treatment will be defined as those

discontinuing study treatment due to disease progression or those continuing study treatment at the end of the study.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the safety analysis set will be summarized for each group in Part 1, for each cohort in Part 2, for the combined groups in each part, and for all study groups combined. Continuous demographic and baseline variables include age and weight. Categorical variables include sex, race, ethnicity, ECOG-PS, primary lesion site, presence or absence of prior treatment (surgical therapy, radiation therapy, anticancer therapy, other therapies), use or non-use of contact lenses, and presence or absence and type of FGF/FGFR genetic abnormalities (translocation, point mutation, amplification, other).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the safety analysis set for each group in Part 1, for each cohort in Part 2, for the groups combined in each part, and for all study groups combined. In addition, the number (percentage) of subjects who took prior and concomitant medications will be summarized by appropriate Anatomical Therapeutic Chemical (ATC) class showing treatment classes (when specifying relevant ATC classes, such as anatomical class, therapeutic class, pharmacologic class, and chemical class) and WHO DD preferred terms. Prior medications will be defined as medications stopped before the first dose of the study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the last observation. All prior medications and concomitant medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Efficacy analyses will be performed using the efficacy analysis set.

9.7.1.6.1 Primary Efficacy Analysis

No primary efficacy endpoint will be established because this study is a phase 1 study.

Part 1

On the basis of tumor assessments according to RECIST 1.1, the number and percentage of subjects with a BOR will be summarized for each group and overall. The BOR includes complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE). In subjects with non-target lesions only, a BOR of non-CR/non-PD will be categorized into SD, where SD must to be achieved beyond 7 weeks after the first dose. In this study, CR and PR will require no confirmation based on the next response evaluation beyond 4 weeks.

Part 2

Analysis results will be summarized for each cohort and for all cohorts combined.

When there are 2 treatment groups, analysis results will be summarized for each treatment group and for all treatment groups combined.

In addition to the analyses for Part 1, the number and proportion of subjects with ORR or DCR and their corresponding exact two-sided 95% confidence intervals will be calculated. ORR is defined as the proportion of subjects with a BOR of CR or PR. DCR is defined as the proportion of subjects with a BOR of CR, PR, or SD.

PFS and OS will also be summarized and plotted over time using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the date of the first event (disease progression or death due to any cause, whichever comes first). OS is defined as the time from the date of the first dose to the date of death due to any cause.

When appropriate, a waterfall plot will be created for the percent change from baseline in the sum of the diameters of target lesions at the time of maximum tumor reduction after administration.

When appropriate, changes over time in tumor markers will also be analyzed.

9.7.1.6.2 Secondary Efficacy Analyses

Not applicable.

9.7.1.6.3 Exploratory Efficacy Analyses

Not applicable.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 Pharmacokinetic Analyses

The PK analysis set will be used to summarize E7090 plasma concentrations and PK parameters and perform other PK analyses. A non-compartmental analysis of plasma and urine E7090 concentrations will be performed to calculate PK parameters including C_{max}, t_{max}, AUC, and renal clearance. Detailed methods and results of the exploratory metabolite analysis will be provided in separately prepared analysis plan and report, and its results will not be included in the clinical study report.

9.7.1.7.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacodynamic and PGx analyses

PD and PGx analyses will be performed using the PD and PGx analysis set. Measurements of biomarkers (in blood and tumor tissue) and their percent changes will be evaluated

visually with the use of figures and tables. If necessary, correlations of measurements of biomarkers and their percentage changes with the efficacy and safety of E7090 will be analyzed, or various exploratory analyses will be performed. Results of other comprehensive analyses will not be included in the clinical study report.

9.7.1.8 Safety Analyses

DLT analyses will be performed using the DLT analysis set. Other safety analyses will be performed using the safety analysis set. Descriptive statistics for safety data (number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables; number and percentage of subjects for categorical variables) will be calculated on an "as treated" basis for each group in Part 1, for each cohort in Part 2, for all groups combined in each part, and for all study groups combined. Safety variables include adverse events (AEs), clinical laboratory parameters, vital signs, transcutaneous arterial oxygen saturation, weight, 12-lead ECG, ECOG-PS, and ophthalmology. For safety analyses, study Day 1 will be defined as the date of the first dose of study drug.

9.7.1.8.1 Extent of Exposure

The number of treatment cycles, duration of treatment, total exposure person-time, number of doses given, total dosage given, strength of dose used, and dose ratio (actual dose/planned dose) will be summarized.

9.7.1.8.2 Adverse Events

Analysis of DLTs

The number (percentage) of subjects with DLTs in Part 1 will be calculated. DLTs will also be tabulated by type. In addition, estimated values based on the posterior distribution of Bayesian statistics will be presented.

The MTD will be estimated on the basis of the DLTs and the method outlined in Section 9.7.4.

Analysis of Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (baseline) or:

- Reemerges during treatment, having been present at pretreatment (baseline) but stopped before treatment, or

- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE v4.03 grade.

TEAEs possibly related to the study drug (ADRs) will be summarized by SOC and PT. ADRs include AEs judged to be causally related to the study drug. In addition, the number (percentage) of subjects with ADRs will also be summarized by highest CTCAE v4.03 grade.

The number (percentage) of subjects with TEAEs leading to death will be summarized by SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by SOC and PT. A subject data listing of all SAEs will be provided.

The numbers (percentages) of subjects with TEAEs leading to discontinuation from study drug, subjects with TEAEs leading to the dose reduction, and subjects with TEAEs leading to dose interruption will be summarized by SOC and PT. Subject data listings of these AEs will be provided.

9.7.1.8.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all continuous variables listed in Section 9.5.1.5.3, the measured value at and the change from baseline to each postbaseline time point will be calculated for each time point using descriptive statistics. The number (percentage) of subjects for ordinal categorical variables will be summarized, and changes from baseline to each postbaseline time point will be reported using shift tables. Percentages will be calculated on the basis of the number of subjects with both nonmissing baseline and relevant postbaseline results.

The CTCAE grades at each evaluation time point and highest postdose grade will be summarized for those variables included in the classification according to CTCAE ver. 4.03. Changes in grade from baseline to each postbaseline time point will be reported using shift tables.

Laboratory test results will be classified according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range and will be tabulated.

Treatment-emergent markedly abnormal laboratory values (TEMAVs) seen postdose will be identified according to CTCAE ver. 4.03 as required.

9.7.1.8.4 Vital Signs

For vital signs parameters (systolic and diastolic BP, pulse, respiratory rate, and body temperature), transcutaneous arterial oxygen saturation, and weight, the measured value at and the change from baseline to each postbaseline time point will be calculated for each time point using descriptive statistics.

9.7.1.8.5 Electrocardiograms

ECG assessments will be performed using the results obtained at each time point. For ECG parameters, the measured value at and the change from baseline to each postbaseline time point will be calculated for each time point using descriptive statistics.

Changes in ECG parameters from baseline to each time point will be classified as normal, abnormal not clinically significant, or abnormal clinically significant, and presented using shift tables.

In addition, the number (percentage) of subjects with at least 1 postdose abnormal ECG result that falls under any of the following categories will be calculated:

- Absolute QTcF interval prolongation >450 ms
- Absolute QTcF interval prolongation >480 ms
- Absolute QTcF interval prolongation >500 ms

- QTC interval increases from baseline >30 ms
- QTC interval increases from baseline >60 ms

9.7.1.8.6 Other Safety Analyses

ECOG-PS

The classification of ECOG-PS at each time point and the worst postdose classification of ECOG-PS will be summarized.

Ophthalmology

For the measured value of corneal epithelial thickness at each time point and its change from baseline, descriptive statistics for each time point will be calculated.

9.7.2 Determination of Sample Size

The primary objective of this study is to evaluate the tolerability and safety of E7090.

The sample size for Part 1 has been set to approximately 20 subjects, assuming the number of dose levels to be evaluated of 9 and a cohort size of 2 on the basis of the recommended sample size to reach the MTR in the mTPI design (Ji Y, et al., 2013). When deemed necessary, the sample size may be adjusted, depending on the actual number of dose levels to be evaluated and the number of evaluable subjects for DLT.

The sample size for Part 2 has been set to approximately 10 subjects or 5 to 10 subjects per cohort, considering its feasibility, to allow further safety evaluation and preliminary antitumor effect evaluation.

9.7.3 Interim Analysis

No interim analysis taking into consideration adjustment for type I and II errors will be performed in this study.

In the gastric cancer cohort in Part 2, an interim efficacy evaluation will be performed, and if no responder is observed in 5 evaluable subjects, the cohort may discontinue further enrollment. The duration of follow-up of subjects with continuous SD will be determined through discussion with the sponsor.

This criterion is based on the posterior distribution of Bayesian statistics. When a non-informative beta prior distribution Beta (1,1) is used, the discontinuation criterion corresponds to the case where the probability of ORR being 40% or higher is less than 10% in the posterior distribution of the 5 subjects at the time of evaluation. In cases other than the number of evaluable subjects established as the discontinuation criterion, if necessary, it will be acceptable to consider interim evaluations and discontinuation of enrollment based on the posterior distribution and criteria described above.

The ORR threshold of 40% has been established as a beneficial effect size, taking the mechanism of action of E7090 into consideration.

9.7.4 Other Statistical/Analytical Issues

Study Design

The MTD of E7090 will be determined using the mTPI design (Ji Y, et al., 2010). The mTPI design uses a beta/binomial hierarchical model in a Bayesian statistical framework to calculate the posterior probabilities of 3 intervals that reflect the relative distance between the target DLT rate of 25% and the DLT rate for each dose level.

The decision rules for finding doses are based on the calculation of the unit probability mass (UPM) of the 3 intervals corresponding to 0% to 20% (underdosing), 20% to 30% (proper dosing), and 30% to 100% (overdosing) in terms of toxicity. The UPM of each interval is defined as the probability of the interval divided by the length of the interval, and the interval with the largest UPM indicates the decision on the next dose level to be assigned: dose escalation (E), staying at the current dose (S), and dose de-escalation (D).

These dose assignment rules minimize the posterior expected loss in the Bayes' rule when equal prior expected losses are used for E, S, and D in a decision-theoretic framework. The decision rules for all dose assignment will be calculated in advance.

Determination of the MTD

The MTD will be determined when the posterior probability of the DLT rate at the initial dose exceeding 25% exceeds 95% (ie, an unacceptable DLT rate exceeding the target DLT rate) or when a prespecified maximum sample size of approximately 20 subjects is reached. However, the maximum sample size will be adjusted as necessary according to the actual number of dose levels to be evaluated and the number of subjects evaluable for DLT. In addition, if the Bayesian predictive probability of being S when another 10 subjects are added to a dose level is 80% or higher (ie, if it is highly likely that subsequent registered subjects will also be assigned to the dose level), subject registration may be closed early to determine the MTD.

The MTD will be defined as the dose with the smallest difference between the target DLT rate of 25% and an estimated DLT rate at each dose among all the evaluated doses for which the posterior probability of the DLT rate exceeding 25% is 95% or lower. The isotonically transformed posterior mean under a beta posterior distribution with non-informative beta prior distribution Beta (0.005, 0.005) will be used to determine the estimated DLT rate at each dose. The pooled-adjacent-violators algorithm (PAVA) will be used to maintain the monotonic increase of the DLT rate with increasing dose level (Bartholomew, D, 1983).

9.7.5 Procedures for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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Bartholomew, D. Isotonic inference. In: Samuel K, Norman LJ, editors. Encyclopedia of Statistical Science volume 4, New York: Wiley-Interscience. 1983;260-5.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the head of the medical institution should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the head of the medical institution detailing such changes.

