Title: A Phase 2, Open-Label, Single-Arm Study of Cabozantinib in Japanese Patients With Advanced Hepatocellular Carcinoma Who Have Received Prior Systemic Anticancer Therapy

NCT Number: NCT03586973

Protocol Approve Date: 30-OCT-2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

PROTOCOL

A Phase 2, Open-Label, Single-Arm Study of Cabozantinib in Japanese Patients With Advanced Hepatocellular Carcinoma Who Have Received Prior Systemic Anticancer Therapy

A Phase 2 Study of Cabozantinib in Japanese Patients With Advanced Hepatocellular Carcinoma

Sponsor:	Takeda Pharmaceutical Company, Ltd 1-1 Doshomachi 4-chome, Chuo-ku, Osaka 540-8645		
Study Number:	Cabozantinib-2003		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Cabozantinib		
Date:	30 October 2018	**Version:**	Amendment 01

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
SAE and pregnancy reporting	See protocol annex
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	See protocol annex

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD Date

PPD Date

PPD Date

1.3 Protocol Amendment 01 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 01.

The primary changes of Amendment 01 are as follows:

- The subject, who continued the study treatment after determination of PD per RECIST 1.1, should discontinue study treatment after the second determination of disease progression.
- If the subsequent systemic anticancer treatment is conducted within 30 days after the last dose of study drug, 30-Day Posttreatment Followup is completed at that time.
- If the subsequent systemic anticancer treatment is conducted within 30 days after the last dose of study drug, AEs collection and recording in the eCRF are to be completed at that time.

Other changes were also made to clarify the study procedures. In addition, minor revisions (including grammatical and editorial changes) are included for clarification purposes. The details on changes of text are given in Appendix J.

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LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company, Ltd.	**Compound:** Cabozantinib	
Title of Protocol: A Phase 2, Open-Label, Single-Arm Study of Cabozantinib in Japanese Patients With Advanced Hepatocellular Carcinoma Who Have Received Prior Systemic Anticancer Therapy	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: Cabozantinib-2003	**Phase:** 2	

Study Design:

This is a phase 2, open-label, single-arm study to evaluate the efficacy and safety of cabozantinib in Japanese patients with advanced hepatocellular carcinoma (HCC) who have received prior systemic anticancer therapy (Cohort A: patients who have received prior sorafenib, Cohort B: patients who have not received prior sorafenib).

Following the Screening period, patients will be enrolled and treated with cabozantinib. A subject is considered to be enrolled in the study when the first dose of study drug will be administered.

Screening Period: Potential subjects will be screened to determine if they meet the required eligibility criteria after informed consent. Qualifying screening assessments must be performed within 28 days before the first day of study drug administration (Week 1 Day 1) unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria will receive cabozantinib 60 mg orally, once daily (QD) in the fasted state (dose at least 2 hours after meal and no more food intake for 1 hour postdose), preferably at bedtime. Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver directed local anticancer therapy, or until there are any other reasons for treatment discontinuation listed in the protocol. Treatment may continue after radiographic HCC progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks. However the subject should discontinue study treatment after the second determination of disease progression.

Posttreatment Period: A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug or until the start of subsequent systemic anticancer treatment, whichever occurs first. Radiographic tumor assessments, Child-Pugh assessments, alpha-fetoprotein (AFP) assessments, and health-related quality of life (HRQOL) assessments will continue, regardless of whether study treatment is given, reduced, held or discontinued until the day of the last tumor imaging assessment. Subjects will be contacted every 8 weeks (±7 days) after the 30-day posttreatment followup visit to assess survival status and document receipt of subsequent anticancer therapy. Subjects will be followed until death, withdrawal of consent, or the sponsor decision to discontinue collection of these data in the study.

Primary Objective:

The primary objective is to evaluate the efficacy of cabozantinib measured by Independent Radiology Committee (IRC)-assessed 24-week progression-free survival rate (PFSR) per RECIST 1.1 in Japanese patients with advanced HCC who have received prior sorafenib.

Secondary Objectives:

- To evaluate the efficacy of cabozantinib measured by IRC-assessed progression-free survival (PFS) per RECIST 1.1 in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by IRC-assessed objective response rate (ORR) per RECIST 1.1 in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by IRC-assessed disease control rate (DCR) per RECIST 1.1 in the patient population under study.

• To evaluate the efficacy of cabozantinib measured by overall survival (OS) in the patient population under study.	
Safety Objective: • To evaluate the safety of cabozantinib in the patient population under study.	
Subject Population: Previously treated advanced HCC	
Planned Number of Subjects: Approximately 32 subjects • Cohort A (subjects who have received prior sorafenib): at least 17 subjects • Cohort B (subjects who have not received prior sorafenib): approximately 15 subjects	**Planned Number of Sites:** Approximately 18 sites in Japan
Dose Level: Cabozantinib 60 mg (60 mg tablet×1), QD	**Route of Administration:** Oral
Duration of Treatment: Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver directed local anticancer therapy, or until there are any other reasons for treatment discontinuation listed in the protocol.	**Study Length:** The duration of the study, including enrollment, treatment, and followup, will be approximately 3 years.

Main Criteria for Inclusion:

1. Male or female Japanese patients 20 years of age or older on the day of consent.
2. Histological or cytological diagnosis of HCC (results of a previous biopsy will be accepted).
3. Measurable disease per RECIST 1.1 as determined by the investigator.
4. Patients who have disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation).
5. Patients who have received 1 or 2 prior systemic anticancer therapies for advanced HCC.
   - Cohort A: patients who have received prior sorafenib.
   - Cohort B: patients who have not received prior sorafenib.

   Note: Additional prior systemic therapies used as adjuvant or local therapy are allowed.
6. Radiographic progression following prior systemic anticancer therapy for advanced HCC.
7. Recovery to ≤Grade 1 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy.
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and life expectancy of at least 3 months.
9. Child-Pugh Score of A.
10. Adequate organ and marrow function at Screening (within 10 days before Week 1 Day 1):
    a) Absolute neutrophil count (ANC) ≥1,200/mm^3.
    b) Platelets ≥60,000/mm^3.
    c) Hemoglobin ≥8 g/dL.
    d) Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥40 mL/min using

the Cockroft-Gault equation.

e) Urine protein-to-creatinine ratio (UPCR) ≤1 mg/mg.

f) Total bilirubin ≤2 mg/dL.

g) Serum albumin ≥2.8 g/dL.

h) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5.0 × ULN.

i) Hemoglobin A1c (HbA1c) ≤8% (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤160 mg/dL).

11. Antiviral therapy per local standard of care if active hepatitis B virus (HBV) infection.
12. Female patients who:

a) Are postmenopausal (natural amenorrhea, not due to other medical reasons) for at least 1 year before the Screening visit, OR

b) Are surgically sterile, OR

c) If they are of childbearing potential, agree to practice 1 highly effective method of birth control with a condom, which is an effective barrier method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, OR

d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

e) Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug. If their partner are of childbearing potential, their female partner should use 1 highly effective method of birth control at the same time, OR

f) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

13. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
14. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

Main Criteria for Exclusion:

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma.
2. Any type of anticancer agent within 14 days before the first day of study drug administration (Week 1 Day 1).
3. Radiation therapy within 28 days (14 days for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 42 days before Week 1 Day 1 (patient is excluded if there are any clinically relevant ongoing complications from prior radiation therapy).
4. Prior cabozantinib treatment.
5. Treatment with any investigational products (excluding anticancer products approved in Japan) within 28 days before Week 1 Day 1.
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before Week 1 Day 1. Eligible patients must be without corticosteroid treatment at Week 1 Day 1.

7. Concomitant anticoagulation, with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).

   Note: Low-dose aspirin for prophylactic use (per local applicable guidelines) and low-dose, low molecular weight heparins (LMWH) are permitted (LMWH has not been approved for the use for cardioprotection in Japan). Anticoagulation with therapeutic doses of LMWH is allowed in patients without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before Week 1 Day 1, and who have had no complications from a thromboembolic event or the anticoagulation regimen.

8. Patients who have uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
   a) Cardiovascular disorders including
      i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias.
      ii. Uncontrolled hypertension defined as sustained blood pressure >150 mm Hg systolic, or >100 mm Hg diastolic despite optimal antihypertensive treatment.
      iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, or other ischemic event within 6 months before Week 1 Day 1.
      iv. Thromboembolic event within 3 months before Week 1 Day 1.
      v. A left-ventricular ejection fraction ≤50%.
   b) Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
      i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
      ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before Week 1 Day 1.

         Note: Complete healing of an intra-abdominal abscess must be confirmed prior to Week 1 Day 1.
   c) Major surgery within 2 months before Week 1 Day 1. Complete healing from major surgery must have occurred 1 month before Week 1 Day 1. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before Week 1 Day 1. Patients with clinically relevant complications from prior surgery are not eligible.
   d) Cavitating pulmonary lesion(s) or endobronchial disease.
   e) Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Patients with invasion or thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible.
   f) Clinically significant bleeding risk including the following within 3 months before Week 1 Day 1: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors.
   g) Other clinically significant disorders such as:
      i. Active infection requiring systemic treatment.
      ii. Known infection with human immunodeficiency virus, or known acquired immunodeficiency syndrome -related illness.
      iii. Active hepatitis B and/or C. Patients with active hepatitis virus infection controlled with antiviral therapy are eligible.
      iv. Serious non-healing wound/ulcer/bone fracture.
      v. Malabsorption syndrome.

vi. Uncompensated/symptomatic hypothyroidism.
vii. Requirement for hemodialysis or peritoneal dialysis.
viii. History of solid organ transplantation.

9. Patients with untreated or incompletely treated varices with bleeding or high risk for bleeding. Patients treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months before Week 1 Day 1 are eligible.
10. Moderate or severe ascites.
11. Corrected QT interval calculated by the Fridericia formula (QTcF) >500 msec within 14 days before Week 1 Day 1.

    Note: If the QTcF is >500 msec in first electrocardiogram (ECG), a total of 3 ECGs each separated by at least 3 minutes should be performed within 30 minutes. If the average of these 3 consecutive results for QTcF is ≤500 msec, the patient meets eligibility in this regard.
12. Inability to swallow tablets.
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
14. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.

    Note: Female patients who are in the lactation period, even if they discontinue breastfeeding, will be excluded from the study.
15. Previously diagnosed with another malignancy and have any evidence of residual disease within 2 years before Week 1 Day 1.

    Note: Patients with superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy are not excluded.
16. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
17. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of cabozantinib.
18. Use of strong CYP3A4 inhibitors and CYP3A4 inducers within 14 days before Week 1 Day 1.
19. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

- 24-week PFSR, per RECIST 1.1, by IRC.

Secondary Endpoints:

- PFS, per RECIST 1.1, by IRC.
- ORR, per RECIST 1.1, by IRC.
- DCR, per RECIST 1.1, by IRC.
- OS

Safety Endpoints:

- Treatment-emergent adverse events (TEAEs).
- Grade 3 or higher TEAEs.
- Serious TEAEs.
- Permanent discontinuation by TEAEs.
- Dose modification (dose reduction or interruption) by TEAEs.

- Clinically significant abnormal laboratory values.
- Clinically significant abnormal vital sign measurements.

Additional Endpoints

- PFS, per RECIST 1.1, by investigator.
- ORR, per RECIST 1.1, by investigator.
- DCR, per RECIST 1.1, by investigator.
- Plasma concentrations of cabozantinib.
- HRQOL assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L).
- Efficacy biomarker(s).
  - Candidate biomarkers that may include, but are not limited to, plasma biomarkers associated with study treatment and/or clinical outcome.
- Possible safety biomarker(s).
  - Association of genetic polymorphisms in genes encoding drug-metabolizing enzymes and/or transporters with study treatment and/or clinical outcome.

Statistical Considerations:

Primary Endpoint:

- 24-week PFSR, per RECIST 1.1, by IRC

  PFS is defined as time from the first day of study drug administration to the earlier of progressive disease (PD) per RECIST 1.1 or death due to any cause. 24-week PFSR is defined as PFS proportion at Study Day of Week 25 Day 1 + 7 days.

  Primary Analysis

  For 24-week PFSR by IRC, Kaplan-Meier estimate will be provided and the corresponding 2-sided 90% CI will be calculated for Cohort A using the Greenwood's formula and the complementary log-log transformation.

  Other Analysis

  The same analysis as that in the primary analysis will be conducted for Cohort B and overall (ie, Cohort A + Cohort B)

Secondary Endpoints:

- PFS, per RECIST 1.1, by IRC

  For PFS by IRC, median PFS will be estimated using the Kaplan-Meier method, and the Kaplan-Meier plot will be presented for each Cohort and overall.

- ORR, per RECIST 1.1, by IRC

  ORR is defined as proportion of subjects whose best overall response is complete response (CR) or partial response (PR) per RECIST 1.1, which is confirmed by a subsequent evaluation conducted ≥28 days later.

  For ORR by IRC, point estimate and the 2-sided 95% exact CI will be calculated for each Cohort and overall.

- DCR, per RECIST 1.1, by IRC

  DCR is defined as proportion of subjects whose best overall response is CR, PR or stable disease (SD) per RECIST 1.1. CR and PR require confirmation by a subsequent evaluation conducted ≥28 days later, and SD have to be maintained for at least 8 weeks (51 days) after the first day of study drug administration.

  For DCR by IRC, point estimate and the 2-sided 95% exact CI will be calculated for each Cohort and overall.

- OS

  OS is defined as time from the first day of study drug administration to death due to any cause. The same analyses as

those for PFS will be performed for OS.

Safety Endpoints:

For safety endpoints, summary of the results will be displayed for each Cohort and overall.

Additional Endpoints:

Summary of additional endpoints will be displayed.

Sample Size Justification:

A study with 17 subjects will provide at least 80% probability that the lower limit of the two-sided 90% CI for the 24-week PFSR by Kaplan-Meier method results in ≥11.1% when assuming the true 24-week PFSR ≥38.4%.