11.2 Adherence to the Protocol

The investigator or subinvestigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to the study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments (eg, x-rays, sonograms, CT scans, MRI images, radioactive images, ECGs, EEGs, polysomnograms, pulmonary function tests)

regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test results)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following items, the data recorded directly on the CRF are to be considered source data:

- DMC: Ethnicity, Race
- ANTI-CAN: Given As, Best response for procedure
- PREV RADTHRPY: Has Tumor Lesion at the Site Progressed Since Radiotherapy?
- SCRN DISP: Primary Reason for Discontinuation
- FINAL/ET-TRT: Did the subject complete study treatment as defined per protocol?, Are there any other reasons for discontinuation?
- FINAL/ET-STUDY: Primary reason for discontinuation from the study, Are there any other reasons for discontinuation?
- SMED ORAL: Dose Reason

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the head of the medical institution is responsible for retaining all study documents, including but not limited

to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for 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 at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to a designated pharmacist by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The study drug manager must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The study drug manager must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the study drug manager will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable guidelines and regulations.

12 APPENDICES

Appendix 1: NYHA Classification

Appendix 2: Drugs Affecting the Activity of Drug-Metabolizing Enzyme CYP3A

Appendix 3: Study Administrative Structure

Appendix 4: Dose Allocation according to the Modified Toxicity Probability Interval (mTPI) Design

Appendix 5: Type, Packaging, and Labeling of Study Drug

Appendix 6: Subject Registration Form

Appendix 7: RECIST Criteria for Evaluation of Tumor Shrinkage Effect

Appendix 8: Procedures for Collecting, Handling, and Shipping Samples for Drug Concentration Measurement

Appendix 9: Procedures for Collecting, Handling, and Shipping Samples for Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Appendix 10: ECOG Performance Status

Appendix 11: Serious Adverse Event Report Form

Appendix 12: Pregnancy Report Form

Appendix 13: Pregnancy Outcome Report Form

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

Section	Before Revision (Version 8.0, Date: 25 Oct 2017)	After Revision (Version 9.0, Date: 13 Jul 2018)	Reason for Revision
2	**Number of Subjects** Part 1 20 subjects (planned) Part 2 15 subjects (planned) (10 with gastric cancer and 5 with cholangiocarcinoma)	**Number of Subjects** Part 1 20 subjects (planned) Part 2 15 to 20 subjects (planned) (10 with gastric cancer and 5 to 10 with cholangiocarcinoma)	To increase subjects with cholangiocarcinoma
2	The sample size for Part 2 has been set to approximately 10 subjects or 5 subjects per cohort, considering its feasibility, to allow further safety evaluation and the preliminary antitumor effect evaluation.	The sample size for Part 2 has been set to approximately 10 subjects or 5 to 10 subjects per cohort, considering its feasibility, to allow further safety evaluation and the preliminary antitumor effect evaluation.	The same as above
9.3	Approximately 20 subjects will be enrolled in Part 1. Approximately 10 subjects with gastric cancer confirmed to carry an amplified FGFR2 gene or an overexpressed FGFR2 protein and approximately 5 subjects with cholangiocarcinoma confirmed to harbor FGFR2-fusion genes will be enrolled in Part 2. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to take the study drug.	Approximately 20 subjects will be enrolled in Part 1. Approximately 10 subjects with gastric cancer confirmed to carry an amplified FGFR2 gene or an overexpressed FGFR2 protein and approximately 5 to 10 subjects with cholangiocarcinoma confirmed to harbor FGFR2-fusion genes will be enrolled in Part 2. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to take the study drug.	The same as above
9.7.2	The sample size for Part 2 has been set to approximately 10 subjects or 5 subjects per cohort, considering its feasibility, to allow further safety evaluation and preliminary antitumor effect evaluation.	The sample size for Part 2 has been set to approximately 10 subjects or 5 to 10 subjects per cohort, considering its feasibility, to allow further safety evaluation and preliminary antitumor effect evaluation.	The same as above

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

25 Oct 2017

Section	Before Revision (Version 7.0, Date: 03 Jul 2017)	After Revision (Version 8.0, Date: 25 Oct 2017)	Reason for Revision
9.3.1	**9.3.1 Inclusion Criteria** Patients with the following time intervals between prior therapy and study treatment in this study: … Supportive therapy Blood transfusions, blood products, hematopoietic factor products including granulocyte colony-stimulating factor (G-CSF) products: ≥3 weeks	**9.3.1 Inclusion Criteria** Patients with the following time intervals between prior therapy and study treatment in this study: … Supportive therapy Blood transfusions, blood products, hematopoietic factor products including granulocyte colony-stimulating factor (G-CSF) products: ≥2 weeks	To reset the therapy duration based on the common criterion, considering the data in Part 1
9.3.2	**9.3.2 Exclusion Criteria** No corresponding criterion	**9.3.2 Exclusion Criteria** (8) Patients with active malignancy within 36 months before the start of study treatment (excluding the primary disease, and carcinomas in situ such as completely treated melanoma in situ, basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and early-stage large bowel cancer)	To accurately evaluate the preliminary efficacy in Part 2
9.4.5	**9.4.5 Method of Assigning Subjects to Treatment Groups** [Part 2] After the investigator and the subinvestigator determine the eligibility of the patient through the screening test, the investigator, subinvestigator, or clinical study collaborator will promptly notify the sponsor by e-mail or fax of the eligibility/ineligibility determined by the screening test, the planned start date of study treatment (when the patient is eligible), and the planned date of baseline assessment (when the baseline assessment is performed separately).	**9.4.5 Method of Assigning Subjects to Treatment Groups** [Part 2] After the investigator and the subinvestigator determine the eligibility of the patient through the screening test, the investigator, subinvestigator, or clinical study collaborator will promptly document the eligibility/ineligibility determined by the screening test, the planned start date of study treatment (when the patient is eligible), and the planned date of baseline assessment (when the baseline assessment is performed separately) in the Subject Eligibility Confirmation Form (Appendix 6: Part 2) and notify the sponsor by e-mail or fax.	To clarify the operation management

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

03 Jul 2017

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
2	**Site(s)** Study sites: 1 site in Part 1, multiple sites in Part 2 (the number of sites undetermined)	**Site(s)** Study sites: 1 site in Part 1, about 14 to 17 sites in Part 2 (planned)	For updated information
2	**Study Period and Phase of Development** FPI: November 2014 LPI: November 2017 (planned)	**Study Period and Phase of Development** FPI: November 2014 LPI: September 2018 (planned)	For updated information
2	**Study Design** Part 2 will include patients with solid tumors carrying the FGF/FGFR genetic abnormalities (such as translocation, point mutation and amplification) (including patients with cholangiocarcinoma harboring FGFR2-fusion genes [such as FGFR2-AHCYL1 translocation and FGFR2-BICC1 translocation]).	**Study Design** Part 2 will include patients with gastric cancer carrying the FGFR2 gene amplification or FGFR2 protein overexpression and patients with cholangiocarcinoma harboring FGFR2-fusion genes among patients with solid tumors.	To clarify targeted patients
2	Study Design Overview Part 2 will include patients with solid tumors carrying the FGF/FGFR genetic abnormalities (cholangiocarcinoma and others).	Study Design Overview Part 2 will include patients with gastric cancer carrying FGFR2 gene amplification or protein overexpression, or patients with cholangiocarcinoma harboring FGFR2-fusion genes.	To clarify targeted patients
2 9.1.2	(2) Part 2: Part 2 will include patients with solid tumors harboring FGF/FGFR gene abnormalities. Part 2 will consist of a pretreatment period, a treatment period, and a follow-up period. The pretreatment period consists of informed consent obtainment, screening, enrollment, and baseline assessment. In Part 2, 1 or 2 doses will be selected from the doses considered in Part 1. Dose-selection will be made in consideration of efficacy, safety, pharmacokinetics and changes in pharmacodynamic markers, through discussion among the investigator, the sponsor and the medical expert (plus Data and Safety Monitoring member if necessary). The effect of food on E7090 pharmacokinetics will be considered in 6 patients (aim). A pharmacokinetic comparison will be carried out between the fasting state and the high fat-fed state of the same patients. The date for blood sampling will be determined after the review of	(2) Part 2: Part 2 will include patients with solid tumors, consisting of the following cohorts: Gastric cancer cohort: Patients with gastric cancer carrying an amplified FGFR2 gene or overexpressed FGFR2 protein (including patients with gastroesophageal junction cancer diagnosed as adenocarcinoma) Cholangiocarcinoma cohort: Patients with cholangiocarcinoma harboring FGFR2-fusion genes Part 2 will consist of a pretreatment period, a treatment period, and a follow-up period. The pretreatment period consists of Screening 1, Screening 2, and baseline assessment. In Screening 1, each subject will be examined for FGFR genetic abnormalities in the tumor, and in Screening 2, each subject will be examined for the other eligibility criteria. Separate written informed consent will be obtained before the start of Screening	To clarify the screening method To delete the consideration of the food effect

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
	pharmacokinetics in Part 1.	1 and Screening 2. Screening 1 will include gastric cancer patients with documented FGFR2 gene amplification and cholangiocarcinoma patients with documented FGFR2-fusion genes. In addition, Screening 1 will also include any gastric cancer patient with an unknown FGFR2 amplification status who has an archived tumor sample available for the confirmation of FGFR2 protein expression. No biopsy should be performed at Screening 1 In Screening 1, the following will be confirmed: • For patients with the documented genetic abnormalities mentioned above, the documents necessary for genetic testing will be submitted to the sponsor to confirm the presence of genetic abnormalities. • For gastric cancer patients with unknown genetic abnormalities who have an archived tumor sample available for the confirmation of the FGFR2 protein expression mentioned above, the archived tumor sample will be sent to the central laboratory to confirm the presence of FGFR2 protein overexpression with immunohistochemical staining. Patients considered eligible according to either of the criteria above are eligible to enter into Screening 2. Because no biopsy is permitted in Screening 1, adverse advents will be collected only after informed consent for Screening 2 is obtained. Patients meeting all of the inclusion criteria and not meeting any of the exclusion criteria in Screening 2 will be considered eligible for treatment, and study treatment will be started after baseline assessment. In Screening 2, a biopsy will be performed in all patients, other than those who have only a tumor lesion not amenable to biopsy for safety reasons. The treatment period will consist of 28-day treatment cycles, and patients will take the study drug once daily continuously until any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met. The follow-up period will involve the early discontinuation procedures and the final observation.	
2	**Number of Subjects** Part 2 10 subjects per cohort (planned)	**Number of Subjects** Part 2 15 subjects (planned) (10 with gastric cancer and 5 with cholangiocarcinoma)	To change the study design
2 9.3.1	**Inclusion Criteria (for both Part 1 and Part 2)** (6) Patients with adequate major organ function 1) Hemoglobin ≥9.0 g/dL 5) AST and ALT ≤3.0 times the ULN	**Inclusion Criteria (for both Part 1 and Part 2)** (6) Patients with adequate major organ function 1) Hemoglobin ≥9.0 g/dL (≥8.0 g/dL in Part 2) 5) AST and ALT ≤3.0 times the ULN (≤5.0 times the ULN in the presence of intrahepatic bile duct cancer or liver metastases)	To change the criteria, considering the targeted population and

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
	(10) Patients expected to survive for 3 months or longer after registration (12) Women of childbearing potential must have practiced contraception since 28 days before registration, and …. **Inclusion Criteria (for Part 2 only)** (14) Patients with solid tumors harboring FGF/FGFR genetic abnormalities (such as amplification, point mutation and translocation)	(10) Patients expected to survive for 3 months or longer after registration (Part 1) or the start of study treatment (Part 2) (12) Women of childbearing potential must have practiced contraception since 28 days before registration (Part 1) or 28 days before the start of study treatment (Part 2), and …. **Inclusion Criteria (for Part 2 only)** (14) Patients whose solid tumors have been confirmed to meet either of the following in Screening 1: 1) Patients with gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2 protein (including patients with gastroesophageal junction cancer diagnosed as adenocarcinoma) 2) Patients with cholangiocarcinoma harboring FGFR2-fusion genes (15) Patients with a target lesion that can be evaluated according to RECIST 1.1 (16) Patients meeting both of the following criteria 1) and 2) concerning tumor sample submission: 1) Patients agreeing to submit any tumor sample collected in the past 2) Patients agreeing to submit any biopsy sample in Screening 2 (excluding those who have only a tumor lesion not amenable to biopsy for safety reasons)	the data in Part 1 To clarify the criteria
2 9.3.2	**Exclusion Criteria** (2) Patients with any of the following clinically significant cardiovascular disorders: 2) Unstable angina pectoris or myocardial infarction within 6 months before enrollment in this study (6) Patients with previous or concurrent Grade ≥2 corneal disorder (7) Patients in whom the adverse effects (except for alopecia) of prior treatment have not recovered to Grade 1 or lower (11) Patients unable to take drugs orally or with malabsorption syndrome	**Exclusion Criteria** (2) Patients with any of the following clinically significant cardiovascular disorders: 2) Unstable angina pectoris or myocardial infarction within 6 months before enrollment in this study (Part 1) or within 6 months before the start of study treatment (Part 2) (6) Patients with any of the following previous or concurrent corneal or retinal diseases: 1) Grade ≥2 corneal disorder 2) Active macular disease (eg, age-related macular degeneration, central serous chorioretinopathy) (7) Patients in whom the adverse effects of prior treatment have not recovered to Grade 1 or lower, except for alopecia and Grade 2	To change the criteria, considering the targeted population and the data in Part 1

<table>
<tr><th>Section</th><th>Before Revision
(Version 6.0, Date: 22 Apr 2016)</th><th>After Revision
(Version 7.0, Date: 03 Jul 2017)</th><th>Reason for Revision</th></tr>
<tr><td></td><td></td><td>peripheral neuropathy
(9) Patients with prior therapy targeting FGFR2
(12) Patients unable to take drugs orally or with malabsorption syndrome (patients undergoing gastrectomy may be enrolled)</td><td></td></tr>
<tr><td>2
9.4
9.4.2.2</td><td>Study Treatment
E7090 will be administered orally once daily. Study drug consists of 1, 1.5, 5, 20, and 60 mg capsules. The initial dose will be 1 mg.

Administration schedule
(2) Part 2
Subjects will take E7090 at least 2 hours after breakfast and will not eat anything for 1 hour after administration. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.
A pharmacokinetic comparison will be carried out between the fasting state and the high fat-fed state of the same patients, to review the effect of food on E7090 pharmacokinetics in 6 patients (aim). When E7090 is administered to subjects in the fasting state, the subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. When E7090 is administered to subjects in the high fat-fed state, the subjects will take E7090 within 30 minutes after starting to eat a high fat diet as a breakfast. The dates for PK evaluation in the fasting state and in the high-fat fed state will be determined after PK evaluation in Part 1.</td><td>Study Treatment
E7090 will be administered orally once daily. Study drug consists of 1, 1.5, 5, 20, and 60 mg capsules (Part 1) and 35 mg tablets (Part 2). The initial dose in Part 1 will be 1 mg and the starting dose in Part 2 will be 140 mg.

Administration schedule
(2) Part 2
Subjects will take E7090 at least 2 hours after breakfast and will not eat anything for 1 hour after administration. On Day 1 and Day 8 of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.</td><td>To add tablets

For updated information

To delete consideration of food effect</td></tr>
<tr><td>2
9.4.2.2</td><td>Methods of dose interruption and reduction
(2) Part 2
The criteria for dose interruption and reduction (dose and the possible number of dose reduction) will be determined after evaluation of safety data in Part 1.</td><td>Methods of dose interruption and reduction
(2) Part 2
If any E7090-related toxicity or hyperphosphatemia is observed, the “Criteria for Dose Interruption/Reduction” and the “Criteria for Dose Interruption/Reduction Based on Hyperphosphatemia,” respectively, should be followed. If study treatment is continued after the dose reduction, the dose will be reduced step-by-step to 105 mg, 70 mg, and then 35 mg.

Criteria for Dose Interruption/Reduction
<table><tr><th>E7090-related</th><th>Management</th><th>Dose after restart</th></tr></table></td><td>To set the data based on the data in Part 1</td></tr>
</table>

<table>
<tr><th>Section</th><th>Before Revision
(Version 6.0, Date: 22 Apr 2016)</th><th>After Revision
(Version 7.0, Date: 03 Jul 2017)</th><th>Reason for Revision</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>toxicity [a]</td><td></td><td></td></tr>
<tr><td>Grade 1 or tolerable Grade 2 [b]</td><td>Continue study treatment</td><td>No change</td></tr>
<tr><td>Intolerable Grade 2 [b] or Grade 3</td><td>Interrupt treatment until the toxicity resolves to Grade 0 to 1 or baseline [c]</td><td>Same dose or 1-level dose reduction</td></tr>
<tr><td>Grade 4 [d]</td><td>Discontinue study treatment</td><td>NA</td></tr>
</table>
a: Laboratory abnormalities not requiring treatment will be excluded.
b: The tolerability of Grade 2 will be determined by the investigator or subinvestigator.
c: When the investigator or subinvestigator considers interruption clinically acceptable, study treatment may be restarted also when the toxicity resolves to tolerable Grade 2.
d: Any laboratory abnormality considered non-life-threatening will be excluded and managed as a Grade 3 event.
</td><td></td></tr>
<tr><td>2
9.4.2.2</td><td>Methods of dose interruption and reduction
No corresponding description</td><td>Methods of dose interruption and reduction
Criteria for Dose Interruption/Reduction Based on Hyperphosphatemia
<table>
<tr><th>Criteria</th><th>Management</th></tr>
<tr><td>Serum phosphate level is ≥5.5 mg/dL and ≤7.0 mg/dL.</td><td>Start treatment of hyperphosphatemia.</td></tr>
<tr><td>Despite appropriate treatment of hyperphosphatemia,[a] serum phosphate levels ≥7.1 and ≤9.0 mg/dL last for ≥2 weeks,[b] or serum phosphate levels are ≥9.1 mg/dL.</td><td>Interrupt treatment until serum phosphate levels decrease to ≤7.0 mg/dL and restart treatment at a 1-level dose reduction.</td></tr>
</table>
a: This refers to treatments, such as diet therapy and hyperphosphatemia drugs, considered appropriate by the investigator or subinvestigator.
b: Any subject with a serum phosphate level of ≥7.1 mg/dL should visit the study site 1 week later and undergo measurement of serum phosphate levels for the evaluation of hyperphosphatemia.</td><td>To set the data based on the data in Part 1</td></tr>
<tr><td>2
9.3.3.1</td><td>Duration of Treatment
Treatment with E7090 will be continued until any of the following discontinuation criteria is met.
Discontinuation Criteria for Individual Subjects</td><td>Duration of Treatment
Treatment with E7090 will be continued until any of the following discontinuation criteria is met.
Discontinuation Criteria for Individual Subjects</td><td>To clarify the terms

For updated</td></tr>
</table>

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
	(2) Major inclusion/exclusion criteria violation after registration (6) Dose reduction to <1 mg required due to an adverse drug reaction	(2) Major inclusion/exclusion criteria violation after registration (Part 1) or enrollment (Part 2) (6) Dose reduction to <1 mg (Part 1) or 35 mg (Part 2) required due to an adverse drug reaction	information
2 9.4.9.2	**Concomitant Drug/Therapy** Prohibited concomitant drugs/therapies (1) Cycle 0 and Cycle 1 (Part 1 only) 1) Treatments, changes in dosage, and changes in drugs to prevent DLT occurrence (2) From the time of registration to the time of the discontinuation of study treatment 1) Treatments for malignant tumors other than E7090 (eg, surgical therapy, chemotherapy, endocrine therapy, palliative radiotherapy, or immunotherapy) except for drugs for bone lesions (eg, bisphosphonates, anti-RANKL monoclonal antibodies) that have been used since before the registration in this study	**Concomitant Drug/Therapy** Prohibited concomitant drugs/therapies (1) Cycle 0 and Cycle 1 (Part 1 only) 1) Treatments, changes in dosage, and changes in drugs to prevent DLT occurrence (2) From the time of registration (Part 1) or the start of study treatment (Part 2) to the time of the discontinuation of study treatment 1) Treatments for malignant tumors other than E7090 (eg, surgical therapy, chemotherapy, endocrine therapy, palliative radiotherapy, or immunotherapy) except for drugs for bone lesions (eg, bisphosphonates, anti-RANKL monoclonal antibodies) that have been used since before the registration in this study (Part 1) or the start of study treatment (Part 2)	To clarify the terms
2	**Assessments** (1) Efficacy assessments Tumor assessment (target lesion, non-target lesion, presence/absence of new lesions) will be performed using RECIST 1.1. Tumor markers will also be determined.	**Assessments** (1) Efficacy assessments Tumor assessment (target lesion, non-target lesion, presence/absence of new lesions) will be performed using RECIST 1.1. Tumor markers will also be determined. Survival follow-up will be terminated 2 years after the last subject's registration (Part 2).	To clarify the follow-up period
2	(3) PD and PGx assessments For 2) and 3) above, comprehensive genomic analysis will be performed to evaluate their correlation with the efficacy of E7090. In addition, samples will be archived for the development of diagnostic agents.	(3) PD and PGx assessments [Part 2] 1) Blood Blood samples will be collected to determine the following biomarkers (but not limited to): (a) FGF23 (b) 1,25-(OH)2-Vitamin D (c) CCI [redacted] (d) Angiogenesis markers (eg, VEGF, FGF) (e) Circulating tumor DNA 2) Archived tumor If any sample collected in the past is available, an archived tumor sample should be submitted (mandatory).	To clarify the measurement items in Part 2

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
		3) Biopsied tumor Except for subjects who have only a tumor lesion not amenable to biopsy for safety reasons, samples obtained from the biopsy performed in Screening 2 must be submitted (mandatory). In addition, samples obtained from the biopsy performed on the 15th day of Cycle 1 will be submitted (optional). For 2) and 3) above, immunohistochemical staining or comprehensive genomic analysis will be performed to evaluate their correlation with the efficacy of E7090. In addition, samples will be archived for the development of diagnostic agents.	
2	**Bioanalytical Methods** E7090 concentrations in plasma and urine and PD markers in blood will be determined using a validated method of measurement.	**Bioanalytical Methods** Concentrations of E7090 and its metabolites in plasma and urine and PD markers in blood will be determined using a validated method of measurement.	To clarify that the metabolites of E7090 will be measured as well
2	**Analysis sets** The efficacy analysis set is the group of subjects receiving at least 1 dose of E7090 with at least 1 tumor assessment at baseline and after administration. **Efficacy analyses** **Part 2**: In addition to the analyses similar to those for Part 1, ORR, DCR, and their exact two-sided 95% confidence intervals will be calculated.	**Analysis sets** The efficacy analysis set is the group of subjects receiving at least 1 dose of E7090 with at least 1 tumor assessment at baseline and after administration. This analysis set will be used for the interim assessment in Part 2. **Efficacy analyses** **Part 2**: Analysis results will be summarized for each cohort and overall. In addition to the analyses similar to those for Part 1, ORR, DCR, and their exact two-sided 95% confidence intervals will be calculated.	Changes based on the updated study design
2 9.7.3	**Interim Analyses** No interim analysis is planned in this study.	**Interim Analyses** No interim analysis taking into consideration adjustment for type I and II errors will be performed in this study. In the gastric cancer cohort in Part 2, an interim efficacy evaluation will be performed, and if no responder is observed in 5 evaluable subjects, the cohort may discontinue further enrollment. The duration of follow-up of subjects with continuous SD will be determined through discussion with the sponsor. This criterion is based on the posterior distribution of Bayesian statistics. When a non-informative beta prior distribution Beta (1,1) is used, the discontinuation criterion corresponds to the case where the probability of ORR being 40% or higher is less than 10% in the posterior distribution of the 5 subjects at the time of evaluation. In	To change the study design