In Study XL184-309 in subjects with advanced HCC who have received prior sorafenib, the 24-week PFSR by investigator was 38.4% (95% CI: [33.5, 43.3]%) and 11.1% (95% CI: [7.2, 15.8]%) in cabozantinib and placebo group, respectively. In reference to the above results, a 24-week PFSR of 38.4% is assumed and the threshold is set at 11.1% in this study.

This study will enroll at least 17 subjects who have received prior sorafenib in Cohort A. In addition, for better understanding of the efficacy and safety profile of cabozantinib in Japanese patients, similar number of subjects who have received prior sorafenib in Cohort A and who have not received prior sorafenib in Cohort B will be enrolled, resulting in approximately 32 subjects in total.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the protocol annex. The identified vendors in the protocol annex for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Signatory Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the CSR and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
BP	blood pressure
CAP	chest/abdomen/pelvis
CI	confidence interval
CL/F	oral clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
%CV	percent coefficient of variation
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DICOM	Digital Imaging and Communications in Medicine
DILI	drug-induced liver injury
DVT	deep vein/venous thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	EuroQol Health questionnaire instrument
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GB	glioblastoma multiforme
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	γ-glutamyl transferase (gamma-glutamyl transferase)

GI	gastrointestinal
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HDPE	high-density polyethylene
HR	hazard ratio
HRQOL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IRB	institutional review board
IRC	independent radiology committee
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MET	hepatocyte growth factor receptor protein
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PopPK	population pharmacokinetic(s)
PPES	palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)
PR	partial response

PS	performance status
PT	preferred term
PT-INR	prothrombin time-international normalized ratio
QD	once daily
QT	time interval in ECG reading
QTcF	corrected QT interval calculated by the Fridericia formula
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RPLS	reversible posterior leukoencephalopathy syndrome
RP2D	recommended phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoD	baseline sum of the diameters
SUSARs	suspected unexpected serious adverse reactions
TBS	technetium bone scans
TEAEs	treatment-emergent adverse events
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
XL184	research name for investigational product cabozantinib

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Under Treatment: Hepatocellular Carcinoma

4.1.1.1 Epidemiology

The number of individuals who developed cancer in 2012 is estimated to be 14,068,000 around the world. The number of individuals who developed liver cancer is estimated to be 782,000 and the number of deaths is estimated to be 746,000. Liver cancer is the second highest cause of cancer-related deaths in the world, behind only lung cancer. The incidence and mortality rates of liver cancer tends to increase globally. There are regional differences in the incidence rate of liver cancer, and most of individuals who developed hepatocellular carcinoma (HCC) are in the East Asia, South-Eastern Asia and North African countries. The incidence and mortality rates of liver cancer are similar in each country/region.

In Japan, the incidence rate of liver cancer has tended to decrease since late 1990, but has still been higher than that in the world [1]. According to the Center for Cancer Control and Information Services, National Cancer Center in Japan, the number of individuals who developed cancer in 2013 was approximately 862,000. The number of individuals who developed liver cancer is estimated to be 40,938 and the number of deaths is estimated to be 30,173 [2].

4.1.1.2 Receptor Tyrosine Kinases in HCC

The vascular endothelial growth factor (VEGF) receptors and ligands are central mediators of tumor neo-angiogenesis and lymphangiogenesis [3]. High tumor microvessel density appears predictive of poor disease-free survival after HCC resection, and tumor vascular invasion is a well-established negative prognostic factor [4,5]. Resistance to VEGF-targeted therapies may arise from the upregulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the hepatocyte growth factor receptor protein (MET) pathway. Consistent with this, combined inhibition of VEGF receptor (VEGFR) and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in some tumor models [6-9].

The receptor tyrosine kinase (RTK) MET and its cognate ligand hepatocyte growth factor play an important role in diverse aspects of tumor pathobiology, including tumor growth, survival, neo-angiogenesis, invasion, and dissemination [10]. MET pathway activation and dysregulation have been implicated in multiple cancers, including HCC. Although its prevalence is not well characterized and may be influenced by source of tissue or methodology, MET has been found to be overexpressed in HCC compared with nontumor liver tissue, with higher MET expression linked to poorer prognosis [11-13]. Moreover, small-molecule inhibitors of MET have been shown to exhibit efficacy in preclinical models of HCC [9,14] and in early-phase clinical studies [15].

Like MET, RTK AXL plays an important role in diverse aspects of tumor pathobiology, including angiogenesis, epithelial-to-mesenchymal transition, invasion and dissemination, as well as suppressing antitumor immunity in the tumor microenvironment [16,17]. AXL has been shown to

be frequently activated in HCC cell lines [18]. Activating mutations in the gene encoding AXL appear to be extremely rare, making overexpression of AXL and/or its ligand GAS6 the primary mechanisms of activation in a wide range of human cancers; further, expression levels often correlate with poor prognosis [19]. Like VEGF and MET, AXL is upregulated by hypoxia inducible factors in response to hypoxia in a range of tumors [20-23]. High AXL expression in HCC patient samples correlates with increased invasiveness and poor prognosis [24,25]. Downregulation of expression or inhibition of AXL has been shown to decrease the invasiveness of HCC cell lines and inhibited metastasis development in vivo [18,26,27]. In other settings, AXL signaling has been linked to resistance to VEGFR inhibitors [28].

Given the known oncogenic potential of the MET and AXL signaling pathways, targeting these two oncoproteins in addition to VEGFRs may provide additional anticancer effects in HCC patients over more selective VEGFR inhibition strategies.

4.1.1.3 Treatment Approaches

Approximately 90% of liver cancer is HCC, which is the highest incidence rate of primary liver cancer. Other types of liver cancer include bile duct cancer, hepatoblastoma and angiosarcoma. Some patients who are found to have localized disease can undergo curative resection and other patients with advanced HCC can also be treated with regional therapy (local ablation, chemoembolization or other transcatheter therapies), but patients who present with advanced, particularly unresectable disease or who recur after regional therapy have a poor prognosis. If surgical resection or regional therapy is not eligible, systemic anticancer therapy is performed [29].

As a systemic anticancer therapy, sorafenib has been shown to prolong the overall survival (OS) and progression-free survival (PFS) in patients with HCC [30] in a placebo-controlled study, and has been approved in the United States (US) and the European Union (EU) in 2007, and then in Japan in 2009. In a placebo-controlled study, regorafenib demonstrated to prolong the OS in patients with unresectable HCC that has progressed after prior sorafenib [31], and has been approved as the second-line therapy of HCC in the US in April 2017, in Japan in June 2017, and in the EU in August 2017. Nivolumab has already received accelerated approval from the Food and Drug Administration (FDA) in September 2017 based on the response rate and the sustained response reported in an open-label phase 1/2 study of nivolumab conducted in patients with HCC who have received prior sorafenib, but has not yet been approved in Japan.

4.1.2 Study Drug

Cabozantinib (research name: XL184) is a multiple RTKs inhibitor targeting VEGFR/MET(c-MET)/RET/AXL/KIT/TIE-2, implicated in tumor growth, metastasis, and angiogenesis.

Cabozantinib is provided as both capsules and tablets, but the 2 formulations are not interchangeable. Cometriq (cabozantinib capsules) at an oral dose of 140 mg once daily (QD) was approved by the US FDA on 29 November 2012 for the treatment of patients with progressive,

metastatic medullary thyroid cancer (MTC). On 21 March 2014, cabozantinib capsules were approved by the European Commission for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic MTC. Cabometyx (cabozantinib tablets) at an oral dose of 60 mg QD was approved in the US for the treatment of patients with advanced renal cell carcinoma (RCC) following prior anti-angiogenic therapy and in the EU for the treatment of advanced RCC following prior VEGF-targeted therapy [32,33]. Cabometyx was also approved by FDA on 19 December 2017 for patients with previously untreated advanced RCC, and by European Commission on 17 May 2018 for the previously untreated adults patients with intermediate-or poor-risk advanced RCC. In the same month of 2018, an application for marketing approval of Cabometyx was submitted to the US and the EU for the treatment of previously treated patients with advanced HCC. Regulatory submissions are underway in other regions.

4.1.3 Nonclinical Experience

4.1.3.1 Pharmacology

Cabozantinib exhibits potent inhibitory activity against several RTKs that are known to influence tumor growth, metastasis, and angiogenesis. The primary targets of cabozantinib are VEGFR2/KDR, MET, AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TYRO3, MER, 2 additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely related RTKs KIT and FLT 3. In vivo pharmacodynamic activity of cabozantinib against VEGFR2, MET, AXL, and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis and tumor invasiveness and metastasis.

Data from pharmacodynamic experiments have shown that cabozantinib inhibits VEGFR2 and MET in vivo. Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung cancer, and glioblastoma multiforme (GB) [34]. In additional preclinical studies, cabozantinib treatment has also been shown to inhibit tumor invasiveness and metastasis, and the progression of tumors in bone [34,35].

A summary of cabozantinib pharmacology can be found in the Investigator's Brochure (IB). The IB should be reviewed in conjunction with this study protocol.

4.1.3.2 Toxicology

Cabozantinib nonclinical toxicology has been characterized in single- and repeat-dose studies in multiple species. Details can be found in the IB.

4.1.4 Clinical Experience

In clinical studies, cabozantinib has been evaluated in multiple tumor types including MTC, castration-resistant prostate cancer (CRPC), ovarian cancer, breast cancer, HCC, non-small cell lung cancer, melanoma, differentiated thyroid cancer, RCC, and GB. To date, cabozantinib has demonstrated broad clinical activity in these tumor types. Refer to the IB for more detail.

A phase 2, randomized, discontinuation trial in nine different advanced tumor types including a cohort of subjects with HCC (Study XL184-203 RDT) was conducted [36]. The study consisted of a 12 week Lead in Stage in which all subjects received open-label cabozantinib at an assigned dose of 100 mg/day and a Randomized Stage in which subjects with stable disease (SD) at Week 12 were randomized in a blinded manner to receive cabozantinib or placebo. Subjects who at Week 12 had a partial response (PR) or complete response (CR) were continued on open-label cabozantinib. In subjects who had a progressive disease (PD), cabozantinib treatment was discontinued at Week 12.

Study XL184-309 (CELESTIAL) is an ongoing phase 3, double-blinded, placebo-controlled, randomized study in patients with advanced HCC who have received prior systemic anticancer therapy. The study was designed to enroll 760 patients with advanced HCC who received prior sorafenib and may have received up to two prior systemic cancer therapies for HCC and had adequate liver function. Enrollment of the study was completed in September 2017. Patients were randomized 2:1 to receive 60 mg of cabozantinib QD or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia versus other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms during the blinded treatment phase of the study. The primary endpoint is OS, and the secondary endpoints include the investigator-assessed PFS and objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

In Japan, a phase 1 study of cabozantinib in Japanese patients with advanced or metastatic solid tumors (Study XL184-014) has already been completed. In addition, a phase 2 study of cabozantinib in Japanese patients with advanced RCC who had progressed after prior VEGFR-tyrosine kinase inhibitor (TKI) (Study Cabozantinib-2001) is ongoing.

4.1.4.1 Clinical Safety of Cabozantinib

Safety in HCC Patients

In Study XL184-203 RDT, 41 subjects with advanced HCC treated with cabozantinib received an assigned dose of 100 mg/day. Fifty-nine percent of subjects required at least 1 dose reduction throughout both the Lead-in and Randomized Stages.

The most frequently reported adverse events (AEs) during the study were consistent with those in subjects with other tumor types who received single-agent cabozantinib and included diarrhea (68%), fatigue (59%), palmar-plantar erythrodysesthesia syndrome (PPES) (54%), vomiting

(42%), and nausea (39%). Common Grade 3 or higher AEs included diarrhea (22%), thrombocytopenia (17%), PPES (15%), aspartate aminotransferase (AST) increased (12%).

In Study XL184-309, the results of safety population (467 in the cabozantinib arm, 237 in the placebo arm) as of database cutoff date (1 June 2017) are summarized below.

Grade 3 or 4 AEs were reported for 68% of subjects in the cabozantinib arm and 36% in the placebo arm. Grade 3 or 4 AEs reported for ≥ 5% of subjects in either arm were PPES (cabozantinib 17%, placebo 0%), hypertension (16%, 2%), AST increased (12%, 7%), fatigue (10%, 4%), diarrhea (10%, 2%), asthenia (7%, 2%), decreased appetite (6%, < 1%), and anemia (4%, 5%). The incidence of Grade 5 AEs was similar for both treatment arms (12% for each arm). Most Grade 5 AEs were related to disease progression. Six Grade 5 AEs were assessed as treatment-related in the cabozantinib arm (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism [PE], and upper gastrointestinal [GI] hemorrhage), and one Grade 5 AE was assessed as treatment-related in the placebo arm (hepatic failure).

Study treatment discontinuation due to treatment-related AEs was reported for 16% of cabozantinib subjects and 3% of placebo subjects.

Safety in Japanese Patients

Study XL184-014 was an open-label, multiple dose-escalation phase 1 study of cabozantinib administered orally to Japanese subjects with advanced or metastatic solid tumors for determination of maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).

1. Dose-Escalation Phase

   Study treatment for the capsule cohorts in the Dose-Escalation Phase was administered as a single-agent at dose levels of 40 mg QD (Cohort 1; n=3), 60 mg QD (Cohort 2, n=6), and 80 mg QD (Cohort 3; n=5). One of the last 2 subjects enrolled in the 80 mg QD cohort were dose-reduced to 60 mg QD during the dose limiting toxicity (DLT) Evaluation Period, and experienced a DLT of Grade 3 hypertension on Day 20. One subject enrolled in Cohort 2 (60 mg) also experienced a DLT of Grade 3 hypertension during the DLT Evaluation Period. As 1 out of 6 subjects enrolled in Cohort 2 (60 mg) experienced a DLT, 60 mg daily was determined to be the MTD for the capsule formulation in Japanese subjects. Subsequently, the tablet formulation was also evaluated in the Dose-Escalation Phase at dose levels of 40 mg QD (Cohort 1T; n=3) and 60 mg QD (Cohort 2T; n=6). One of 6 subjects experienced DLTs at the 60 mg QD tablet dose level; the subject experienced 2 DLTs of Grade 2 protein in urine and Grade 3 venous embolism. A dose level above 60 mg was not assessed in the tablet formulation; therefore, the 60 mg dose level was designated the RP2D and an MTD was not established.