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		cases other than the number of evaluable subjects established as the discontinuation criterion, if necessary, it will be acceptable to consider interim evaluations and discontinuation of enrollment based on the posterior distribution and criteria described above. The ORR threshold of 40% has been established as a beneficial effect size, taking the mechanism of action of E7090 into consideration.	
2 9.7.2	**Sample Size Rationale** The sample size for Part 2 has been set to approximately 10 subjects per cohort, to allow further safety evaluation and the preliminary antitumor effect evaluation.	**Sample Size Rationale** The sample size for Part 2 has been set to approximately 10 subjects or 5 subjects per cohort, considering its feasibility, to allow further safety evaluation and the preliminary antitumor effect evaluation.	To change the study design
5.3	**5.3 Subject Information and Informed Consent** The ICF for genetic testing will be prepared separately from that for study participation, and genetic testing will be conducted in subjects who have consented to the testing. Genetic testing involving the use of blood samples is required and subjects who do not consent to such testing cannot be included in this clinical study, whereas those who do not consent to genetic testing of tumor samples can still be eligible for this study.	**5.3 Subject Information and Informed Consent** The ICF for genetic testing will be prepared separately from that for study participation, and genetic testing will be conducted in subjects who have consented to the testing. In Part 1, genetic testing involving the use of blood samples is required and subjects who do not consent to such testing cannot be included in this clinical study, whereas those who do not consent to genetic testing of tumor samples can still be eligible for this study. In Part 2, genetic testing involving the use of blood and tumor samples are required (tumor samples will not be obtained from subjects who cannot submit an archived tumor sample collected in the past or who are not amenable to biopsy).	To change the study design
6	**6. INVESTIGATORS AND STUDY PERSONNEL** This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor). Part 1 will be conducted at 1 medical institution in Japan.	**6. INVESTIGATORS AND STUDY PERSONNEL** This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor). Part 1 will be conducted at 1 medical institution in Japan, and Part 2 will be conducted at approximately 14 to 17 medical institutions (planned) in Japan.	For updated information
7.3.1	**7.3.1 Pharmacodynamics** **[Primary Pharmacodynamic Studies]** In nude mouse models transplanted subcutaneously with SNU-16 and NCI-H1581, E7090 (6.25 to 50 mg/kg as E7090 succinate) given orally once daily for 14 days exhibited significant, dose-dependent antitumor effects, without decreasing body weight. At 50 mg/kg, tumor growth was inhibited almost completely.	**7.3.1 Pharmacodynamics** **[Primary Pharmacodynamic Studies]** In nude mouse models transplanted subcutaneously with SNU-16 and NCI-H1581, E7090 (6.25 to 50 mg/kg as E7090 succinate) given orally once daily for 14 days exhibited significant, dose-dependent antitumor effects, without decreasing body weight. At 50 mg/kg, tumor growth was inhibited almost completely. In nude mouse models transplanted subcutaneously with cholangiocarcinoma derived from patients with the FGFR2-BICC1 fusion gene, E7090 (5 to 50 mg/kg as E7090 succinate) given orally once daily for 15 days exhibited significant antitumor effects at 15 mg/kg or higher. At 50 mg/kg, tumor reduction was observed.	For updated information

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7.4	No corresponding description	**7.4 Clinical Experience** As of 28 March 2017, 24 patients (2 each in the 1, 2, 4, 8, 16, and 30 mg groups and 3 each in the 60, 100, 140, and 180 mg groups) have been enrolled in Part 1 of this study. Commonly reported adverse events (≥20% across the groups) included hyperphosphatemia (37.5%); increased blood creatinine and nausea (33.3% each); diarrhea (29.2%); increased ALT and fatigue (25.0% each); and constipation, increased lipase, pyrexia, and tumor pain (20.8% each). Reported Grade ≥3 adverse events included increased ALT (2 subjects in the 180 mg group), increased AST (1 subject in the 180 mg group), decreased appetite (1 subject in the 180 mg group), decreased neutrophil count (1 subject in the 180 mg group), vomiting (1 subject in the 180 mg group), and decreased lymphocyte count (1 subject in the 60 mg group), all of which were Grade 3 in severity. DLTs (Grade 3 increased AST and increased ALT) occurred in 1 subject in the 180 mg group. Three serious adverse events were reported in 2 subjects in the 8 mg group (cancer pain and dyspnea each in 1 subject) and 1 subject in the 30 mg group (pyrexia), all of which were assessed as unrelated to study treatment. No adverse events led to death or treatment discontinuation.	For updated information
7.5.1.3	No corresponding description	**7.5.1.3 Rationale for the Starting Dose for Part 2** On the basis of the data from Part 1, the starting dose for Part 2 has been set at 140 mg. In Part 1, patients were enrolled in the following order: 1 mg (n = 2), 2 mg (n = 2), 4 mg (n = 2), 8 mg (n = 2), 16 mg (n = 2), 30 mg (n = 2), 60 mg (n = 3), 100 mg (n = 3), 180 mg (n = 3), and 140 mg (n = 3). Because a DLT was observed in 1 subject in the 180-mg cohort (Grade 3 increased AST/ALT) and no DLT was observed in the 140-mg cohort, 140 mg has been selected as the recommended dose for Part 2.	For updated information
7.5.1.8	**7.5.1.8 Rationale for Including Patients with Solid Tumors Harboring FGF/FGFR Genetic Abnomalities** Although E7090 is expected to be effective by targeting genetic abnormalities strongly contributing to FGF/FGFR signal activation, it is not easy to make an accurate prediction of its contribution level. There are many kinds of genetic abnormalities including translocation, point mutation, amplification. It was reported that there were some cases in which the contribution level of the same genetic abnormality	**7.5.1.8 Rationale for Including Patients with Gastric Cancer Carrying an Amplified FGFR2 Gene or an Overexpressed FGFR2 Protein and Patients with Cholangiocarcinoma Harboring FGFR2-Fusion Genes in Part 2** Given that responses were achieved in patients with gastric cancer carrying an amplified FGFR2 gene in Part 1 of this study, gastric cancer carrying an amplified FGFR2 gene or an overexpressed FGFR2	For updated information

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	differed dependent on the cancer type (Dienstmann R1, etc., 2014). Therefore, it is reasonable to include patients with solid tumors harboring FGF/FGFR genetic abnormalities, to search for cancer type or genetic abnormalities for which E7090 seems to be effective. A Japanese research group recently identified an in-frame fusion transcript (FGFR2 fusion gene) involving FGFR2 and other genes (BICC1 gene or AHCYL1 gene) in cholangiocarcinoma (Arai Y1, et al., 2014), suggesting that it may be a promising target for FGFR inhibitors. Therefore, cholangiocarcinoma harboring FGFR2-fusion genes is expected to be a promising target for E7090.	protein is expected to be a promising target for E7090. In addition, a Japanese research group recently identified an in-frame fusion transcript (FGFR2 fusion gene) involving FGFR2 and other genes (BICC1 gene or AHCYL1 gene) in cholangiocarcinoma (Arai Y1, et al., 2014), suggesting that it may be a promising target for FGFR inhibitors. Therefore, cholangiocarcinoma harboring FGFR2-fusion genes is expected to be a promising target for E7090.	
7.5.2	**7.5.2 Methods of Evaluating Adverse Drug Reactions Expected from Nonclinical Toxicity Studies** **[Evaluation of mineralization]** Since mineralization is induced by the deposition of phosphate combined with calcium in the blood, it is important to evaluate and control serum phosphate levels. In this study, it is stipulated that serum phosphate levels must be measured at study visits and that high phosphate levels will be managed in a medically proper manner. **[Evaluation of thinning of the corneal epithelium]** Serious corneal thinning could greatly reduce the patient's QOL, therefore requiring special attention. In Part 1, the dose-escalation part of this study, to rigorously evaluate the effect of E7090 on the eyes, the ophthalmologist at each study site participated in the study as a subinvestigator and performed the following tests on prespecified evaluation days: visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and anterior segment optical coherence tomography (OCT) to evaluate the corneal epithelium. After the review of clinical findings for each test, the necessity for each test in Part 2 will be reconsidered.	**7.5.2 Methods of Evaluating Adverse Drug Reactions Expected from Nonclinical Toxicity Studies** **[Evaluation of mineralization]** Since mineralization is induced by the deposition of phosphate combined with calcium in the blood, it is important to evaluate and control serum phosphate levels. In this study, it is stipulated that serum phosphate levels must be measured at study visits and that high phosphate levels will be managed in accordance with the criteria for dose interruption/reduction shown in Table 6. **[Evaluation of thinning of the corneal epithelium]** Serious corneal thinning could greatly reduce the patient's QOL, therefore requiring special attention. In Part 1, the dose-escalation part of this study, to rigorously evaluate the effect of E7090 on the eyes, the ophthalmologist at each study site participated in the study as a subinvestigator and performed the following tests on prespecified evaluation days: visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and anterior segment optical coherence tomography (OCT) to evaluate the corneal epithelium. In Part 1, prespecified tests have revealed no significant thinning of the corneal epithelium, but Grade 1 retinal adverse events were observed. In Part 2, taking these findings into consideration, anterior segment OCT will be replaced by posterior segment OCT to evaluate the retina. More specifically, visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and posterior segment OCT to evaluate the retina will be performed on prespecified evaluation days in Part 2.	To update the method of evaluation based on the data in Part 1
9.1	**9.1 Overall Study Design and Plan** No corresponding description	**9.1 Overall Study Design and Plan** Part 2 will include patients with solid tumors, consisting of a gastric	To clarify the targeted patients