   All subjects (across all dose levels and both formulations) in the Dose-Escalation Cohorts experienced at least one AE on study. The most frequent AEs (≥50%) reported were PPES (100.0%), alanine aminotransferase (ALT) increased (95.7%), AST increased (95.7%), hypertension (87.0%), blood thyroid-stimulating hormone (TSH) increased (82.6%), diarrhea

(78.3%), blood lactate dehydrogenase (LDH) increased (69.6%), leukopenia (60.9%), weight decreased (56.5%), dysphonia (52.2%), and protein urine present (52.2%). A total of 70% of subjects experienced an AE of ≥Grade 3. The ≥Grade 3 AEs reported for 2 or more subjects (≥8.7%) were γ-glutamyltransferase (GGT) increased (17.4%), hypertension (13.0%), lymphopenia (13.0%), PPES (8.7%), weight decreased (8.7%), lipase increased (8.7%), neutropenia (8.7%), hypokalemia (8.7%), hypophosphatemia (8.7%), and hyponatremia (8.7%). The majority of laboratory abnormalities and associated AEs were <Grade 3.

Among all subjects in the Dose-Escalation Cohorts, 6 subjects (26.1%) experienced 9 serious AEs (SAEs). The reported SAEs were anemia, bile duct stone, dyspnea, venous embolism, hematemesis, intestinal obstruction, melena, pleural effusion, and protein urine. No SAE preferred term (PT) was experienced by more than one subject in the Dose-Escalation Cohorts.

In the Dose-Escalation Cohorts, there were no deaths reported through 30 days after last dose and no treatment-related deaths >30 days after last dose.

2. Subjects Treated with RP2D 60 mg Tablet

The most frequent AEs (≥50%) were ALT increased (92.3%), AST increased (92.3%), PPES (84.6%), hypertension (73.1%), diarrhea (65.4%), blood TSH increased (53.8%), decreased appetite (53.8%), proteinuria (50.0%), and stomatitis (50.0%). The ≥Grade 3 AEs reported for 2 or more subjects (≥7.7%) who received the 60 mg tablet starting dose were hypertension (23.1%), neutropenia (19.2%), GGT increased (15.4%), dyspnea (15.4%), ALT increased (11.5%), PPES (11.5%), hypophosphatemia (11.5%), hyponatremia (11.5%), lymphopenia (11.5%), hypokalemia (11.5%), lipase increased (7.7%), amylase increased (7.7%), and performance status (PS) decreased (7.7%). The majority of laboratory abnormalities and associated AEs were <Grade 3.

Among subjects who received the 60 mg tablet starting dose, 10 subjects experienced 23 SAEs. Three SAE PTs were reported for more than 1 subject: dyspnea was reported for 3 subjects (11.5%), and PS decreased and pleural effusion were reported for 2 subjects each (7.7%).

One subject who received the 60 mg tablet starting dose died through 30 days after the last dose of treatment with a primary cause of death reported as respiratory failure. The death was reported as related to study treatment due to possible heart strain from study treatment-induced hypertension. However, the investigator also noted other possible reasons for respiratory failure, including worsening of underlying disease or potential ischemic disease. There were no treatment-related deaths >30 days after last dose. Further details are provided in the most recent version of the IB.

The most frequently reported AEs were similar among subjects treated in the Dose-Escalation Phase and all subjects treated at the tablet RP2D of 60 mg. PPES, hypertension, and selected laboratory abnormalities, specifically increases in ALT and AST, were among the most frequent AEs reported for both of these groups of subjects. There were no hepatic AEs that led to treatment discontinuation, and there were no confirmed cases of drug-induced liver injury (DILI) assessed

by using the laboratory screening conditions defined by Hy's Law. There were no cases of PPES that led to treatment discontinuation. One case of hypertension led to treatment discontinuation, but no hypertensive crisis (Grade 4) or death due to hypertension (Grade 5) was reported.

4.1.4.2 Clinical Efficacy of Cabozantinib in HCC

Phase 2: Study XL184-203 (HCC Cohort)

In Study XL184-203 RDT, 2 subjects (5%) had a confirmed PR during the 12-week Lead-in Stage (at any time through Week 12) and 31 subjects (76%) had SD; the disease control rate (PR+SD) at Week 12 was 66%. One subject with SD at Week 12 was subsequently randomized to receive placebo (see below) and achieved a PR. Twenty-eight (78%) of 36 subjects with a post-baseline scan had at least 1 scan demonstrating a reduction in measurable disease.

Twenty-two of the 41 subjects enrolled in the Lead-in Stage were randomized at Week 12 to receive either placebo or continuing cabozantinib after demonstrating SD. The median PFS for all subjects from the initial cabozantinib dose was 5.2 months by Kaplan-Meier estimate and did not appear to be influenced by sorafenib pretreatment status (5.2 months for sorafenib pretreated subjects [n=22] and 4.2 months for sorafenib naïve subjects [n=19]). No statistically significant difference in the median PFS between randomized treatment groups was observed from the point of randomization: median PFS was 1.4 months (95% CI: 1.3, 4.2) for placebo and 2.5 months (95% CI: 1.3, 6.8) for cabozantinib.

The median OS for all treated patients (n=41) from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) [36].

Phase 3:Study XL184-309

In Study XL184-309, a total of 707 subjects were randomized in a 2:1 ratio to receive cabozantinib (470 subjects) or placebo (237 subjects) (intent-to-treat population) at the time of data cutoff for the second prespecified interim analysis (1 June 2017). The second prespecified interim analysis results showed that Study XL184-309 met its primary endpoint of OS in the cabozantinib arm, providing a statistically significant improvement in OS compared to placebo. The independent data monitoring committee (IDMC) for the study recommended that the study should be stopped for efficacy.

This study has subsequently fully enrolled (773 subjects as of 18 September 2017, planned total 760) and closed to enrollment. Subjects continued to receive blinded study treatment as of the data cutoff date.

Cabozantinib provided a statistically significant and clinically meaningful improvement versus placebo in OS, the trial's primary endpoint, at the planned second interim analysis (pre-specified critical p-value ≤0.021): the hazard ratio (HR), adjusted for stratification factors (per interactive voice/web response system [IxRS]), was 0.76 (95% CI: 0.63, 0.92; stratified logrank p-value = 0.0049 [met the critical p-value ≤0.021]). The Kaplan-Meier estimates for median duration of OS were 10.2 months in the cabozantinib arm versus 8.0 months in the placebo arm.

The median PFS was more than doubled in the cabozantinib arm (5.2 months) compared to the placebo arm (1.9 months) (HR 0.44 [95% CI: 0.36, 0.52], p<0.0001). The ORR per RECIST 1.1 were 4% in the cabozantinib arm and 0.4% in the placebo arm (p=0.0086).

4.1.4.3 Pharmacokinetics of Cabozantinib

An integrated population pharmacokinetic (PopPK) analysis of cabozantinib in healthy subjects and cancer patients with different types of malignancies was performed that included pharmacokinetic (PK) data from 10 clinical studies (three phase 1, two phase 2 and five phase 3) for a total of 9510 cabozantinib concentration records from 2023 subjects. The PopPK analysis included 489 HCC subjects from Study XL184-309 in addition to patients with RCC, CRPC, MTC, GB and other malignancies. The current analysis included data from a 2-compartment model with first order elimination and a dual absorption (first order + zero-order) process adequately described the observed cabozantinib PK data. Results from the PopPK analysis indicated that for a white male subject the predicted terminal plasma half-life of cabozantinib was approximately 99 hours; the terminal phase volume of distribution for the central compartment was approximately 212 L; and the oral clearance (CL/F) at steady-state was estimated to be approximately 2.48 L/h. Inter-individual variability in clearance (percent coefficient of variation [%CV] of CL/F) was estimated to be 46%. Compared to healthy subjects, the MTC population was the only cancer type to have a notable difference in cabozantinib PK, with an approximately 90% increase in CL/F. HCC patients showed a small but significant difference in CL/F (12% lower) and not likely to be clinically meaningful. Female gender had a significant effect on CL/F (24% lower than in males) which resulted in moderately increased exposure also not considered to be clinically meaningful. Covariates showing no statistically significant effect on CL/F included race (including Asian race), age and weight. Patients with mild or moderate/severe liver dysfunction were predicted to have minimal differences (12% or less) in CL/F and Vc/F relative to subjects with normal liver function.

Within a 48-day collection period after a single dose of ^{14}C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine. Results from a PK study of cabozantinib in subjects with renal impairment (Study XL184-017) indicated that the ratios of geometric least square mean for plasma cabozantinib maximum observed concentration (C_{max}) and area under the plasma drug concentration time curve (AUC) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. For subjects with moderate renal impairment, both C_{max} and AUC appeared to be similar when compared to subjects with normal renal function (differences: <3% and <7%, respectively). Results from a PK evaluation of cabozantinib in subjects with hepatic impairment (Study XL184-003) indicated that AUC of cabozantinib was increased by about 81% and 63% in subjects with mild and moderate hepatic impairment, respectively.

A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively, relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose (Study

XL184-004). Concomitant administration of the proton pump inhibitor esomeprazole resulted in no clinically relevant effect on cabozantinib plasma PK in healthy subjects (Study XL184-018).

Exposure (C_{max} and AUC) of cabozantinib in capsule and tablet formulations was assessed in Japanese subjects (Study XL184-014, n=43). At steady-state exposure, AUC increased approximately dose proportionally from 40 mg to 80 mg capsule doses and from 40 mg to 60 mg tablet doses. Exposure between capsule and tablet formulations appeared to be similar. Mean trough concentration at steady-state was about 30% higher in Japanese subjects when compared with non-Japanese subjects; this is not considered clinically relevant since it is within the inter-subject variability.

Additional results from clinical PK trials may be found in the IB.

4.1.5 DDI Risk of Cabozantinib

Cytochrome P450

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate). Co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampicin, rifabutin, rifapentin, phenobarbital, and St. John's wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib plasma concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided.

Protein Binding

Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein-bound drugs (eg, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. A single case of a drug-drug interaction (DDI) between cabozantinib and warfarin has been reported in the literature [37], which is consistent with a protein-displacement interaction. Because warfarin is a highly protein-bound

drug with a low therapeutic index, administration of warfarin is not allowed in subjects receiving cabozantinib due to the potential for a protein-binding displacement interaction.

Other Interactions

In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (eg, fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

Cabozantinib was shown to be a substrate of drug transporter multidrug resistance-associated protein 2 (MRP2) in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (eg, cyclosporine, delaviridine, efavirenz, emtricitabine) should be approached with caution, and subjects taking MRP2 inhibitors should be monitored for AEs.

Additional details regarding potential drug interactions with cabozantinib can be found in the IB.

4.2 Rationale for the Proposed Study

Cabozantinib is a multiple RTKs inhibitor targeting VEGFR, MET, and AXL, implicated in tumor growth, metastasis, and angiogenesis. In the US and the EU, cabozantinib has already been approved for the treatment of progressive metastatic MTC and for the treatment of advanced RCC.

HCC is usually resistant to systemic anticancer therapy. Sorafenib, a small-molecule inhibitor of VEGFR and other protein kinases, has been shown to improve PFS and OS in patients with HCC, who eventually progress and succumb to their disease despite treatment [30]. At the time of initiation of Study XL184-309, a randomized, global phase 3 trial of cabozantinib versus placebo in patients with advanced HCC who have been previously treated with sorafenib, no drug had demonstrated efficacy in patients with unresectable or metastatic HCC that had progressed after treatment with sorafenib. Study XL184-309 met its primary endpoint of OS, with cabozantinib providing a statistically significant and clinically meaningful improvement in the median OS compared to placebo. The IDMC for the study recommended that the study should be stopped for efficacy following review of the second planned interim analysis. Based on results from Study XL184-309, an application for marketing approval of Cabometyx was submitted to the US and the EU for the treatment of previously treated patients with advanced HCC in March 2018.

Recently, regorafenib has been approved for the treatment of unresectable HCC that progressed after anticancer therapy in Japan, the EU and the US. This is only one systemic treatment option currently available for the patients who have already received systemic anticancer therapy in Japan. However, in a pivotal phase 3 study of regorafenib (RESORCE study), actual target population was limited to patients who have received only 1 systemic anticancer therapy with sorafenib, excluding those who were intolerant to sorafenib. On the other hand, Study XL184-309 included patients with prior 2 lines of treatment for advanced HCC and did not exclude those who

were intolerant to sorafenib. According to the positive result of OS in broader targeting population in the Study XL184-309 and wider target receptors of cabozantinib including MET and AXL compared to regorafenib, the anticancer effect of cabozantinib is highly expected in the Japanese patients with previously treated advanced HCC.

The safety and tolerability of cabozantinib at same dosing regimen as Study XL184-309 has been shown in the completed phase 1 study conducted in Japan (Study XL184-014).

We will conduct this study to evaluate the efficacy and safety of cabozantinib in the Japanese patients with advanced HCC who have received prior sorafenib comparing the Study XL184-309 as a primary objective of this study. Furthermore, we will also evaluate the safety and efficacy of cabozantinib in Japanese patients with previously treated advanced HCC who have not received prior sorafenib, for better understanding of the efficacy and safety profile of cabozantinib in Japanese patients, considering the change of standard of care for HCC in the future in Japan.

This study consists of 2 cohorts: Cohort A and Cohort B. Patients who have received prior sorafenib for advanced HCC will be enrolled in Cohort A, and patients who have not received sorafenib treatment for advanced HCC prior to this study will be enrolled in Cohort B. To evaluate the safety and efficacy in Cohorts A and B, the sample size of Cohort B will be similar to that of Cohort A.