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		cancer cohort and a cholangiocarcinoma cohort.	
9.3	**9.3 Selection of Study Population** Approximately 20 subjects will be enrolled in Part 1. Approximately 10 subjects will be enrolled per dose cohort in Part 2. In other words, selection of 1 dose in Part 1 will lead to approximately 10 subjects, while selection of 2 doses will lead to approximately 20 subjects. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to take the study drug.	**9.3 Selection of Study Population** Approximately 20 subjects will be enrolled in Part 1. Approximately 10 subjects with gastric cancer confirmed to carry an amplified FGFR2 gene or an overexpressed FGFR2 protein and approximately 5 subjects with cholangiocarcinoma confirmed to harbor FGFR2-fusion genes will be enrolled in Part 2. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to take the study drug.	To change the study design
9.4.5	**9.4.5 Method of Assigning Subjects to Treatment Groups** This is an open-label study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to take E7090. There is no randomization in this study. The subject registration procedure is shown in Figure 6.	**9.4.5 Method of Assigning Subjects to Treatment Groups** This is an open-label study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to take E7090. There is no randomization in this study. The subject registration procedure is shown in Figure 6 (Part 1) and Figure 7 (Part 2).	For updated information
9.4.5	**9.4.5 Method of Assigning Subjects to Treatment Groups** No corresponding description	**9.4.5Method of Assigning Subjects to Treatment Groups** [Part 2] (1) The investigator, subinvestigator, or clinical study collaborator will assign a sponsor-specified subject ID number to each patient providing written informed consent for Screening 1 and document this information in the Subject Screening Log. (2) For a patient known to have FGF/FGFR genetic abnormality, the investigator, subinvestigator, or clinical study collaborator will submit necessary documents about the genetic abnormality to the sponsor. The sponsor will check the documents about the genetic abnormality and notify the investigator, subinvestigator, or clinical study collaborator of the patient's eligibility/ineligibility by e-mail or fax. (3) If it is not known whether a gastric cancer patient has a FGF/FGFR genetic abnormality, the investigator, subinvestigator, or clinical study collaborator will submit an archived sample to the central laboratory. The central laboratory will report the result of genetic abnormality test to the sponsor and the study site. The patient will be determined to be eligible for Screening 1 if the test result is positive and ineligible for Screening 1 if the test result is negative. (4) The investigator, subinvestigator, or clinical study collaborator will enter the result of the patient's eligibility for Screening 1 in	For updated information

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		the Subject Screening Log, and patients who are determined to be eligible will go to the procedure for Screening 2. (5) The investigator or subinvestigator will screen the patient providing written informed consent for Screening 2 and determine his/her eligibility according to the inclusion/exclusion criteria. The investigator, subinvestigator, or clinical study collaborator will document the result of eligibility determination in the Subject Screening Log. (6) After the investigator and the subinvestigator determine the eligibility of the patient through the screening test, the investigator, subinvestigator, or clinical study collaborator will promptly notify the sponsor by e-mail or fax of the eligibility/ineligibility determined by the screening test, the planned start date of study treatment (when the patient is eligible), and the planned date of baseline assessment (when the baseline assessment is performed separately). (7) The investigator or subinvestigator will check the result of the baseline assessment against the inclusion/exclusion criteria to determine the eligibility of the patient again, and document the result of eligibility determination in the Subject Screening Log. After confirmation of his/her eligibility, the patient will start study treatment.	
9.4.5	No corresponding description	Figure 7 Subject Enrollment Procedure (Part 2) was added.	For updated information
9.4.6	**9.4.6 Selection of Doses in the Study** The appropriateness of selection of the doses is justified in Section 7.5.1 "Rationale for the Study Design" and Section 7.5.1.2 "Rationale for the Initial Dose."	**9.4.6 Selection of Doses in the Study** The appropriateness of selection of the doses for Part 1 and Part 2 of this study is justified in Section 7.5.1 "Rationale for the Study Design," Section 7.5.1.2 "Rationale for the Initial Dose for Part 1," and Section 7.5.1.3 "Rationale for the Starting Dose for Part 2."	For updated information
9.4.9	**9.4.9 Prior and Concomitant Therapy** All concomitant therapies used after the time of informed consent until the date of final observation will be recorded in the CRF.	**9.4.9 Prior and Concomitant Therapy** All concomitant therapies used after the time of informed consent (after the time of informed consent for Screening 2 in Part 2) until the date of final observation will be recorded in the CRF.	To clarify the statement
9.5.1.1	**9.5.1.1 Demographic Assessments** The investigator, subinvestigator, or clinical study collaborator will assess each patient providing written informed consent for necessary information to confirm the inclusion and exclusion criteria, and document this information in the Subject Registration Form. The investigator, subinvestigator, or clinical study collaborator will also assess each patient providing written informed consent for the	**9.5.1.1 Demographic Assessments** The investigator, subinvestigator, or clinical study collaborator will assess each patient providing written informed consent for necessary information to confirm the inclusion and exclusion criteria, and document this information in the Subject Registration Form (Part 1) and the Subject Eligibility Confirmation Form (Part 2). The investigator, subinvestigator, or clinical study collaborator will also	To clarify the statement

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	following subject demography information, and document the information in the CRF. For any information already assessed during the confirmation of the inclusion and exclusion criteria, the investigator, subinvestigator, or clinical study collaborator may enter the data entered in the Subject Registration Form in the CRF, instead of assessing such information again.	assess each patient providing written informed consent for the following subject demography information, and document the information in the CRF. For any information already assessed during the confirmation of the inclusion and exclusion criteria, the investigator, subinvestigator, or clinical study collaborator may enter the data entered in the Subject Registration Form (Part 1) and the Subject Eligibility Confirmation Form (Part 2) in the CRF, instead of assessing such information again.	
9.5.1.2.2	**9.5.1.2.2 Other Pretreatment Assessments Specific to the Study or Target Disease** (1) For subjects with tumors harboring FGF/FGFR genetic abnormality, the following information will be recorded in the CRF: 1) Type of FGF/FGFR genetic abnormality (translocation, point mutation, amplification, other) 2) Diagnostic method for FGF/FGFR genetic abnormality (FISH, immunostaining, RT-PCR, NGS, other) 3) Date of the sample collected for FGF/FGFR genetic abnormality 4) Date of FGF/FGFR genetic abnormality test	**9.5.1.2.2 Other Pretreatment Assessments Specific to the Study or Target Disease** (1) For subjects with tumors harboring FGF/FGFR genetic abnormality (Part 1) and all subjects entering Screening 2 (Part 2), the following information will be recorded in the CRF: 1) Type of FGF/FGFR genetic abnormality (translocation, point mutation, amplification, other) 2) Diagnostic method for FGF/FGFR genetic abnormality (FISH, immunostaining, RT-PCR, NGS, other) 3) Site of the sample tested for FGF/FGFR genetic abnormality and date of the sample collected 4) Date of FGF/FGFR genetic abnormality test 5) Status of FGF/FGFR protein expression	To clarify the statement For updated information
9.5.1.3.1	**9.5.1.3.1 Assessment of Tumor Lesions** Chest X-rays will not be used to assess target lesions. Assessment methods for each site are as follows: ● Brain: CT or MRI	**9.5.1.3.1 Assessment of Tumor Lesions** Chest X-rays will not be used to assess target lesions. Assessment methods for each site are as follows: ● Head: CT or MRI	Correction in view of consistency of the term
9.5.1.3.3	No corresponding description	**9.5.1.3.3 Survival Follow-up** Subjects will be followed for survival every 12 weeks (±2 weeks) from the time of study treatment discontinuation. Follow-up is to be continued until the confirmation of death. For any antitumor therapy, which is known as of the assessment to be provided for the subject after completion of study treatment, its start date and end date will be recorded. Survival follow-up will be terminated 2 years after the last subject's registration (Part 2).	To clarify the method of survival follow-up
9.5.1.4.1	**9.5.1.4.1 Pharmacokinetic Assessments** **(1) Plasma concentration measurement** Blood samples will be collected at the time points shown in Table 8	**9.5.1.4.1 Pharmacokinetic Assessments** **(1) Plasma concentration measurement** Blood samples will be collected at the time points shown in Table 8	To clarify that the metabolite of E7090 will

<table>
<tr><th>Section</th><th>Before Revision
(Version 6.0, Date: 22 Apr 2016)</th><th>After Revision
(Version 7.0, Date: 03 Jul 2017)</th><th>Reason for Revision</th></tr>
<tr><td></td><td>(Part 1) and Table 9 (Part 2), and the plasma concentrations of E7090 will be determined using a validated LC-MS/MS method.</td><td>(Part 1) and Table 9 (Part 2), and the plasma concentrations of E7090 and its active metabolite, E7090-M2, will be determined using a validated LC-MS/MS method.</td><td>be measured.</td></tr>
<tr><td>9.5.1.4.1</td><td>Table 9 Blood Sampling Schedule for PK Evaluation (Part 2)
<table>
<tr><th>Cycle</th><th>Sampling day</th><th>Sampling time point</th><th>Allowable sampling time interval</th><th>Blood sampling volume</th></tr>
<tr><td rowspan="13">Cycle 1</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td><td rowspan="13">2 mL at each time point</td></tr>
<tr><td>Day 8</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td>Day 15</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td rowspan="10">Date undetermined[a)] (in the fasting condition)</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td>30 minutes postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>1 hour postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>2 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>3 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>5 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>10 hours postdose</td><td>Within ±30 minutes</td></tr>
<tr><td>24 hours postdose</td><td>Within ±60 minutes</td></tr>
<tr><td>Date undetermined</td><td>Predose</td><td>Within −60 minutes</td></tr>
</table></td><td>Table 9 Blood Sampling Schedule for PK Evaluation (Part 2)
<table>
<tr><th>Cycle</th><th>Sampling day</th><th>Sampling time point</th><th>Allowable sampling time interval</th><th>Blood sampling volume</th></tr>
<tr><td rowspan="11">Cycle 1</td><td rowspan="10">Day 1</td><td>Predose</td><td>Within −60 minutes</td><td rowspan="11">2 mL at each time point</td></tr>
<tr><td>30 minutes postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>1 hour postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>2 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>3 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>5 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td>10 hours postdose</td><td>Within ±30 minutes</td></tr>
<tr><td>24 hours postdose (Predose on Day 2)</td><td>Within −60 minutes</td></tr>
<tr><td>Day 8</td><td>Predose</td><td>Within −60 minutes</td></tr>
</table></td><td>To update the measurement time points

To delete consideration of food effect</td></tr>
</table>

<table>
<tr><th>Section</th><th>Before Revision
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(Version 7.0, Date: 03 Jul 2017)</th><th>Reason for Revision</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>[a] (in the high fat-fed condition)</td><td>30 minutes postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>1 hour postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>2 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>3 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>5 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>10 hours postdose</td><td>Within ±30 minutes</td></tr>
<tr><td></td><td></td><td>24 hours postdose</td><td>Within ±60 minutes</td></tr>
<tr><td>Cycle 2 and subsequent cycles</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
</table>
</td><td>
<table>
<tr><td></td><td></td><td>30 minutes postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>1 hour postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>2 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>3 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>5 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>10 hours postdose</td><td>Within ±30 minutes</td></tr>
<tr><td></td><td></td><td>24 hours postdose (Predose on Day 9)</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 15</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td>Cycle 2 and subsequent cycles</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
</table>
</td><td></td></tr>
<tr><td>9.5.1.4.2</td><td>9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments
No corresponding description</td><td><u>9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments</u>
[Part 2]
<u>(1) In blood samples</u>
<u>Blood samples will be collected according to the procedures and methods shown in Table 11 to determine blood biomarkers. For sampling time points, the actual time of blood sampling will be recorded in the CRF. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples.</u></td><td>For updated information</td></tr>
</table>

<table>
<tr><th>Section</th><th>Before Revision
(Version 6.0, Date: 22 Apr 2016)</th><th>After Revision
(Version 7.0, Date: 03 Jul 2017)</th><th>Reason for Revision</th></tr>
<tr><td></td><td></td><td>The following measurements will be determined:
1) FGF23
2) 1,25-(OH)2-Vitamin D
3) CCI
4) Angiogenesis markers (eg, VEGF, FGF)
5) Circulating tumor DNA

Table 11 Blood Sampling Schedule for PD and PGx Evaluations (Part 2)
<table>
<tr><th>Cycle</th><th>Sampling day</th><th>Sampling time point</th><th>Allowable sampling time interval</th><th>Sampling volume</th><th>Measurement</th></tr>
<tr><td>At baseline</td><td colspan="3">Within 4 days after start of treatment</td><td>15 mL</td><td>5)</td></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td><td>7 mL</td><td rowspan="3">1) to 4)</td></tr>
<tr><td>Day 8</td><td>Predose</td><td>Within −60 minutes</td><td>7 mL</td></tr>
<tr><td>Day 15</td><td>Predose</td><td>Within −60 minutes</td><td>7 mL</td></tr>
<tr><td>Odd-numbered cycles (Cycle 3 and subsequent cycles)</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td><td>10 mL</td><td>5)</td></tr>
</table></td><td></td></tr>
<tr><td>9.5.1.4.2</td><td></td><td>9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments
(2) In archived tumor samples
If any sample collected in the past is available, an archived tumor sample should be submitted (mandatory). If known, the date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF.</td><td>For updated information</td></tr>
</table>

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
		(3) In biopsied tumor samples Except for subjects who have only a tumor lesion not amenable to biopsy for safety reasons, samples obtained from the biopsy performed in Screening 2 must be submitted (mandatory). Any reason for infeasible biopsy will be recorded in source documents. The date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF. In addition, a biopsy tumor sample will be collected on Day 15 of Cycle 1 (optional). Tumor biopsies should be taken from the same organ whenever possible. The actual time of sample collection will be recorded in the CRF. See Appendix 9 for a description of collection, handling, and shipping procedures of the samples. The date of sample collection and the organ from which the tumor has been collected will be recorded in the CRF.	
9.5.1.5.1	**9.5.1.5.1 Adverse Events** An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E7090. The criteria for identifying AEs in this study are: ● Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product	**9.5.1.5.1 Adverse Events** An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E7090. The criteria for identifying AEs in this study are: ● Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (For Part 2, events observed after informed consent for Screening 2 will be assessed)	To clarify the statement
9.5.1.5.1	**9.5.1.5.1 Adverse Events** All AEs observed during the study will be recorded in the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the informed consent form through the last visit (30 days after the last dose of study treatment).	**9.5.1.5.1 Adverse Events** All AEs observed during the study (for Part 2, after informed consent for Screening 2) will be recorded in the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the informed consent form (for Part 2, after informed consent for Screening 2) through the last visit (30 days after the last dose of study treatment).	To clarify the statement
9.5.1.5.3	**9.5.1.5.3 Laboratory Measurements** **[Monitoring of serum phosphorus levels]** Nonclinical toxicity studies have reported mineralization associated with hyperphosphatemia, which are considered attributable to the inhibition of FGFR kinase, the pharmacological action of E7090.	**9.5.1.5.3 Laboratory Measurements** **[Monitoring of serum phosphorus levels]** Nonclinical toxicity studies have reported mineralization associated with hyperphosphatemia, which are considered attributable to the inhibition of FGFR kinase, the pharmacological action of E7090.	For updated information

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
	Given that similar events have also been observed in clinical studies of similar drugs, attention needs to be paid to such toxicities in this study. If high serum phosphorus levels are observed, they should be managed in a medically proper manner (such as diet therapy, dose interruption, dose reduction and hyperphosphatemia drugs). In addition, any necessary test (eg, X-ray) should be performed if any clinical symptom suggestive of mineralization is observed.	Given that similar events have also been observed in clinical studies of similar drugs, attention needs to be paid to such toxicities in this study. If high serum phosphorus levels are observed, the criteria for dose interruption/reduction shown in Table 6 should be followed. In addition, any necessary test (eg, X-ray) should be performed if any clinical symptom suggestive of mineralization is observed.	
9.5.1.5.7	**9.5.1.5.7 Ophthalmological Examinations** Ophthalmological examinations will be performed at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Examinations in Part 1 will include visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and anterior segment optical coherence tomography (OCT) to evaluate the corneal epithelium. Corneal epithelial thickness will be measured by anterior segment OCT and recorded in the CRF. The necessity for examinations in Part 2 will be reconsidered, after the effect of E7090 on the eyes is reviewed.	**9.5.1.5.7 Ophthalmological Examinations** Ophthalmological examinations will be performed at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Examinations in Part 1 will include visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and anterior segment optical coherence tomography (OCT) to evaluate the corneal epithelium. Corneal epithelial thickness will be measured by anterior segment OCT and recorded in the CRF. Examinations in Part 2 will include visual acuity, funduscopy (mydriatic test when necessary), slit-lamp examination (fluorescein staining when necessary), and posterior segment OCT to evaluate the retina.	For updated information
9.5.1.7	**9.5.1.7 Concomitant Drugs and Therapies** The investigator, subinvestigator, or clinical study collaborator will instruct subjects to comply with the stipulations on prohibited concomitant treatments in Section 9.4.9.2 "Prohibited Concomitant Therapies and Drugs," and investigate concomitant treatment according to the following. (1) Concomitant drugs At each visit, all drugs used from the time of written informed consent through the end of the last observation period will be investigated, and the information listed below will be recorded in the CRF. If the subject is treated at another department or hospital, the treating physician will be interviewed if necessary. If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent. Drug name, reason for use, start date of treatment, and end date of treatment (date when the treatment is completed or "continued treatment after the last visit")	**9.5.1.7 Concomitant Drugs and Therapies** The investigator, subinvestigator, or clinical study collaborator will instruct subjects to comply with the stipulations on prohibited concomitant treatments in Section 9.4.9.2 "Prohibited Concomitant Therapies and Drugs," and investigate concomitant treatment according to the following. (1) Concomitant drugs At each visit, all drugs used from the time of written informed consent (for Part 2, informed consent for Screening 2) through the end of the last observation period will be investigated, and the information listed below will be recorded in the CRF. If the subject is treated at another department or hospital, the treating physician will be interviewed if necessary. If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent. Drug name, route of administration, reason for use, start date of treatment, and end date of treatment (date when the treatment is	To clarify the statement

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
	(2) Concomitant therapies At each visit, all therapies provided from the time of written informed consent through the end of the last observation period will be investigated, and the information listed below will be recorded in the CRF. If the subject is treated at another department or hospital, the treating physician will be interviewed if necessary.	completed or "continued treatment after the last visit") (2) Concomitant therapies At each visit, all therapies provided from the time of written informed consent (for Part 2, informed consent for Screening 2) through the end of the last observation period will be investigated, and the information listed below will be recorded in the CRF. If the subject is treated at another department or hospital, the treating physician will be interviewed if necessary.	
9.5.2	**Table 14 Schedule of Procedures/Assessments in Part 2** a) To be performed only when consent is obtained. b) Any available viral test data obtained within 6 months before the start of study treatment may be used as screening data. c) Any data obtained within 28 days before the start of study treatment may be used (any data obtained before informed consent may also be used). d) For assessments performed at both screening and baseline, if screening assessment is performed within 4 days after the start of study treatment, baseline assessment may be omitted. e) To be performed predose. f) The test/observation may be omitted only if the investigator or subinvestigator considers that the safety of the subject is ensured. g) To be performed on Day 1 of Cycle 2. To be performed every 8 weeks (on Day 1 [±3 days] of even-numbered cycles) thereafter. h) Tumor evaluation and tumor marker assessment will be performed every 8 weeks (on Day 1 [±7 days] of odd-numbered cycles) after Day 1 of Cycle 1, and more frequently if clinically indicated. i) To be performed predose on Day 8 and Day 15. In addition, the effect of food on E7090 pharmacokinetics will be considered. A pharmacokinetic comparison will be carried out between the fasting state and the high fat-fed state of the same patients during Cycle 1. The dates for PK evaluation in the fasting state and in the high-fat fed state will be determined after PK evaluation in Part 1. j) To be performed in odd-numbered cycles after Cycle 3. k) To be obtained during the study period whenever possible. l) Any available data obtained within 7 days before discontinuation may be used as data at discontinuation. m) Any available data obtained within 28 days before discontinuation may be used as data at discontinuation. n) If it is necessary to start a new anticancer agent immediately due to	**Table 14 Schedule of Procedures/Assessments in Part 2** a) Only in gastric cancer patients with available samples to allow confirmation of FGFR2 protein expression at the time of informed consent for Screening 1. Patients in whom the presence of FGFR2 gene amplification is unknown but the presence of FGFR2 protein overexpression is confirmed by central laboratory may enter Screening 2. b) Any available viral test data obtained within 6 months before the start of study treatment may be used as screening data. c) Any data obtained within 28 days before the start of study treatment may be used (any data obtained before informed consent may also be used). d) Excluding patients with only a tumor lesion not amenable to biopsy for safety reasons. e) For assessments performed at both screening and baseline, if screening assessment is performed within 4 days after the start of study treatment, baseline assessment may be omitted. f) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours (predose on Day 2) postdose. g) To be performed predose. h) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours (predose on Day 9) postdose on Day 8. PK evaluation may be performed within +1 or +2 days (not −2 or −1 days). i) To be performed within ±3 days. j) Tumor evaluation and tumor marker assessment will be performed every 8 weeks (on Day 1 [±7 days] of odd-numbered cycles) after Day 1 of Cycle 1, and more frequently if clinically indicated. k) Only in patients providing consent (optional). l) In Cycle 3 and subsequent cycles, test/observation may be omitted only if the investigator or subinvestigator considers the subject safe.	To change the study design For updated information

Section	Before Revision (Version 6.0, Date: 22 Apr 2016)	After Revision (Version 7.0, Date: 03 Jul 2017)	Reason for Revision
	deterioration of the subject's condition, the final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent. o) To be performed every 12 weeks (±1 weeks) after the time of discontinuation of study treatment.	However, if the blood phosphorus level is ≥7.1 mg/dL on Day 1 or Day 15, blood phosphorus levels should be measured to evaluate hyperphosphatemia. m) To be performed on Day 1 (±3 days) of Cycle 2. To be performed every 8 weeks (on Day 1 [±3 days] of even-numbered cycles) thereafter. n) To be performed in odd-numbered cycles after Cycle 3. o) To be obtained during the study period whenever possible. p) Any available data obtained within 7 days before discontinuation may be used as data at discontinuation. q) Any available data obtained within 28 days before discontinuation may be used as data at discontinuation. r) If it is necessary to start a new anticancer agent immediately due to deterioration of the subject's condition, the final observation may be performed before 30 days after the last dose of study treatment but must be performed before the start of the new anticancer agent. s) To be performed every 12 weeks (±2 weeks) after the time of discontinuation of study treatment.	