4.2.1 Rationale for Study Design and Primary Endpoint

This is an open-label, single-arm study. Since regorafenib has been already approved in Japan, it is unfeasible from ethical point of view to conduct 2-arm study with placebo arm as a comparator. Additionally, it is inappropriate to conduct the head-to-head study with regorafenib arm as a comparator since Japanese HCC guideline [29] recommend regorafenib as second line therapy ONLY for patients who were tolerate with sorafenib meanwhile cabozantinib showed its efficacy in Study XL184-309 in population which did not exclude those who were intolerant to sorafenib. For these reasons, we selected single-arm study design.

The primary endpoint of this study is independent radiology committee (IRC)-assessed progression-free survival rate at 24 weeks from the start of study drug treatment (24-week PFSR) per RECIST 1.1. In a clinical study of a cytotoxic anticancer agent, especially in a phase 2, single-arm study, ORR has generally been used as the primary endpoint based on a concept that a reduction of tumor size should be considered a certain clinical benefit. Molecularly targeted agents, including cabozantinib, demonstrate the inhibition of tumor cell proliferation, invasion and distant metastasis but do not demonstrate a drastic tumor shrinkage in some malignancies such as HCC, even if tumor necrosis is seen[30,31]. Therefore, the selection of ORR as the primary endpoint is not always appropriate. PFSR (ClinicalTrials.gov Identifier: NCT00639509, NCT00427973, NCT00605722, NCT00639509, NCT01180959, NCT01281943, NCT01545804, NCT01180959, NCT01545804) has also been selected as the primary endpoint in phase 2, single-arm studies in patients with advanced HCC so far.

Study XL184-309 demonstrated a significant prolongation of OS and PFS in the cabozantinib arm, but ORR (RECIST 1.1) was 4% in the cabozantinib arm and 0.4% in the placebo arm. It means that

longer SD contributed to prolongation of PFS and OS. Therefore, PFSR was selected as the primary endpoint in this study. The duration of 24 weeks for PFSR was determined referring to the median PFS (5.2 months) in the cabozantinib arm (95% CI: 4.0, 5.5, HR: 0.44, 95% CI: 0.36, 0.52) in Study XL184-309. This duration of 24 weeks means that approximately 90 % of patients without active treatment reach disease progression or death, according to the PFS in the placebo arm in Study XL184-309.

Based on the above, the 24-week PFSR is selected as the primary endpoint of this study. Thus, it is supposed that 24-week PFSR to be assessed in this study will be a clinically significant indicator.

4.2.2 Rationale for Dose

The same dose regimen as Study XL184-309 (60 mg orally QD) is selected in this study. The safety and tolerability of Japanese patients were confirmed at 60 mg orally QD in Study XL184-014. No clinically meaningful difference in steady-state plasma exposures was observed between Japanese subjects (Study XL184-014) and non-Japanese subjects (Study XL184-309); the mean trough concentration was 1,628 ng/mL (%CV=37) in Japanese subjects (n=26) and 1,180 ng/mL (%CV=47) in non-Japanese subjects (n=181).

4.2.3 Rationale for PK Assessments

Blood samples will be obtained from all subjects at specified time points to measure the plasma concentration of cabozantinib. The results will be used to confirm the exposure to cabozantinib. The PopPK may be further characterized in this population.

4.2.4 Rationale for Biomarker Analysis

Correlative studies will be conducted to identify potential candidate biomarkers (protein expression in signal pathway, metabolic signature, etc) that are significantly associated with observed clinical response to cabozantinib in Japanese patients with advanced HCC who have received prior systemic anticancer therapy. These candidate biomarkers may include, but are not limited to, soluble-VEGFR2/MET/AXL/VEGF/HGF/GAS6-signaling protein expression profiles and metabolic profiles. The candidate biomarkers will be prospectively validated in an independent patient population.

4.2.5 Rationale for Pharmacogenomic Assessments

Genetic variation in drug-metabolizing enzymes and/or transporters potentially involved in the disposition of cabozantinib could contribute to interindividual variability in cabozantinib plasma exposures, and subsequently, safety and efficacy. Somatic DNA will be obtained from whole blood samples and be genotyped for clinically relevant germline mutations including polymorphisms in genes encoding drug-metabolizing enzymes and/or transporters. Additional pharmacogenomic analyses may be conducted in the future to further investigate the contribution of genetic variance on drug response.

As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples. Pharmacogenomic analyses will be conducted in accordance with Ethical Guidelines for Human Genome/Gene Analysis Research.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to evaluate the efficacy of cabozantinib measured by IRC-assessed 24-week PFSR per RECIST 1.1 in Japanese patients with advanced HCC who have received prior sorafenib.

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of cabozantinib measured by IRC-assessed PFS per RECIST 1.1 in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by IRC-assessed ORR per RECIST 1.1 in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by IRC-assessed disease control rate (DCR) per RECIST 1.1 in the patient population under study.
- To evaluate the efficacy of cabozantinib measured by OS in the patient population under study.

5.1.3 Safety Objective

The safety objective is:

- To evaluate the safety of cabozantinib in the patient population under study.

5.1.4 Additional Objectives

The additional objectives are:

- To evaluate the efficacy of cabozantinib measured by investigator-assessed PFS, ORR, and DCR per RECIST 1.1 in the patient population under study.
- To characterize the plasma PK of cabozantinib in the patient population under study.
- To assess health-related quality of life (HRQOL) by the EuroQol Health questionnaire instrument (EQ-5D-5L) in the patient population under study.
- To explore candidate biomarkers predictive of response to cabozantinib.
- To explore possible candidate biomarkers predictive of safety of treatment with cabozantinib.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is:

- 24-week PFSR, per RECIST 1.1, by IRC.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- PFS, per RECIST 1.1, by IRC.
- ORR, per RECIST 1.1, by IRC.
- DCR, per RECIST 1.1, by IRC.
- OS

5.2.3 Safety Endpoints

The safety endpoints are:

- Treatment-emergent adverse events (TEAEs).
- Grade 3 or higher TEAEs.
- Serious TEAEs.
- Permanent discontinuation by TEAEs.
- Dose modification (dose reduction or interruption) by TEAEs.
- Clinically significant abnormal laboratory values.
- Clinically significant abnormal vital sign measurements.

5.2.4 Additional Endpoints

The additional endpoints are:

- PFS, per RECIST 1.1, by investigator.
- ORR, per RECIST 1.1, by investigator.
- DCR, per RECIST 1.1, by investigator.
- Plasma concentrations of cabozantinib.
- HRQOL assessed by the EQ-5D-5L.
- Efficacy biomarker(s).

  - Candidate biomarkers that may include, but are not limited to, plasma biomarkers associated with study treatment and/or clinical outcome.

- Possible safety biomarker(s).
  - Association of genetic polymorphisms in genes encoding drug-metabolizing enzymes and/or transporters with study treatment and/or clinical outcome.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 2, open-label, single-arm study to evaluate the efficacy—as measured by 24-week PFSR and other efficacy variables including PFS, ORR, DCR, and OS—and safety of cabozantinib in Japanese patients with advanced HCC who have received prior systemic anticancer therapy (Cohort A: patients who have received prior sorafenib, Cohort B: patients who have not received prior sorafenib).

Screening Period

Potential subjects will be screened to determine if they meet the required eligibility criteria after informed consent. Qualifying screening assessments must be performed within 28 days before the first day of study drug administration (defined as Week 1 Day 1) unless otherwise specified.

Treatment Period

Subjects who meet all study eligibility criteria will receive cabozantinib 60 mg orally, QD in the fasted state (dose at least 2 hours after meal, and no more food intake for 1 hour postdose), preferably at bedtime. A subject is considered to be enrolled in the study when the first dose of study drug will be administered.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver directed local anticancer therapy, or until there are any other reasons for treatment discontinuation listed in the protocol (see Section 9.7). Treatment may continue after radiographic HCC progression per RECIST 1.1 as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks. However the subject should discontinue study treatment after the second determination of disease progression.

Posttreatment Period

A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug or until the start of subsequent systemic anticancer treatment, whichever occurs first. Radiographic tumor assessments, Child-Pugh assessments, alpha-fetoprotein (AFP) assessments, and HRQOL assessments will continue, regardless of whether study treatment is given, reduced, held or discontinued until the day of the last tumor imaging assessment (See Appendix A [Schedule of Events]). Subjects will be contacted every 8 weeks (±7 days) after the 30-day posttreatment followup visit to assess survival status and document receipt of subsequent anticancer therapy. Subjects will be followed until death, withdrawal of consent, or the sponsor decision to discontinue collection of these data in the study.

Major assessments of the study are described below.

Radiographic Tumor Assessment

Subjects will be monitored for radiographic response and progression per RECIST 1.1. Response and progression will be assessed by the IRC and by the investigator. Tumor assessments should continue on the protocol-defined schedule regardless of whether study treatment is given, reduced, held or discontinued. The duration of radiographic tumor assessments for individual subjects is described in Section 9.4.15. The same imaging modalities used at Screening will be used for subsequent tumor assessments after enrollment.

Chest/Abdomen/Pelvis: Computerized tomography (CT) (or magnetic resonance imaging [MRI]) of chest/abdomen/pelvis (CAP) will be performed in all subjects at Screening. These assessments will be performed on Week 9 Day 1 and every 8 weeks (±7 days) thereafter. If MRI of the CAP study is performed at Screening, then a noncontrast CT of the chest should be performed as well.

Brain: MRI (or CT) of the brain will be performed in all subjects at Screening. After Week 1 Day 1, MRI (or CT) scans of the brain are required only in subjects with known brain metastasis. Assessments will be performed on Week 9 Day 1 and every 8 weeks (±7 days) thereafter. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 3 months before enrollment. Subjects without documented brain metastasis during the screening assessment are not required to undergo postenrollment brain imaging unless clinically indicated.)

Bone: Whole body technetium bone scans (TBS) will be performed in all subjects at Screening. After Week 1 Day 1, bone scans will be performed only in subjects with known bone metastasis on Week 9 Day 1, Week 17 Day 1, and every 16 weeks (±7 days) thereafter until last CT/MRI scan. (Note: Subjects without documented bone metastasis during the screening assessment are not required to undergo postenrollment bone scan imaging unless clinically indicated.) Lesions identified on bone scan are not to be recorded as target, nontarget, or new lesions. Bone scans are to be used to direct corroborative imaging with CT/MRI if necessary (these CT/MRI findings will be used for RECIST 1.1 evaluation). Bone scan findings alone cannot be used for the determination of progression per RECIST 1.1.

Tumor Marker Assessment

A blood sample for AFP will be obtained at the time of each radiographic tumor assessment visit according to the schedule in Appendix A. These assessment will continue regardless of whether study treatment is given, reduced, held or discontinued until last tumor assessment.

Safety Assessments

Safety will be assessed on Week 1 Day 1 and at minimum every 2 weeks up to Week 9 Day 1, and every 4 weeks thereafter. A 30-day posttreatment followup visit will be performed at least 30 days (+14 days) after the last dose of study drug, and subjects will report and will be queried on, AEs experienced through the 30 days. Routine safety evaluations will include physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) PS, 12-lead electrocardiogram (ECG), echocardiogram, hematology, serum chemistries, coagulation tests, urine tests (including urine

protein-to-creatinine ratio [UPCR]), serum or urine pregnancy tests (in females of childbearing potential), and thyroid function tests.

AE seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

HRQOL Assessments

Subjects will complete the HRQOL assessments (the EQ-5D-5L questionnaire) on Week 1 Day 1 prior to dosing. After Week 1 Day 1, the HRQOL assessments will be collected every 4 weeks (±2 days) up to Week 9 Day 1, and every 4 weeks (±7 days) thereafter through 6 months on study. Upon completion of 6 months on study, the HRQOL assessments will be collected every 8 weeks (±7 days) thereafter until last tumor assessment. The HRQOL questionnaires should be completed by the patient before any other study procedures are performed or study drug is administered on scheduled visits. These assessments are to be conducted regardless of whether study treatment is given, reduced, held or discontinued until the day of the last tumor imaging assessment as described in Section 9.4.15. Consequently these assessments may be required in the Posttreatment period for some subjects.

Child-Pugh Assessments

The Child-Pugh assessments should be performed in all subjects at Screening. Assessments will be performed on Week 1 Day 1, Week 9 Day 1, and every 8 weeks (±7 days) thereafter. These assessments will continue regardless of whether study treatment is given, reduced, held, or discontinued until last tumor assessment. Determination of severity of ascites and encephalopathy will be made by clinical assessment.

PK Assessments

PK blood samples will be obtained from all subjects on Week 1 Day 1, Week 3 Day 1, Week 5 Day 1, and Week 9 Day 1. The plasma concentration of cabozantinib will be measured, and the results will be used to confirm exposure to cabozantinib. The PopPK may be further characterized in this population. Collection of PK samples may be halted early or sampling frequency may be reduced at the discretion of the sponsor.

Pharmacogenomic Assessments

A pharmacogenomic blood sample will be collected from all subjects predose on Week 1 Day 1 for single nucleotide polymorphism variation analysis by DMET™ Plus Array to investigate the contribution of genetic variance on PK, safety and tolerability to study treatment. Unless failure to grant informed consent for this purpose, or sponsor decision, additional pharmacogenomic analyses (eg, the contribution of genetic variance on drug response) may be conducted in the future.

Biomarker Assessments

Assessment of biomarkers in plasma (protein expression in signal pathway, metabolic signature, etc) will be performed. Samples for these studies will be obtained on Week 1 Day 1, Week 3 Day

1, Week 5 Day 1, and Week 9 Day 1. After Week 9 Day 1, samples for signaling protein expression profile assessment will be obtained every 8 weeks (±5 days) through Week 25 Day 1.