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

22 Apr 2016

<table>
<tr><th>Section</th><th>Before Revision
(Version 5.0, Date: 04 Apr 2016)</th><th>After Revision
(Version 6.0, Date: 22 Apr 2016)</th><th>Reason for Revision</th></tr>
<tr><td>2</td><td>Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group.</td><td>Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert. At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group <u>(including changes in the assignment of a dose and the percentage of dose escalation)</u>.</td><td rowspan="2">To clarify the statement</td></tr>
<tr><td>9.4.1.6</td><td>9.4.1.6 Determination of Transition to the Next Dose Group
Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert according to Section 9.4.1.3 “Method of Subject’s Dose Assignment” and Section 9.4.1.4 “Method of Determining the Dose for the Next Dose Group.” At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group.</td><td>9.4.1.6 Determination of Transition to the Next Dose Group
Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert according to Section 9.4.1.3 “Method of Subject’s Dose Assignment” and Section 9.4.1.4 “Method of Determining the Dose for the Next Dose Group.” At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group <u>(including changes in the assignment of a dose and the percentage of dose escalation)</u>.</td></tr>
<tr><td>9.5.2</td><td>Table 13 Schedule of Procedures/Assessments in Part 1
<table>
<tr><th>Period</th><th colspan="5">Cycle 1</th></tr>
<tr><th>Day</th><th>1 [i]</th><th>3</th><th>8 (±1)</th><th>15 (±1)</th><th>22 (±1)</th></tr>
<tr><td>Hematology
Blood chemistry
Blood coagulation</td><td>X [j]</td><td></td><td>X</td><td>X</td><td>X</td></tr>
</table></td><td>Table 13 Schedule of Procedures/Assessments in Part 1
<table>
<tr><th>Period</th><th colspan="5">Cycle 1</th></tr>
<tr><th>Day</th><th>1 [i]</th><th>3</th><th>8 (±1)</th><th>15 (±1)</th><th>22 (±1)</th></tr>
<tr><td>Hematology
Blood chemistry
Blood coagulation</td><td>X [j]</td><td><u>X [w]</u></td><td>X</td><td>X</td><td>X</td></tr>
</table>
<u>w) Only blood chemistry (blood phosphorus level) will be performed.</u></td><td>To monitor blood phosphorus levels</td></tr>
</table>

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

04 Apr 2016

Section	Before Revision (Version 4.0, Date: 29 Jan 2016)	After Revision (Version 5.0, Date: 04 Apr 2016)	Reason for Revision
2	**Study Treatment** E7090 will be administered orally once daily. Study drug consists of 1, 1.5, 5, and 20 mg capsules.	**Study Treatment** E7090 will be administered orally once daily. Study drug consists of 1, 1.5, 5, 20, and 60 mg capsules.	
9.4	**9.4 Treatment** The study drug for this study is E7090 in the following formulations, 1, 1.5, 5, and 20 mg capsules ….	**9.4 Treatment** The study drug for this study is E7090 in the following formulations, 1, 1.5, 5, 20, and 60 mg capsules ….	To use 60 mg capsules
9.4.1.4	**9.4.1.4 Method of Determining the Dose for the Next Dose Group** …. Since theoretical values calculated using the above method of determining the dose may become fractions that cannot be formulated with the capsule potencies (1, 1.5, 5, and 20 mg) used in this study, ….	**9.4.1.4 Method of Determining the Dose for the Next Dose Group** …. Since theoretical values calculated using the above method of determining the dose may become fractions that cannot be formulated with the capsule potencies (1, 1.5, 5, 20, and 60 mg) used in this study, ….	

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

29 Jan 2016

Section	Before Revision (Version 3.0, Date: 13 Nov 2014)	After Revision (Version 4.0, Date: 29 Jan 2016)	Reason for Revision
2	**Administration schedule** 2) Cycle 1 and subsequent cycles (for 28 days each) Subjects will start Cycle 1 between the 8th and 10th days after administration in Cycle 0 and take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, and will not eat anything for 1 hour after administration. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.	**Administration schedule** 2) Cycle 1 and subsequent cycles (for 28 days each) Subjects will start Cycle 1 between the 8th and 10th days after administration in Cycle 0 and take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, and will not eat anything for 1 hour after administration. On the 8th day of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. Study treatment may be continued unless any of the criteria in Section 9.3.3.1 “Discontinuation Criteria for Individual Subjects” is met.	Because it is thought that the steady-state PK can be evaluated on the 8th day of Cycle 1, based on the half life of E7090
9.4.1.2	**(2) Cycle 1 (28 days)** Subjects will start Cycle 1 between the 8th and 10th days after administration in Cycle 0 and take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, without eating anything for 1 hour after administration. For PK evaluation, subjects will be instructed not to take E7090 on the morning of each visit day. **(3) Cycle 2 and subsequent cycles (28 days each)** Subjects will take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, without eating anything for 1 hour after administration. For PK evaluation, subjects will be instructed not to take E7090 on the morning of Day 1 of each cycle. On Day 1 of Cycle 2, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water.	**(2) Cycle 1 (28 days)** Subjects will start Cycle 1 between the 8th and 10th days after administration in Cycle 0 and take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, without eating anything for 1 hour after administration. For PK evaluation, subjects will be instructed not to take E7090 on the morning of each visit day. On Day 8 of Cycle 1, however, subjects will take E7090 in the fasting state on waking after an at least 10-hour overnight fast for PK evaluation. Subjects will be prohibited from eating or drinking for 2 hours after administration, except for drinking water. **(3) Cycle 2 and subsequent cycles (28 days each)** Subjects will take E7090 once daily continuously. Subjects will take E7090 at least 2 hours after breakfast, without eating anything for 1 hour after administration. For PK evaluation, subjects will be instructed not to take E7090 on the morning of Day 1 of each cycle.	

<table>
<tr>
<td>9.5.1.4.1</td>
<td>Table 8 Blood Sampling Schedule for PK Evaluation (Part 1)
<table>
<tr><th>Cycle</th><th>Sampling day</th><th>Sampling time point</th><th>Allowable sampling time interval</th></tr>
<tr><td>Cycle 0</td><td>…</td><td>…</td><td>…</td></tr>
<tr><td>Cycle 1</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 3</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 8</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 15</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 22</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td></td><td>30 minutes postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>1 hour postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>2 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>3 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>5 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>10 hours postdose</td><td>Within ±30 minutes</td></tr>
<tr><td></td><td>Day 2</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td>Cycle 3 and subsequent cycles</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
</table></td>
<td>Table 8 Blood Sampling Schedule for PK Evaluation (Part 1)
<table>
<tr><th>Cycle</th><th>Sampling day</th><th>Sampling time point</th><th>Allowable sampling time interval</th></tr>
<tr><td>Cycle 0</td><td>…</td><td>…</td><td>…</td></tr>
<tr><td>Cycle 1</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 3</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 8</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td></td><td>30 minutes postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>1 hour postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>2 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>3 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>5 hours postdose</td><td>Within ±10 minutes</td></tr>
<tr><td></td><td></td><td>10 hours postdose</td><td>Within ±30 minutes</td></tr>
<tr><td></td><td>Day 9</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 15</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td></td><td>Day 22</td><td>Predose</td><td>Within −60 minutes</td></tr>
<tr><td>Cycle 2 and subsequent cycles</td><td>Day 1</td><td>Predose</td><td>Within −60 minutes</td></tr>
</table></td>
<td>Because it is thought that the steady-state PK can be evaluated on the 8th day of Cycle 1, based on the half life of E7090</td>
</tr>
<tr>
<td>9.5.1.4.1</td>
<td>(2) Urinary concentration measurement
Urinary PK measurements will be performed in Part 1 only. On Day 1 of Cycle 2 in Part 1, a 24-hour urine collection will be performed to determine the urinary concentration of unchanged E7090.</td>
<td>(2) Urinary concentration measurement
Urinary PK measurements will be performed in Part 1 only. On Day 8 of Cycle 1 in Part 1, a 24-hour urine collection will be performed to determine the urinary concentration of unchanged E7090.</td>
<td>Because it is thought that the steady-state metabolite analysis can be performed on the 8th day of Cycle 1, based on the half life of E7090</td>
</tr>
</table>

<table>
<tr>
<td>9.5.2</td>
<td>
Table 13 Schedule of Procedures/Assessments in Part 1
<table>
<tr><th>Phase</th><th colspan="5">Treatment</th><th></th></tr>
<tr><th>Period</th><th colspan="5">Cycle 1</th><th>Cycle 2</th></tr>
<tr><th>Day</th><th>1 [i]</th><th>3</th><th>8 (±1)</th><th>15 (±1)</th><th>22 (±1)</th><th>1 (±3)</th></tr>
<tr><td>PK (blood)</td><td>X [j]</td><td>X [j]</td><td>X [j]</td><td>X [j]</td><td>X [j]</td><td>X [p]</td></tr>
<tr><td>PK (urine)</td><td></td><td></td><td></td><td></td><td></td><td>X [q]</td></tr>
</table>
j) To be performed predose.
p) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours postdose only in Cycle 2. To be performed predose in Cycle 3 and subsequent cycles.
q) A 24-hour urine collection will be performed only in Cycle 2.
</td>
<td>
Table 13 Schedule of Procedures/Assessments in Part 1
<table>
<tr><th>Phase</th><th colspan="5">Treatment</th><th></th></tr>
<tr><th>Period</th><th colspan="5">Cycle 1</th><th>Cycle 2</th></tr>
<tr><th>Day</th><th>1 [i]</th><th>3</th><th>8 (±1)</th><th>15 (±1)</th><th>22 (±1)</th><th>1 (±3)</th></tr>
<tr><td>PK (blood)</td><td>X [j]</td><td>X [j]</td><td>X [k]</td><td>X [j]</td><td>X [j]</td><td>X [i]</td></tr>
<tr><td>PK (urine)</td><td></td><td></td><td>X [l]</td><td></td><td></td><td></td></tr>
</table>
j) To be performed predose.
k) To be performed predose and 0.5, 1, 2, 3, 5, 10, and 24 hours postdose.
l) A 24-hour urine collection will be performed.
</td>
<td>Because the above changes were reflected in Table 13 Schedule of Procedures/Assessments in Part 1</td>
</tr>
<tr>
<td>9.7.1.7.2</td>
<td>Pharmacodynamic and PGx analyses
PD and PGx analyses will be performed using the PD and PGx analysis set.</td>
<td>Pharmacodynamic and PGx analyses
PD and PGx analyses will be performed using the PD and PGx analysis set.</td>
<td>Deletion of the underline (correction of error)</td>
</tr>
</table>

A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

13 Nov 2014

<table>
<tr><th>Section</th><th>Before Revision
(Version 2.0, Date: 04 Sep 2014)</th><th>After Revision
(Version 3.0, Date: 13 Nov 2014)</th><th>Reason for Revision</th></tr>
<tr><td>2
9.4.1.4</td><td>
<table>
<tr><th>Dose escalation for the next dose group (%)</th><th>Toxicities observed during Cycle 0 and Cycle 1 (except for alopecia)</th></tr>
<tr><td>100</td><td>Grade ≤1 toxicity only</td></tr>
<tr><td>50</td><td>Grade 2 toxicity in 1 subject</td></tr>
<tr><td>33</td><td>Grade 2 toxicity in 2 subjects or
Grade ≥3 toxicity in ≥1 subject</td></tr>
</table>
</td><td>
<table>
<tr><th>Dose escalation for the next dose group (%)</th><th>Toxicities observed during Cycle 0 and Cycle 1[(a)]</th></tr>
<tr><td>100</td><td>Grade ≤1 toxicity only</td></tr>
<tr><td>50</td><td>Grade 2 toxicity in 1 subject</td></tr>
<tr><td>33</td><td>Grade 2 toxicity in 2 subjects or
Grade ≥3 toxicity in ≥1 subject</td></tr>
</table>
(a) Excluding clinically insignificant events such as laboratory abnormalities requiring no treatment
</td><td>Correction of the description (based on the actual operation)</td></tr>
<tr><td>9.5.1.3.1</td><td>9.5.1.3.1 Assessment of Tumor Lesions
….
(1) CT or MRI
CT or MRI will be performed with contrast, except in subjects allergic to oral/intravenous contrast agents. In subjects allergic to contrast agents, a plain CT scan without contrast will be performed. In subjects allergic to intravenous contrast agents, CT with oral contrast may be considered, and for the abdominal or pelvic region, MRI with intravenous gadolinium may be considered.</td><td>9.5.1.3.1 Assessment of Tumor Lesions
….
(1) CT or MRI
CT or MRI will be performed with contrast, except in subjects not amenable to oral/intravenous contrast agents (due to allergy or renal dysfunction). In subjects not amenable to contrast agents, a plain CT scan without contrast will be performed. In subjects not amenable to intravenous contrast agents, CT with oral contrast may be considered, and for the abdominal or pelvic region, MRI with intravenous gadolinium may be considered.</td><td>Correction of the description (based on the actual operation)</td></tr>
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A Phase 1 Study of E7090 in Subjects with Solid Tumor
（Protocol Number: E7090-J081-101）