Serum bone biomarkers (bone specific alkaline phosphatase [ALP]) will be also assessed. Samples for these studies will be obtained from all subjects on Week 1 Day 1, Week 3 Day 1, Week 5 Day 1, and Week 9 Day 1.

Collection of biomarker samples may be halted early or sampling frequency may be modified at the discretion of the sponsor.

A schedule of assessments is listed in Appendix A.

6.2 Number of Subjects

Approximately 32 subjects will be enrolled in this study from approximately 18 study sites in Japan.

- Cohort A (subjects who have received prior sorafenib): at least 17 subjects.
- Cohort B (subjects who have not received prior sorafenib): approximately 15 subjects.

A patient is considered to be enrolled in the study when the first dose of study drug has been administered.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Treatment may continue after radiographic HCC progression per RECIST 1.1 as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks. However the subject should discontinue study treatment after the second determination of disease progression.

A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug or until the start of subsequent systemic anticancer treatment, whichever occurs first. Radiographic tumor assessments, Child-Pugh assessments, AFP assessments, and HRQOL assessments will continue regardless of whether study treatment is given, reduced, held or discontinued until the day of the last tumor imaging assessment. Subjects will be contacted every 8 weeks (±7 days) after the 30-day posttreatment followup visit to assess survival status and document receipt of subsequent anticancer therapy. Subject will be followed until death, withdrawal of consent, or the sponsor decision to discontinue collection of these data in the study.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion

The primary analysis for the efficacy and safety endpoints and authoring of a clinical study report (CSR) may be conducted after all patients enrolled in the study have had the opportunity to complete 24 weeks of treatment with study drug and assessments at Week 25 Day 1.

Other Planned Analyses

A CSR efficacy and safety addendum is planned at study completion.

Study Completion

The estimated time frame for study completion is approximately 3 years. The study will end at the time of commercial cabozantinib placing on the market for this study indication in Japan at the latest.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame (a)
Primary:		
• 24-week PFSR, per RECIST 1.1, by IRC	The PFS proportion as assessed by the IRC per RECIST 1.1 at Study Day of Week 25 Day 1 + 7 days.	Up to approximately 2 years after enrollment of the last subject.
Secondary:		
• ORR, per RECIST 1.1, by IRC	The proportion of subjects in the FAS whose best overall response is CR or PR, as assessed by the IRC per RECIST 1.1, which is confirmed by a subsequent evaluation conducted ≥28 days later.	Up to approximately 2 years after enrollment of the last subject.
• PFS, per RECIST 1.1, by IRC	The time from the first day of study drug administration to the earlier of PD, as assessed by the IRC per RECIST 1.1 or death due to any cause.	Up to approximately 2 years after enrollment of the last subject.
• DCR, per RECIST 1.1, by IRC	The proportion of subjects in the FAS whose best overall response is CR, PR or SD, as assessed by the IRC per RECIST 1.1. CR and PR require confirmation by a subsequent evaluation conducted ≥28 days later, and SD have to be maintained for at least 8 weeks (51 days) after the first day of study drug administration.	Up to approximately 2 years after enrollment of the last subject.
• OS	The time from the first day of study drug administration to death due to any cause.	Up to approximately 2 years after enrollment of the last subject.

CR=complete response, DCR=disease control rate, FAS=full analysis set, IRC=independent radiology committee, ORR=objective response rate, OS=overall survival, PD= progressive disease, PFS=progression-free survival, PFSR=progression-free survival rate, PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors, SD=stable disease.
(a) Time to last assessment for that endpoint for an individual patient.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 3 years.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female Japanese patients 20 years of age or older on the day of consent.
2. Histological or cytological diagnosis of HCC (results of a previous biopsy will be accepted).
3. Measurable disease per RECIST 1.1 as determined by the investigator.
4. Patients who have disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation).
5. Patients who have received 1 or 2 prior anticancer therapies for advanced HCC.
   - Cohort A: patients who have received prior sorafenib.
   - Cohort B: patients who have not received prior sorafenib.

   Note: Additional prior systemic therapies used as adjuvant or local therapy are allowed.
6. Radiographic progression following prior systemic anticancer therapy for advanced HCC.
7. Recovery to ≤Grade 1 CTCAE Version 4.03 from toxicities related to any prior treatments, unless the AEs are clinically nonsignificant and/or stable on supportive therapy.
8. ECOG PS of 0 or 1, and life expectancy of at least 3 months.
9. Child-Pugh Score of A.
10. Adequate organ and marrow function at Screening (within 10 days before Week 1 Day 1) :
    a) Absolute neutrophil count (ANC) ≥1,200/mm^3.
    b) Platelets ≥60,000/mm^3.
    c) Hemoglobin ≥8 g/dL.
    d) Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥40 mL/min using the Cockroft-Gault equation (see Appendix H).
    e) UPCR ≤1 mg/mg Cr.
    f) Total bilirubin ≤2 mg/dL.
    g) Serum albumin ≥2.8 g/dL.
    h) ALT and AST ≤5.0 × ULN.
    i) Hemoglobin A1c (HbA1c) ≤8% (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤160 mg/dL).
11. Antiviral therapy per local standard of care if active hepatitis B virus (HBV) infection.
12. Female patients who:

a) Are postmenopausal (natural amenorrhea, not due to other medical reasons) for at least 1 year before the Screening visit, OR

b) Are surgically sterile, OR

c) If they are of childbearing potential, agree to practice 1 highly effective method of birth control with a condom, which is an effective barrier method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, OR

d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

e) Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug. If their partner are of childbearing potential, their female partner should use 1 highly effective method of birth control at the same time, OR

f) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

13. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
14. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma.
2. Any type of anticancer agent within 14 days before the first day of study drug administration (Week 1 Day 1).
3. Radiation therapy within 28 days (14 days for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 42 days before Week 1 Day 1 (patient is excluded if there are any clinically relevant ongoing complications from prior radiation therapy).
4. Prior cabozantinib treatment.

5. Treatment with any investigational products (excluding anticancer products approved in Japan) within 28 days before Week 1 Day 1.
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before Week 1 Day 1. Eligible patients must be without corticosteroid treatment at Week 1 Day 1.
7. Concomitant anticoagulation, with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).

   Note: Low-dose aspirin for prophylactic use (per local applicable guidelines) and low-dose, low molecular weight heparins (LMWH) are permitted (LMWH has not been approved for the use for cardioprotection in Japan). Anticoagulation with therapeutic doses of LMWH is allowed in patients without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before Week 1 Day 1, and who have had no complications from a thromboembolic event or the anticoagulation regimen.
8. Patients who have uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
   a) Cardiovascular disorders including
      i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias.
      ii. Uncontrolled hypertension defined as sustained blood pressure (BP) >150 mm Hg systolic, or >100 mm Hg diastolic despite optimal antihypertensive treatment.
      iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, or other ischemic event within 6 months before Week 1 Day 1.
      iv. Thromboembolic event within 3 months before Week 1 Day 1.
      v. A left-ventricular ejection fraction ≤50%.
   b) GI disorders including those associated with a high risk of perforation or fistula formation:
      i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
      ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before Week 1 Day 1.

      Note: Complete healing of an intra-abdominal abscess must be confirmed prior to Week 1 Day 1.
   c) Major surgery within 2 months before Week 1 Day 1. Complete healing from major surgery must have occurred 1 month before Week 1 Day 1. Complete healing from minor

surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before Week 1 Day 1. Patients with clinically relevant complications from prior surgery are not eligible.

d) Cavitating pulmonary lesion(s) or endobronchial disease.

e) Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Patients with invasion or thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible.

f) Clinically significant bleeding risk including the following within 3 months before Week 1 Day 1: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors.

g) Other clinically significant disorders such as:

i. Active infection requiring systemic treatment.

ii. Known infection with human immunodeficiency virus, or known acquired immunodeficiency syndrome -related illness.

iii. Active hepatitis B and/or C. Patients with active hepatitis virus infection controlled with antiviral therapy are eligible.

iv. Serious non-healing wound/ulcer/bone fracture.

v. Malabsorption syndrome.

vi. Uncompensated/symptomatic hypothyroidism.

vii. Requirement for hemodialysis or peritoneal dialysis.

viii. History of solid organ transplantation.

9. Patients with untreated or incompletely treated varices with bleeding or high risk for bleeding. Patients treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months before Week 1 Day 1 are eligible.
10. Moderate or severe ascites.
11. Corrected QT interval calculated by the Fridericia formula (QTcF) >500 msec within 14 days before Week 1 Day 1.

    Note: If the QTcF is >500 msec in first ECG, a total of 3 ECGs each separated by at least 3 minutes should be performed within 30 minutes. If the average of these 3 consecutive results for QTcF is ≤500 msec, the patient meets eligibility in this regard.
12. Inability to swallow tablets.
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

14. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.

    Note: Female patients who are in the lactation period, even if they discontinue breastfeeding, will be excluded from the study.

15. Previously diagnosed with another malignancy and have any evidence of residual disease within 2 years before Week 1 Day 1.

    Note: Patients with superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy are not excluded.

16. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
17. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of cabozantinib.
18. Use of strong CYP3A4 inhibitors and CYP3A4 inducers within 14 days before Week 1 Day 1.
19. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and recorded prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Subjects will take the cabozantinib tablet(s) orally, QD in the fasted state (dose at least 2 hours after meal, and no more food intake for 1 hour postdose), preferably at bedtime.

The assigned dose is 60 mg (60 mg tablet×1) cabozantinib given QD. A dose of 60 mg should be maintained in the absence of treatment-emergent toxicity.

8.1.1 Cabozantinib Administration on Week 1 Day 1

On Week 1 Day 1, cabozantinib will be administered in the clinic to enable a predose blood sample to be taken for PK evaluation. Subjects should be fasted (with the exception of water) for at least 2 hours before receiving cabozantinib. Required study examinations and blood draws should be done during this time, prior to any study treatment administration. Upon completion of the 2 hour fast, the subject should receive the 60 mg oral dose of cabozantinib with a full glass of water in the clinic and then continue to fast for 1 hour while under observation to monitor for potential AEs.

8.1.2 Subsequent Dose Administration of Cabozantinib

After Week 1 Day 1, cabozantinib will be self-administered at home by taking cabozantinib QD at the same time each day. Any unused study drug must be returned to the study site for drug accountability and disposal. Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their doses of cabozantinib. After the 2 hour fast and before going to bed, subjects are to take cabozantinib with a full glass of water with no more food intake for 1 hour postdose. If the subject's schedule requires taking cabozantinib during the day, the subject should be instructed to follow the same fasting recommendations. The subject should take cabozantinib at approximately the same time every day and should adhere to the fasting requirements described in this section. On Week 3 Day 1, Week 5 Day 1, and Week 9 Day 1, subjects should be instructed to visit the clinic without taking cabozantinib because PK sample should be collected approximately 8 or more hours after the previous dose of study drug.

Subjects should be instructed not to make up vomited doses and to maintain the planned dosing schedule. Subjects should not make up for missed doses if more than 12 hours have elapsed after the time the subject would usually take cabozantinib. In the event of missed doses, subjects should not take 2 doses to make up for the 1 missed.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer treatment or liver directed local anticancer therapy, or until any other reasons for treatment discontinuation listed in the protocol (see Section 9.7).

8.2 Dose Modification Guidelines

8.2.1 Dose Reductions, Interruptions and Discontinuation

Subjects will be monitored for AEs from the time of signing informed consent through 30 days after the last dose of study drug. Subjects will be instructed to notify the investigator immediately of any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. AE severity will be graded by the investigator according to CTCAE Version 4.03. Local laboratory assessments should be obtained and used for dose modification consideration (reductions or interruption) of cabozantinib at the study visit. The following parameters must be included in local laboratory assessment for dose modification: WBC count with differential and platelets , ALP, ALT, AST, and total bilirubin.

The following should be taken into consideration in decisions regarding dose modifications:

- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity considered related to cabozantinib treatment. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- Dose modification criteria for cabozantinib are shown in Table 8.b. Dose reductions and/or interruptions should be implemented for unacceptable toxicity. Doses may be modified at any time while on study.
- The assigned dose for cabozantinib is 60 mg/day. Two dose reduction levels of cabozantinib are permitted (Table 8.a).
- Dose reductions or interruptions may also occur in the setting of lower-grade toxicity than defined in Table 8.b if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for AEs may occur at any time per investigator discretion. If treatment is interrupted due to AEs for more than 6 weeks, cabozantinib should be discontinued.
- Following cases require sponsor approval;
  - Keeping same level of dose despite the toxicity meet the status in the modification guideline that require dose reduction or interruption.
  - Dose re-escalation or dose reinstitution at the same level after dose interruption due to the toxicity.
  - Dose interruptions for reason(s) other than AEs (eg, surgical procedures) for more than 6 weeks. The acceptable length of interruption will depend on agreement between investigator and the sponsor.

Guidelines for the management of specific AEs such as GI disorders, hepatobiliary disorders, hematological disorders, constitutional disorders, skin disorders, hypertension, thromboembolic events, proteinuria, QTc prolongation, hypophosphatemia, thyroid function disorders,

hemorrhagic events, GI perforation/fistula and non-GI fistula formation, osteonecrosis of the jaw, and reversible posterior leukoencephalopathy syndrome (RPLS) are provided in Section 8.6.

Table 8.a Dose Reductions of Cabozantinib

Assigned Dose	First Dose-Level Reduction	Second Dose-Level Reduction
60 mg cabozantinib oral QD (60 mg tablet×1)	40 mg cabozantinib oral QD (20 mg tablet×2)	20 mg cabozantinib oral QD (20 mg tablet×1)

QD=once daily.
Cabozantinib should be discontinued if a QD dose of 20 mg cabozantinib (minimum dose) is not tolerated.

Table 8.b Dose Modifications of Cabozantinib for Treatment Related AEs

CTCAE Version 4.03 Grade	Recommended Guidelines for Managements (a)
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose-reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically nonrelevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically nonrelevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the sponsor. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

AE=adverse event.
Note: The dose delay and modification criteria for specific medical conditions are provided in Section 8.6. For retreatment criteria of study treatment after a dose hold, see Section 8.2.2.
(a) Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

8.2.2 Dose Reinstitution and Re-escalation

If the subject recovers from his or her toxicities to CTCAE Version 4.03 Grade ≤1, to the baseline value, or to within normal range, and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤1, to the baseline value, or to within normal range, and the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 8.a for the schedule of dose reductions).

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose (but not higher than 60 mg/day) may be allowed at the discretion of the investigator and agreement of the sponsor for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (eg, central nervous system [CNS], cardiac, hepatic, renal).

8.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device
- Oral anticoagulants (eg, coumarin-related agents or other direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for prophylactic use per local applicable guidelines).
- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of HCC).
- Any liver-directed local anticancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy [including stereotactic radiotherapy], or surgery).
- interferon treatment

The following medications and procedures should be avoided until study treatment has been permanently discontinued or until the investigator discusses with the sponsor and receives sponsor approval:

- Palliative external radiation to bone metastasis or skin/subcutaneous metastasis should not be performed unless clinically unavoidable. If clinically unavoidable the investigator must seek sponsor approval prior to the procedure. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin [38].

- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment.
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital, and St. John's wort) should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject for enrollment of this study.
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, telaprevir and voriconazole) should be avoided. Grapefruit and Seville oranges with inhibitory effect on CYP3A4 family should be avoided.

  Refer to Appendix I for a nonexhaustive list of medications, supplements, and food products that are strong inhibitors or inducers of the CYP3A4 family based on the final draft of Ministry of Health, Labour and Welfare (MHLW) DDI Guidance.

8.4 Permitted Concomitant Medications and Procedures

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor) are allowed while the subject is enrolled in the study. However, these should not be administered prophylactically before initial treatment with study drug.
- Drugs used to control bone loss (eg, bisphosphonates and denosumab) can be continued if started before Week 1 Day 1 and the benefit outweighs the risk per the investigator's discretion. (Note: Osteonecrosis of the jaw has been reported in subjects using bisphosphonates and denosumab. Oral examinations are recommended before Week 1 Day 1 to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to report symptoms quickly to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.)
- Transfusion should be used in accordance with institutional guidelines.
- Hormone replacement, and short-term steroid treatment (above the physiologic replacement dose) may be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

- *Low-dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
- *Therapeutic doses of LMWH* at the time of Week 1 Day 1 are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 12 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen. (Note: LMWH has not been approved for the use for cardioprotection in Japan.)
- *Therapeutic doses of LMWH* after Week 1 Day 1 are allowed if clinically indicated (eg, for the treatment of deep vein/venous thrombosis [DVT]), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 8.6.7.
- Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction).
- For restrictions on oral anticoagulants, see Section 8.3.

Potential drug interactions with cabozantinib are summarized in Section 4.1.5.

8.5 Precautions and Restrictions

8.5.1 Pregnancy and Contraception

It is not known what effects cabozantinib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female subjects must meet 1 of the following:

- Postmenopausal (natural amenorrhea, not due to other medical reasons) for at least 1 year before the Screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method of birth control (see examples below) with a condom, which is an effective barrier method of contraception, at the same time, from the time of signing the informed consent form (ICF) through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent through 4 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Male subjects, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug. If their partner are of childbearing potential, their female partner should use 1 highly effective method of birth control (see examples below) at the same time, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent through 4 months after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Women of childbearing potential is defined as any sexually active female subjects who meet both of the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy, AND
- Those who have not had natural menopause for 12 consecutive months or longer.

  Note: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Examples of highly effective contraception methods are listed below:

- Hormonal birth control pills.
- Intrauterine device.
- Intrauterine hormone-releasing system.

8.6 Management of Clinical Events

If dose alterations are necessary as a result of the events detailed below, refer to Section 8.2.

8.6.1 GI Disorders

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

8.6.1.1 Diarrhea

Subjects should be instructed to notify their physicians immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 8.c.

Administration of antidiarrheal/antimotility agents is recommended as initial management at the first sign of diarrhea. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 8.a. When the diarrhea is controlled, retreatment with study treatment may be acceptable per investigator decision.

In addition, general supportive measures should be implemented including continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Table 8.c Management of Treatment-Emergent Diarrhea

Status	Management
Tolerable Grade 1-2 (duration <48 hr)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent per institutional guidelines • Dietary modifications (eg, small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hr: – Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 hr diarrhea-free interval. – Diarrhea not resolving: Continue/resume antidiarrheal treatment.
Intolerable Grade 2, Grade 2 >48 hr, or ≥Grade 3	• Interrupt study treatment. • Ask subject to attend clinic. • Rule out infection (eg, stool sample for culture). – Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists >24 hr). • Administer fluids (1-1.5 L/day orally or intravenous [IV], as appropriate) for hydration or to correct electrolyte abnormalities. • For Grade 3-4 or complicated lower-grade diarrhea consider hospitalization and IV hydration. • Re-assess after 24 hr. – Diarrhea resolving to baseline bowel habits or Grade ≤1: consider restarting study treatment at reduced dose. – Diarrhea not resolving: – Start and or continue antidiarrheal treatment per Institutional Guidelines. – Consider starting second line antidiarrheal or referral to gastroenterologist.

AE=adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 8.6. For re-treatment criteria of study treatment after a dose hold see Section 8.2.2.

8.6.1.2 Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. However, the 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists (ie, aprepitant and fosaprepitant) and dexamethasone (NK-1 receptor antagonists can inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus might affect cabozantinib exposure) (see Section 8.3).

8.6.1.3 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk of complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.

During treatment with cabozantinib, good oral hygiene and standard local treatments such as nontraumatic and nonirritating cleansing and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. Lips should be kept well moisturized using moisturizers which do not contain a large amount of artificial chemicals, preservatives, colors and perfumes. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

8.6.2 Hepatobiliary Disorders

Elevations of ALT, AST, and total bilirubin have been observed during treatment with cabozantinib.

A subject who has ALT, AST, and total bilirubin ≤3.0 × ULN at Week 1 Day 1 and who develops ≥Grade 3 elevated ALT, AST, or total bilirubin should have study treatment interrupted and the dose reduced as outlined in Table 8.a and Table 8.b.

Subjects on this study may enter the study with elevations of AST/ALT up to 5.0 × ULN at screening. Elevations of aminotransferases when hepatic tumors are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than 2 times value at Week 1 Day 1) and if there are no progressive elevations in serum total bilirubin concentration or coagulation factors. To predict severe hepatotoxicity, monitoring of prothrombin time-international normalized ratio (PT-INR) is useful. Cabozantinib treatment should be interrupted when transaminase increases are followed by or concurrent with progressive elevations

of total bilirubin, and/or elevations of coagulation tests (eg, PT-INR). More frequent monitoring (eg, at least weekly) of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is clarified, until the laboratory test value return to the Week 1 Day 1 value, or stabilize at clinically acceptable levels. If hepatic toxicity resolves during a temporary hold and was deemed related to study treatment, then study treatment may be restarted at a reduced dose with at least weekly monitoring until acceptable and stable level of transaminase. Study treatment should be discontinued if hepatic dysfunction is not reversible despite temporary interruption of study treatment.

Elevations >3 × ULN of ALT or AST followed by or concurrent with >2 × ULN total bilirubin without other explanation can indicate DILI and drug should be permanently discontinued.

If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or total bilirubin.

Evaluation of subjects with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors such as illnesses which affect liver function (eg, infectious [including reactivation of hepatitis virus] and non-infectious causes of hepatitis, liver cirrhosis, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. AEs which are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions.

8.6.3 Hematological Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of G-CSF support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia. Guidelines for the management of neutropenia and thrombocytopenia are shown in Table 8.d.

Complete blood counts with differentials and platelets should be performed regularly. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines.

Table 8.d Management of Treatment-Emergent Neutropenia and Thrombocytopenia

Status	Action to be Taken
Grade 3 neutropenia with documented infection, Grade 3 neutropenia ≥5 days, Grade 4 neutropenia, or Febrile neutropenia	Interrupt cabozantinib treatment until toxicity resolves to ≤Grade 1, then resume cabozantinib with 1 dose-level reduction.
Grade 3 thrombocytopenia with clinically significant bleeding, or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until toxicity resolves to ≤Grade 1, then resume cabozantinib with 1 dose-level reduction.

8.6.4 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or causes should be treated according to standard of care. Individual nonpharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease-specific morbidities have been excluded. (Note: Chronic use of modafinil, which is an inducer of CYP3A4, should be avoided because of its potential to reduce cabozantinib exposure; see IB.)

Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for ≥Grade 3 fatigue despite optimal management, at the investigator's discretion.

Anorexia and weight loss should be managed according to local standard of care including physical examination and nutritional support. Pharmacologic therapy should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for ≥Grade 3 anorexia or weight loss. If anorexia and/or weight loss do not recur after a dose reduction, dose of cabozantinib may be re-escalated to the previous dose.

8.6.5 Skin Disorders

8.6.5.1 Palmar-planter erythrodysesthesia syndrome (PPES)

PPES (also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥30, avoidance of exposure of hands and feet to hot water, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPES are presented in Table 8.e.

In the case of skin changes (eg, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Table 8.e Management of Treatment-Emergent PPES

CTCAE Version 4.03 Grade	**Action to be Taken**
1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. Start urea 20% cream twice daily AND high-potency steroid cream (eg, clobetasol 0.05% cream) QD. Re-assess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
2	Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose-reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high-potency steroid cream QD and add analgesics (eg, NSAIDs/GABA agonists) for pain control if needed. Re-assess at least weekly; if PPES does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high-potency steroid cream twice daily AND analgesics. Resume cabozantinib at reduced dose if PPES recovers to Grade 0 or 1. Discontinue subject from study treatment if intolerable PPES recurs after dose reduction or does not improve within 6 weeks.

CTCAE=Common Terminology Criteria for Adverse Events, GABA=gamma-aminobutyric acid, NSAID=non-steroidal anti-inflammatory drug, PPES=palmar-plantar erythrodysesthesia syndrome.

8.6.5.2 Wound Healing and Surgery

Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. Shorter treatment holds can be acceptable based on the investigator's medical judgment in terms of the subject's potential benefit/risk balance, but will require prior notification to the sponsor.

The decision to resume treatment with cabozantinib after the surgery should be based on clinical judgment of adequate wound healing.

8.6.6 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported in subjects treated with cabozantinib.

BP should be monitored in a constant position at each visit in a relaxed setting. Treatment guidelines for hypertension are presented in Table 8.f. In general, subjects with known hypertension should be optimally managed prior to study entry. Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Table 8.f Management of Treatment-Emergent Hypertension

Criteria for Dose Modification	Action to be Taken
Subjects NOT receiving optimized antihypertensive therapy	
>150 mm Hg (systolic) (a) and <160 mm Hg OR >100 mm Hg (diastolic) (a) and <110 mm Hg	• Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by 1 dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic. • If subject is symptomatic, interrupt study treatment.
≥160 mm Hg (systolic) OR ≥110 mm Hg (diastolic)	• Reduce cabozantinib treatment by 1 dose level or interrupt cabozantinib treatment per investigator discretion. • Add new or additional antihypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic, cabozantinib treatment should be dose-reduced further or interrupted. • Cabozantinib treatment should be dose-interrupted if upper limits of systolic BP (≥160 mm Hg systolic) are sustained and not adequately manageable or if systolic BP is >180 mm Hg or diastolic BP is >110 mm Hg or if subject is symptomatic. • Restart cabozantinib treatment at the most tolerable dose and re-escalate cabozantinib dose only if BP falls to and is sustained at ≤150 mm Hg systolic and <100 mm Hg diastolic.
Hypertensive emergency (b) or hypertensive encephalopathy	• Discontinue cabozantinib treatment.

BP=blood pressure.
(a) The investigator should consider whether to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 mm Hg or diastolic BP >100 mm Hg based on his/her clinical judgment and assessment of the individual subject.
(b) Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (ie, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

8.6.7 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. DVT and PE have been observed in clinical studies with cabozantinib, including fatal events (please refer to the IB). Subjects who develop a PE and/or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparins (eg, LMWH) is established. (Note: Therapeutic anticoagulation with oral anticoagulants or oral platelet inhibitors such as clopidogrel is not allowed in this study.) Cabozantinib treatment may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated and that they are deriving clinical benefit from cabozantinib treatment. During anticoagulation treatment, subjects need to be monitored on an

ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests according to institutional guidelines. If there are any signs of clinically relevant bleedings, cabozantinib treatment should be interrupted immediately and the sponsor contacted to discuss further study participation. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the sponsor.

Arterial thrombotic events (eg, TIA, myocardial infarction) have been observed in studies with cabozantinib. Subjects should be evaluated for pre-existing risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of study treatment. Cabozantinib treatment should be discontinued in subjects who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

For recurrent/worsening venous thromboembolic events after resumption of cabozantinib treatment, cabozantinib treatment should be discontinued.

8.6.8 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways.

During each safety assessment visit, proteinuria will be quantified by measuring the UPCR performed by the central lab. In addition, urine dipstick analysis will be performed by the local lab in regular intervals (see Appendix A) and as clinically indicated. Management of proteinuria will be based on UPCR results provided by the central lab (see Table 8.g).

However, since dipstick results from the local labs may be available prior to the UPCR results from the central lab, they can be used by the investigator for interim management of proteinuria. For example, if the dipstick analysis shows proteinuria ≥3+ the investigator may decide to interrupt cabozantinib dosing until the UPCR result becomes available and treatment decisions can be made.