Revision History

04 Sep 2014

Section	Before Revision (Version 1.0, Date: 01 Aug 2014)	After Revision (Version 2.0, Date: 04 Sep 2014)	Reason for Revision
2 9.3.1	**Inclusion Criteria (for both Part 1 and Part 2)** (12) Women of childbearing potential must have practiced contraception since 28 days before registration (Part 1) or 28 days before the start of study treatment (Part 2), and must agree to use medically effective contraception (eg, the subject is using intrauterine devices, condoms with spermicide, contraceptive implants, or oral contraceptives; or the subject's male partner is confirmed to have no sperm after vasectomy) throughout the study period (for 30 days after the final study drug administration). Any subject practicing contraception by abstinence must agree to practice contraception with condoms with spermicide during the study period and for 30 days after the final study drug administration. Women of childbearing potential using any oral contraceptive are to use the oral contraceptive at a fixed dose for at least 4 weeks before study drug administration and continue to use the same oral contraceptive during the study period and for 30 days after the final study drug administration. All women will be considered to be of childbearing potential unless they are postmenopausal women (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).	**Inclusion Criteria (for both Part 1 and Part 2)** (12) Women of childbearing potential must have practiced contraception since 28 days before registration (Part 1) or 28 days before the start of study treatment (Part 2), and must agree to use medically effective contraception (eg, the subject is using intrauterine devices,* condoms with spermicide,* contraceptive implants,** or oral contraceptives;* or the subject's male partner is confirmed to have no sperm after vasectomy)[Note] throughout the study period (for 30 days after the final study drug administration). Any subject practicing contraception by abstinence must agree to practice contraception with condoms with spermicide during the study period and for 30 days after the final study drug administration. Women of childbearing potential using any oral contraceptive are to use the oral contraceptive at a fixed dose for at least 4 weeks before study drug administration and continue to use the same oral contraceptive during the study period and for 30 days after the final study drug administration. All women will be considered to be of childbearing potential unless they are postmenopausal women (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Note: Whether the drug/medical device has been approved or authorized in Japan (*, yes; **, no)	To clarify whether the drugs/medical devices have been approved or authorized in Japan
2 9.3.1	**Inclusion Criteria (for both Part 1 and Part 2)** (13) Participants or their female partners meeting the criteria above (when the partner is a woman with no childbearing potential or will use medically effective contraception throughout the study period and for 30 days after final study drug administration)	**Inclusion Criteria (for both Part 1 and Part 2)** (13) Male participants or their female partners meeting the criteria above (when the partner is a woman with no childbearing potential or will use medically effective contraception throughout the study period and for 30 days after final study drug administration)	To clarify the contraception rule in male participants

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2 9.3.2	**9.3.2 Exclusion Criteria** (14) Pregnant or breastfeeding patients	**9.3.2 Exclusion Criteria** (14) Pregnant or breastfeeding patients (breastfeeding patients may not be enrolled even if they discontinue breastfeeding)	To clarify that breastfeeding patients may not be enrolled even if they discontinue breastfeeding
2 9.3.3.1	**9.3.3.1 Discontinuation Criteria for Individual Subjects** Treatment with E7090 will be continued until any of the following discontinuation criteria is met: (1) Subject's refusal to continue study participation or withdrawal of consent (2) Major inclusion/exclusion criteria violation after registration (Part 1) or enrollment (Part 2) (3) Difficulty in continuing the study due to an adverse event in the opinion of the investigator or subinvestigator (4) Subject's pregnancy (5) Disease progression (except when the investigator or subinvestigator considers study treatment clinically beneficial to the subject) (6) Other cases where the investigator or subinvestigator considers study discontinuation appropriate	**9.3.3.1 Discontinuation Criteria for Individual Subjects** Treatment with E7090 will be continued until any of the following discontinuation criteria is met: (1) Subject's refusal to continue study participation or withdrawal of consent (2) Major inclusion/exclusion criteria violation after registration (Part 1) or enrollment (Part 2) (3) Difficulty in continuing the study due to an adverse event in the opinion of the investigator or subinvestigator (4) Subject's pregnancy (5) Disease progression (except when the investigator or subinvestigator considers study treatment clinically beneficial to the subject) (6) Dose reduction to <1 mg required due to an adverse drug reaction (7) Other cases where the investigator or subinvestigator considers study discontinuation appropriate	To clarify that study treatment will be discontinued when dose reduction to <1 mg is required
9.4.1.8	**9.4.1.8 Criteria for Dose Interruption/Reduction** Up to 2 dose reductions due to toxicity will be permitted. At the first dose reduction, the dose will be de-escalated to the dose of the next lower dose group. At the second dose reduction, the dose will be de-escalated to the dose of the second lower dose group. The sponsor should be consulted for more than 2 dose reductions. No dose escalation should be performed in the same subject.	**9.4.1.8 Criteria for Dose Interruption/Reduction** Up to 2 dose reductions due to toxicity will be permitted. At the first dose reduction, the dose will be de-escalated to the dose of the next lower dose group. At the second dose reduction, the dose will be de-escalated to the dose of the second lower dose group. The sponsor should be consulted for more than 2 dose reductions. The study will be discontinued if the dose needs to be reduced below 1 mg. No dose escalation should be performed in the same subject.	

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2 9.4.1.7	**9.4.1.7 Definition of Dose-Limiting Toxicity (DLT)** (1) Febrile neutropenia or Grade 4 neutropenia persisting for ≥7 days	**9.4.1.7 Definition of Dose-Limiting Toxicity (DLT)** (1) Febrile neutropenia, or Grade 4 neutropenia persisting for ≥7 days	To clarify that the onset of febrile neutropenia itself corresponds to DLT
9.1.1.2	**9.1.1.2 Treatment Period** In Cycle 1 and subsequent cycles, each consisting of 28 days, subjects will take repeated doses. Subjects will be hospitalized from Day 1 of Cycle 0 to the morning of Day 15 of Cycle 1. In Cycle 0 and Cycle 1, DLTs will be monitored and evaluated. Treatment may be continued unless any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met.	**9.1.1.2 Treatment Period** In Cycle 1 and subsequent cycles, each consisting of 28 days, subjects will take repeated doses. Subjects will be hospitalized from Day 1 of Cycle 0 to the morning of Day 15 of Cycle 1. The investigator or subinvestigator will carefully evaluate the results of the physical examination performed on Day 15 of Cycle 1 and all test results to determine from a medical standpoint whether each subject can be managed on an outpatient basis. If continued hospitalization is considered necessary from the aspect of subject safety, hospitalization will be continued after Day 15 of Cycle 1. In Cycle 0 and Cycle 1, DLTs will be monitored and evaluated. Treatment may be continued unless any of the criteria in Section 9.3.3.1 "Discontinuation Criteria for Individual Subjects" is met.	To clarify that the investigator or subinvestigator will determine whether each subject can be discharged or not after medical evaluation
9.4.1.2 9.4.2.2	**9.4.1.2 Administration Schedule** **Precautions for administration** No corresponding description **9.4.2.2 Administration Schedule** **Precautions for administration** No corresponding description	**9.4.1.2 Administration Schedule** **Precautions for administration** (4) Since it is currently unknown whether E7090 may cause phototoxicity, subjects will be instructed to avoid long-term sunlight exposure. **9.4.2.2 Administration Schedule** **Precautions for administration** (3) Since it is currently unknown whether E7090 may cause phototoxicity, subjects will be instructed to avoid long-term sunlight exposure.	To notify that long-term sunlight exposure should be avoided, given that phototoxicity due to E7090 cannot be completely ruled out

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2 9.4.1.3	**9.4.1.3 Method of Subject's Dose Assignment** Two subjects will be registered at each dose level.	**9.4.1.3 Method of Subject's Dose Assignment** Two subjects will be registered at each dose level. In a new dose group, the safety of the first subject should be evaluated before enrollment of the second and subsequent subjects.	To clarify that the safety of the first subject will be evaluated before enrollment of the second and subsequent subjects, because of the First-In-Human study of E7090
9.4.1.6	**9.4.1.6 Determination of Transition to the Next Dose Group** Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert according to Section 9.4.1.3 "Method of Subject's Dose Assignment" and Section 9.4.1.4 "Method of Determining the Dose for the Next Dose Group." At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary.	**9.4.1.6 Determination of Transition to the Next Dose Group** Transition to the next dose group will be determined through discussion among the investigator, the sponsor, and the medical expert according to Section 9.4.1.3 "Method of Subject's Dose Assignment" and Section 9.4.1.4 "Method of Determining the Dose for the Next Dose Group." At this time, advice may be obtained from the Data and Safety Monitoring Advisor as necessary. Safety data from subjects excluded from the DLT analysis population will also be considered when determining transition to the next dose group.	To clarify that transition to the next dose group will be determined, after consideration of the safety data from subjects excluded from the DLT analysis population
9.5.1.5.3	**9.5.1.5.3 Laboratory Measurements** **Table 12 Clinical Laboratory Tests** **Category** / **Parameters** No corresponding description / No corresponding description	**9.5.1.5.3 Laboratory Measurements** **Table 12 Clinical Laboratory Tests** **Category** / **Parameters** Blood coagulation tests / Activated partial thromboplastin time (aPTT)	To add a laboratory item

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9.5.1.5.10	No corresponding description	**9.5.1.5.10 Transcutaneous Arterial Oxygen Saturation Measurement** Arterial oxygen saturation will be measured with a pulse oximeter at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14).	To add a laboratory item
9.5.2	**Table 13 Schedule of Procedures/Assessments in Part 1** **Table 14 Schedule of Procedures/Assessments in Part 2** No corresponding description	**Table 13 Schedule of Procedures/Assessments in Part 1** **Table 14 Schedule of Procedures/Assessments in Part 2** Addition of "Transcutaneous arterial oxygen saturation" as a laboratory item with the same frequency as that of vital signs Addition of "Blood coagulation" as a laboratory item with the same frequency as that of hematology and blood chemistry	To add a laboratory item
9.7.1.8	**9.7.1.8 Safety Analyses** Safety variables include adverse events (AEs), clinical laboratory parameters, vital signs, weight, 12-lead ECG, ECOG-PS, and ophthalmology.	**9.7.1.8 Safety Analyses** Safety variables include adverse events (AEs), clinical laboratory parameters, vital signs, transcutaneous arterial oxygen saturation, weight, 12-lead ECG, ECOG-PS, and ophthalmology.	To add a laboratory item
9.7.1.8.4	**9.7.1.8.4 Vital Signs** For vital signs parameters (systolic and diastolic BP, pulse, respiratory rate, and body temperature), and weight, the measured value at and the change from baseline to each postbaseline time point will be calculated for each time point using descriptive statistics.	**9.7.1.8.4 Vital Signs** For vital signs parameters (systolic and diastolic BP, pulse, respiratory rate, and body temperature), transcutaneous arterial oxygen saturation, and weight, the measured value at and the change from baseline to each postbaseline time point will be calculated for each time point using descriptive statistics.	To add a laboratory item