Table 8.g Management of Treatment-Emergent Proteinuria

Severity of Proteinuria (UPCR)	Action to be Taken
≤1 mg/mg (≤113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring.
>1 and <3.5 mg/mg (>113.1 and <395.9 mg/mmol)	• Consider confirming with a 24-hr protein assessment within 7 days. • No change in cabozantinib treatment required if UPCR ≤2 mg/mg on repeat UPCR testing or urine protein ≤2 g/24 hr on 24-hr urine collection. • Dose-reduce or interrupt cabozantinib treatment if UPCR >2 mg/mg on repeat UPCR testing or urine protein >2 g/24 hr on 24-hr urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to ≤2 mg/mg. Consider holding cabozantinib treatment if UPCR remains >2 mg/mg despite a dose reduction until UPCR decreases to ≤2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose hold unless otherwise approved by sponsor. • Repeat UPCR within 7 days and once per week. If UPCR ≤1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains >1 mg/mg and ≤2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥3.5 mg/mg (≥395.9 mg/mmol)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hr urine protein. • If ≥3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR <3.5 mg/mg and >2 mg/mg, continue to hold cabozantinib treatment. If UPCR decreases to ≤2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to ≤1 mg/mg. If UPCR remains >1 mg/mg and ≤2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib treatment.

UPCR=urine protein-to-creatinine ratio.

8.6.9 Corrected QT Prolongation

Only subjects with a baseline QTcF ≤500 msec (single measurement or an average of 3 consecutive results) within 14 days before Week 1 Day 1 are eligible for this study (Exclusion Criterion 11). Subjects will have ECGs performed at times designated by the protocol (see Section 9.4.12 and Schedule of Events [Appendix A]).

If at any time on study after Week 1 Day 1 there is an increase in QTcF interval to an absolute value >500 msec, 2 additional ECGs must be performed with intervals at least 3 minutes apart within 30 minutes after the initial ECG.

If the average QTcF is >500 msec, the following actions must be taken:

- Withhold study treatment.

- Notify the sponsor immediately.
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a prompt cardiology evaluation and management until the average QTcF is ≤500 msec and symptoms have resolved.
- Monitor QTcF closely (approximately every hour or at a frequency deemed clinically indicated by consultation with a cardiologist) until the average QTcF is ≤500 msec on 2 consecutive ECGs at least 1 hour apart or otherwise determined by a cardiologist.
- Check electrolytes, especially magnesium, calcium, and potassium; correct abnormalities as clinically indicated.
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications.

Cabozantinib treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation.
- QTcF value >500 msec is not confirmed or a QTcF >500 msec returns to ≤500 msec.
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤500 msec.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved.
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment.

Following re-initiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

Study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation.
- Recurrence of QTcF prolongation after re-initiation of study treatment at a reduced dose.

8.6.10 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Mild hypophosphatemia is usually asymptomatic or symptoms can be nonspecific such as weakness, bone pain, rhabdomyolysis, or altered mental status. Other causes of hypophosphatemia such as poor nutrition, chronic alcoholism, malabsorption, excessive antacid use, glucocorticoids use, kidney dysfunction, respiratory alkalosis, and vitamin D deficiency should be ruled out and/or these causes treated according to standard of care. Mild to moderate hypophosphatemia should be managed by oral

replacement including foods that are high in phosphate (dairy items, meats, beans) and/or oral phosphate supplements according to standard clinical practice guidelines.

Clinically relevant hypophosphatemia should be managed according to the dose modification guidelines as outlined in Table 8.b or as clinically indicated.

8.6.11 Thyroid Function Disorders

Treatment-emergent elevation of TSH has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in Table 8.b.

8.6.12 Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and should be monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Lung metastasis that invades, encases, or abuts major blood vessels.
- Recent or concurrent radiation to the thoracic cavity.
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease, and ulcerative colitis.
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis.
- History of clinically significant hemoptysis, hematemesis or hematuria.

The risk of hemorrhage in cabozantinib-treated subjects with brain metastasis has not been thoroughly analyzed. Currently, brain metastasis of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastasis should be monitored with a high index of suspicion if symptoms occur that could be due to a CNS hemorrhage.

Discontinue cabozantinib treatment in subjects who have been diagnosed with severe bleeding complications (ie, Grade 2 CNS or pulmonary hemorrhage, or any Grade 3 or 4 hemorrhage).

8.6.13 GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include, but may not be limited to, those listed below.

8.6.13.1 GI perforation/fistula

- Intra-abdominal tumor/metastases invading GI mucosa.
- Active peptic ulcer disease, inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease), diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis.
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.
- Ongoing visceral complications from prior radiation therapy.
- Prior GI surgery (particularly when associated with delayed or incomplete healing).

Complete healing following abdominal surgery and/or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or nonsteroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Discontinue cabozantinib treatment in subjects who have been diagnosed with GI perforation/fistula.

8.6.13.2 Non-GI fistula

Complications from radiation therapy have been identified as possible predisposing risk factors for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors (eg, bevacizumab).

Discontinue cabozantinib treatment in subjects who have been diagnosed with non-GI fistula.

8.6.14 Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, use of corticosteroids, anticancer agents, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer itself. Osteonecrosis has been reported in subjects treated with cabozantinib, the details of which are provided in the current version of the IB. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab.

In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for approximately 4 weeks prior to a dental procedure and resumed after complete healing has occurred. Bone healing may often require a protracted time.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Re-initiation of study treatment must be discussed with and approved by the sponsor on a case-by-case basis.

8.6.15 RPLS

For signs and symptoms suggestive of RPLS (eg, confusion, headache, seizures, cortical blindness) of any grade, interrupt cabozantinib treatment. Suspected RPLS should be investigated with MRI. If RPLS is confirmed, discontinue cabozantinib treatment.

- If RPLS is ruled out via MRI, the decision to resume cabozantinib should be based on the signs and symptoms: for Grade 4 events considered at least possibly related to cabozantinib, discontinue cabozantinib treatment.
- For Grade 3 events, cabozantinib may be resumed if events improve to ≤Grade 1 with 1 dose-level reduction.

8.7 Blinding and Unblinding

This is an open-label study.

8.8 Description of Investigational Agents

Cabozantinib will be supplied as 20 mg or 60 mg (expressed as the free base equivalent weight), yellow film-coated tablets. The 20 mg tablets are round and the 60 mg tablets are oval.

For additional details, refer to the IB and Pharmacy Manual.

8.9 Preparation, Reconstitution, and Dispensation

Detailed instructions for dispensing cabozantinib tablets are provided in the Pharmacy Manual.

Cabozantinib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling cabozantinib.

8.10 Packaging and Labeling

The cabozantinib 20 mg tablets and 60 mg tablets will be provided by the sponsor. The study drug will be provided in 60 cc round high-density polyethylene (HDPE) bottles. Each HDPE bottle contains a total of 30 tablets, sealed with induction seal and a plastic cap with child-resistant closure, labeled in an open fashion with a single panel label. The study drug labels will fulfill all requirements specified by governing regulations.

8.11 Storage, Handling, and Accountability

Cabozantinib tablets should be stored in the original dispensing bottles at 1°C to 30°C. All temperature excursions for the tablets must be reported back to the sponsor for assessment and determination for continued use. Refer to the Pharmacy Manual for additional information. Study medication is to remain in the HDPE bottle until time of dosing. All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All study medication must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained each working day. Temperature excursion must be reported to the sponsor or designee.

Cabozantinib tablets are meant to be taken orally only and are not to be crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy tubes. Cabozantinib tablets should not be administered to subjects who do not have adequate swallowing capacity; they must be stored at controlled room temperature, and inventoried according to applicable governing regulations.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the subjects, will be provided and kept at the study site.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the Takeda clinician, the central laboratory, any additional clinical laboratories or vendors participating on the study as well as the list of investigators can be found in the protocol annex.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB).

9.3 Study Enrollment

After written informed consent has been obtained, the patient will be assigned a subject identification code.

Patient eligibility will be confirmed by a Takeda clinician before enrollment by the investigator into the study. Re-enrollment of the same patient will not be permitted. If a subject discontinues from the study, that subject identification code will not be reused.

A patient is considered to be enrolled in the study when the first dose of study drug has been administered.

Procedures for completing the enrollment information are described in the subjects' enrollment/discontinuation manual.

9.4 Study Procedures

Subjects will be evaluated at scheduled visits over the following study periods: Screening, Treatment and Posttreatment. This protocol generally presents scheduled timelines for study procedures by references to week (W) and day (D) (eg, Week 1 Day 1, Week 3 Day 1, etc). Each timeline will be relative to the date of Week 1 Day 1.

Screening assessments must be performed within 28 days before Week 1 Day 1.

All assessments for efficacy, safety and HRQOL assessments will be scheduled based on Week 1 Day 1. Unscheduled visits for radiographic evaluations and safety evaluations are allowed at any time.

Refer to the Schedule of Events (Appendix A) for timing of assessments.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.4.2 Demographics

The date of birth, race, and sex of the subject are to be recorded during Screening.

9.4.3 Medical History

At Screening and Week 1 Day 1, a complete medical history will be compiled for each subject, including medical and cancer history, surgical history, radiation therapy history, and systemic anticancer treatment history including names and administration dates of all VEGFR-targeting TKI.

Baseline assessments will include information pertinent for staging (eg, tumor morphology, macrovascular invasion and/or extrahepatic spread, sites of disease, and extent of liver involvement) and documentation of the etiology of HCC based on the subject's medical records.

9.4.4 Tumor Biopsy

For subjects who have not had previous histological or cytological diagnosis of HCC, biopsy will be required to establish eligibility at Screening. Healing from biopsy must be complete at least 7 days before Week 1 Day 1.

9.4.5 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events (Appendix A). Physical examinations will include an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. A symptom-directed physical examination will be conducted on Week 1 Day 1 before first dose of study drug.

9.4.6 Height and Weight

Height will be measured during Screening only (within 28 days before Week 1 Day 1).

Weight will be measured as specified in the Schedule of Events (Appendix A).

9.4.7 Vital Signs

Vital sign measurements include seated position (after the subject has been sitting quietly for approximately 5 minutes in this position) measurements of diastolic and systolic BP, pulse, respiratory rate and temperature will be assessed as specified in the Schedule of Events (Appendix A).

9.4.8 ECOG PS

The ECOG PS of the subject will be assessed at Screening to establish eligibility and also assessed at each scheduled visit for safety assessment starting on Week 1 Day 1 (Appendix A).

Refer to Appendix D for the ECOG scale criteria.

9.4.9 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening (after the subject signs the ICF and 7 or more days before Week 1 Day 1). A urine or serum pregnancy test will also be performed predose on Week 1 Day 1 (Note: Considering that there are false negative periods [approximately 7 days for serum test and approximately 10 days for urine test] in early pregnancy, the test methods and the duration between the tests performed at Screening and the predose tests performed on Week 1 Day 1 should be determined.) Negative results must be obtained before the first dose of study drug. Subsequently, urine or serum pregnancy tests will be performed predose every 12 weeks (±5 days) and will also be performed at the 30-day posttreatment followup visit.

9.4.10 Concomitant Medications and Procedures

Medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) and therapeutic procedures completed by the subject and their outcomes will be recorded in the electronic case report form (eCRF) from the time of the signing of the ICF through 30 days after the last dose of study drug or the start of subsequent systemic anticancer treatment, whichever occurs first. See Section 8.3 and Section 8.4 for information on excluded and/or permitted concomitant medications and procedures during the study.

9.4.11 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.12 ECG

Single ECG assessments with standard 12-lead ECG equipment according to standard procedures will be performed and interpreted locally at the time points specified in the Schedule of Events (Appendix A). The QTcF should be determined by the investigator at all time points. ECGs to establish eligibility at Screening must be done within 14 days before Week 1 Day 1 (Appendix A).

All scheduled ECGs should be performed predose and after the subject has rested quietly for at least 5 minutes in a supine position. When the timing of a PK, biomarker or safety laboratory blood sampling coincides with the timing of ECG measurements, the ECG will be completed before the blood sample collection. In some cases, it may be appropriate to repeat an ECG to rule out

improper lead placement contributing to the ECG abnormality. ECGs should be reviewed by the investigator or delegate before the subject leaves the clinic on visit days.

If the result for QTcF is ≤500 msec at Screening, the subject meets eligibility in this regard (Exclusion Criterion 11).

If indicated due to any cardiac abnormalities (see Section 8.6.9), 2 additional ECGs must be performed within 30 minutes after the initial ECG, each with intervals at least 3 minutes apart.

Abnormalities in the ECG that lead to a change in subject management (eg, dose reduced or withheld, treatment discontinued, requirement for additional medication or monitoring) or result in clinical signs and symptoms will be considered clinically significant for the purposes of this study and will be deemed AEs. If values meet the criteria defining them as serious, they must be reported as SAEs (see Section 10.2).

9.4.13 Echocardiogram

Echocardiogram will be performed at Screening and every 24 weeks (±7 days) thereafter. Additional cardiac function tests are required if any signs or symptoms of cardiac dysfunction occur. Echocardiogram should be performed for determination of left ventricle ejection fraction.

9.4.14 Clinical Laboratory Evaluations

Blood and urine samples for analysis of the parameters shown in Table 9.a will be obtained as specified in the Schedule of Events (Appendix A). Handling and shipment of clinical laboratory samples will be outlined in the laboratory manual.

Hematology, serum chemistry, coagulation, UPCR including components (urine protein and creatinine), AFP, bone specific ALP, and thyroid function tests are to be performed by a central laboratory, including labs obtained at unscheduled visits whenever possible. All central laboratory results will be provided to the investigator. Local laboratory tests for dose modification consideration will be performed at each study visit as well as central laboratory tests. On Week 1 Day 1, the results of local laboratory tests at the most recent or Week 1 Day 1 that consideration will be used to start of treatment. WBC count with differential and platelets , ALP, ALT, AST, and total bilirubin must be included in local laboratory assessment for dose modification. Local laboratory assessments for other than the above parameters may be obtained and used if the results are required by the investigator in a rapid timeframe (eg, monitoring for AEs, SAEs). However, the results of local laboratory tests may not be used to establish eligibility. In rare, exceptional circumstances and with approval of the sponsor, local laboratory results may be allowed to use for the purpose of determining eligibility in the event that the results of individual tests performed at the central laboratory are unavailable at the time of subject enrollment or the accuracy of test results is questioned. Qualitative urinalysis (dipstick or routine), microscopic urine examination, and urine or serum pregnancy tests are to be done by local laboratory. These results or the status will be recorded on eCRFs.

A blood sample for AFP (see Section 9.4.16) and a serum sample for bone specific ALP (see Section 9.4.19) will be obtained.

Laboratory tests to establish eligibility must be done within 10 days before Week 1 Day 1 (Appendix A). A serum pregnancy test must be performed after informed consent and 7 or more days before Week 1 Day 1.

HbA1c will only be tested at Screening to confirm eligibility and must be done within 10 days before Week 1 Day 1. For subjects whose HbA1c results are unavailable (eg, hemoglobin variant), a fasting serum glucose test result can be used to confirm eligibility after sponsor approval.

Throughout the study fasted glucose will be monitored. On days when the blood sample is drawn, subjects must fast (no caloric intake for at least 8 hours; consumption of water is allowed) overnight.

Serum virus tests will be performed by central laboratory during the Screening period. Hepatitis B virus (HBV) testing will include hepatitis B surface antigen (HBsAg) and hepatitis B viral load (HBV-DNA). Hepatitis C virus (HCV) testing will include HCV antibody (HCVAb) and hepatitis C viral load (HCV-RNA).

If transaminase increases are followed by or concurrent with progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, PT-INR), more frequent monitoring of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is determined and these abnormalities return to the baseline values or are stabilized to the clinically acceptable levels.

To estimate creatinine clearance, the Cockcroft-Gault equation will be employed (Appendix H).

Table 9.a Clinical Laboratory Tests

Central Laboratory

Hematology
- WBC count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes)
- Hematocrit
- Platelet count
- Red blood cell count
- Hemoglobin
- Reticulocytes

Coagulation
- PT-INR
- APTT

Thyroid function
- TSH
- Free T4 (required at Screening; after Screening only if TSH is outside normal range)

Other Parameters
- AFP
- Bone specific ALP

Serum Chemistry
- Albumin
- ALP
- ALT
- Amylase
- AST
- BUN
- Corrected calcium
- Chloride
- Creatinine
- GGT
- Glucose (fasted)
- LDH
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Bilirubin (total bilirubin, conjugated and unconjugated bilirubin)
- Protein (total protein)
- Glycosylated hemoglobin A1c (HbA1c; only at Screening)

Urine Chemistry
- Protein (spot urine; fully quantitative)
- Creatinine (spot urine; fully quantitative)
- UPCR (spot urine)

Serum Virus Tests
- HBsAg and HBV-DNA
- HCVAb and HCV-RNA

Local Laboratory

Hematology (a)
- WBC count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes)
- Hematocrit
- Platelet count
- Red blood cell count
- Hemoglobin
- Reticulocytes

Serum Chemistry (a)
- ALP
- ALT
- AST
- Bilirubin (total bilirubin, conjugated and unconjugated bilirubin)

Pregnancy Urine or Serum Test
- HCG or β-HCG

Qualitative Urinalysis (Dipstick or Routine)
- pH
- Specific gravity
- Ketones
- Protein
- Glucose
- Nitrite
- Urobilinogen
- Leukocyte
- Occult blood

Microscopic Urine Examination
- Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated

AFP=alpha-fetoprotein, ALP=alkaline phosphatase, ALT=alanine aminotransferase, ANC=absolute neutrophil count, APTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, GGT=gamma-glutamyl transferase, HbA1c=hemoglobin A1c, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCG=human chorionic gonadotropin, HCV=hepatitis C virus, HCVAb=hepatitis C virus antibody, LDH=lactate dehydrogenase, PT-INR=prothrombin time-international normalized ratio, TSH=thyroid-stimulating hormone, UPCR=urine protein-to-creatinine ratio, WBC=white blood cell.
(a) The following parameters must be included in local laboratory assessment for dose modification: WBC count with differential and platelets, ALP, ALT, AST, and total bilirubin.

9.4.15 Tumor Assessment

9.4.15.1 General

Radiographic response and disease progression will be determined using RECIST 1.1 (Appendix F). For the purpose of determination of the study endpoints of PFSR, PFS, ORR and DCR, central review of radiographic images will be conducted by an IRC (see Section 9.4.15.2 and Section 11.1). All radiographic tumor assessments (both scheduled and unscheduled) must be sent to the IRC, which also will review prior radiation history data for the purpose of selection of target lesions.

Radiographic tumor assessments will include the following:

1. **Chest/Abdomen/Pelvis:** CT (or MRI) of CAP will be performed in all subjects at Screening. CT (or MRI) will be performed on Week 9 Day 1 and every 8 weeks (±7 days) thereafter. If MRI of the CAP study is used at Screening, MRI of abdomen and pelvis will be required and noncontrast CT of the chest should be performed as well.
2. **Brain:** MRI (or CT) of the brain will be performed in all subjects at Screening. After Week 1 Day 1, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis. Assessments will be performed on Week 9 Day 1 and every 8 weeks (±7 days) thereafter. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 3 months before enrollment. Subjects without documented brain metastasis during the screening assessment are not required to undergo postenrollment brain imaging unless clinically indicated.)
3. **Bone:** Whole body TBS will be performed in all subjects at Screening. After Week 1 Day 1, bone scans will be performed only in subjects with known bone metastasis on Week 9 Day 1, Week 17 Day 1 (±7 days), and every 16 weeks (±7 days) thereafter until last CT/MRI scan. (Note: Subjects without documented bone metastasis during the screening assessment are not required to undergo postenrollment bone scan imaging unless clinically indicated.) Lesions identified on bone scans are not to be recorded as target, nontarget, or new lesions. Bone scans are to be used to direct corroborative imaging with CT/MRI if necessary (these CT/MRI findings will be used for RECIST 1.1 evaluation). Bone scan findings alone cannot be used for the determination of progression per RECIST 1.1.

Imaging Guidelines

All CT/MRI (CAP, brain) and TBS imaging studies are recommended to be performed using the study-specified imaging protocol (refer to the imaging manual). To ensure image consistency, the same imaging modalities and acquisition protocols used at Screening should be used for subsequent tumor assessments. All imaging must be acquired and transmitted for central review in original Digital Imaging and Communications in Medicine (DICOM) format (not a secondary capture).

CT/MRI

For screening period and all scheduled followup imaging examinations, CT or MRI of CAP should be obtained. CT of CAP should include contrast with triphasic (arterial, portal and delayed venous phase) imaging of the liver. For imaging of the liver, MRI with gadolinium enhanced imaging may be substituted for the contrast enhanced triphasic CT scan. A noncontrast liver study must be acquired (at least at screening). If MRI is used for CAP study, MRI of abdomen and pelvis will be required and noncontrast CT of the chest should be performed as well. For enrolled subjects with treated and stable brain metastasis, the same postcontrast MRI (or postcontrast CT) of the brain as performed at Screening should be performed during subsequent assessments while on study. Volume acquisition CT reconstructed every 3 mm to 5 mm contiguously with a soft tissue filter should be performed. MRI scans should be performed using a body coil and reconstruction every 3 mm to 5 mm without gap. For all followup CT (or MRI) examinations, the same imaging modalities used at Screening will be used. If at a followup imaging time point there is a contraindication to use of contrast (eg, impaired renal function) then a noncontrast CT or MRI should be performed.

TBS

Whole body TBS images must be acquired and injected with a dose in accordance with local standards. The time from injection to scan acquisition should be same at each time point and images acquired with a delay from injection according to local standards.

Lesions identified on TBS are not to be recorded as target, nontarget, or new lesions. Bone scans are to be used to direct corroborative imaging with CT/MRI if necessary (these CT/MRI findings will be used for RECIST 1.1 evaluation). Bone scan findings alone cannot be used for the determination of progression per RECIST 1.1.

Duration of Radiographic Tumor Assessments

Tumor assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued.

End of radiographic tumor assessments by CT/MRI:

- For subjects who discontinue study treatment before radiographic disease progression or within 8 weeks after radiographic disease progression, final radiographic tumor assessments are to be performed 8 weeks after radiographic disease progression. For subjects who discontinued study treatment and commenced a subsequent anticancer therapy (other than radiation therapy to bone), radiographic tumor assessments should be performed prior to the subsequent therapy. No further radiographic tumor assessments are necessary to be performed.
- For subjects who continue to receive study treatment for more than 8 weeks after radiographic disease progression, tumor assessments are to continue per the protocol-defined schedule until study treatment is permanently discontinued.

Bone scan evaluations will end on the day of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI has been performed.

Tumor assessment by investigator

For the purpose of subject management and treatment decisions, radiographic response and disease progression will be assessed by investigators using RECIST 1.1 (Appendix F). The sponsor should be notified of all disease progression as soon as possible. If any doubt or ambiguities exist about radiographic progression, investigators are encouraged to continue study therapy if the subject is tolerating it acceptably, repeat radiographic studies at the next scheduled time, and delay determination of progression until the findings indicating radiographic progression are unequivocal. Radiographic progression determined by the investigator does not warrant discontinuation of tumor assessments or study treatment (see Section 9.7). If the study treatment is continued even after determination of disease progression, the time of disease progression determined by the investigator will be considered "baseline" and tumor assessment will be continued based on the RECIST 1.1 criteria. If a new lesion is identified and determined to be disease progression by the investigator, this lesion will be assessed as a nontarget lesion and tumor assessment will be continued. No radiographic assessment is necessary after the second determination of disease progression.

9.4.15.2 Central Independent Radiology Committee

All radiological studies acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease must be sent to the IRC in original DICOM format (as detailed in the imaging manual). The IRC will evaluate prior radiation history for the purpose of valid identification of target lesions and all images in a central and independent fashion as further described in Section 11.1. Electronic transfer of scan files (via AG Mednet, sFTP, or similar means) is preferred, although transfer on physical media (such as DVDs or CDs) is acceptable. For digital media, each disk should contain one time point for one subject. For this study no paper or film will be acceptable. The site is expected to maintain a copy of digital data for the retention period applicable to the protocol and GCP. The sponsor and or designee will retain the media for the life of the study.

9.4.16 Alpha-Fetoprotein

A blood sample for AFP will be obtained at the time of each radiographic tumor assessment visit according to the schedule in Appendix A.

Samples for AFP measurement should be collected at Screening. Assessments will be performed on Week 9 Day 1, and every 8 weeks (±7 days) thereafter. Assessments will continue regardless of whether study treatment is given, reduced, held, or discontinued until last tumor assessment.

Detailed instructions for sample preparation will be provided in the laboratory manual.

9.4.17 PK Measurements

PK blood samples will be obtained from all subjects as described in Appendix A unless otherwise approved by the sponsor.

The Week 1 Day 1 PK sample should be taken prior to dosing of study drug and at 3 hours after the dosing. The scheduled Week 3 Day 1, Week 5 Day 1 and Week 9 Day 1 on-treatment PK samples should be obtained whether or not study drug is administered on that day. For each on-treatment visit for subjects, the PK sample should be collected approximately 8 or more hours after the previous dose of study drug, and if the study drug will be administered on that day, should be collected prior to the administration. The investigator will ask the subject for the date and time of the most recent prior dose of study drug, and this information will be recorded in the eCRF. Subjects should be encouraged to take the study drug at the same time every day. Collection of these blood samples may be halted early or sampling frequency may be reduced at the discretion of the sponsor.

Detailed instructions for sample preparation will be provided in the laboratory manual.

9.4.18 Pharmacogenomic Blood Sample Collection

A pharmacogenomic blood sample will be collected from all subjects predose on Week 1 Day 1 for single nucleotide polymorphism variation analysis by [redacted] to investigate the contribution of genetic variance on PK, safety and tole ment. Somatic DNA will be obtained from blood samples and be genotyped for clinically relevant germline mutations including polymorphisms in genes encoding drug-metabolizing enzymes and/or transporters. Unless failure to grant informed consent for this purpose, or sponsor decision, additional pharmacogenomic analyses (eg, the contribution of genetic variance on drug response) may be conducted in the future. This additional analyses are limited to analyses of study drug and/or diseases.

The analysis performed with somatic DNA is not intended to make determinations about a subject's health or the likelihood that a subject will develop any disease. In the analytical method used for the study, there are no possibilities that genetic mutation involved in developing any disease will be incidentally discovered. Therefore, no test results will be provided to the investigators and subject, or put into a subject's medical record.

Somatic DNA will be stored at LSI Medience Corporation for up to 15 years after the date of study completion as identified in the CSR and will be degraded and discarded. If subjects withdraw consent, the samples will be degraded and discarded. Details regarding the preparation, processing, and shipping of samples can be found in the laboratory manual.

9.4.19 Biomarker Assessment

Samples for biomarker assessment are for research purposes only and biomarker researches may be conducted when necessary even after the study completion.

Assessment of biomarkers in plasma (candidate biomarkers: soluble-VEGFR2/MET/AXL/VEGF/HGF/GAS6-signaling protein expression profiles and metabolic profiles) will be performed. Samples for these studies will be collected from all subjects according to the schedule outlined in Appendix A. The candidate biomarkers will be prospectively validated in an independent patient population.

Serum bone biomarker (bone specific ALP) will also be assessed. Samples for these studies will be collected according to the schedule outlined in Appendix A.

Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the sponsor. Details regarding the preparation, processing, and shipping of samples can be found in the laboratory manual.

9.4.20 Health-Related Quality of Life Assessments

Subjects will self-report information on HRQOL utilizing the Japanese versions of the EQ-5D-5L (Appendix G) questionnaire. The standardized measure of health status EQ-5D-5L, developed by the EuroQol group, will be used in order to provide a generic measure of health for clinical appraisal [39].

EQ-5D-5L has two pages (Appendix G): a descriptive page with 5 dimensions which assesses changes in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health in patients. Each dimension can be reported on 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). The second page has a 0-100 visual analogue scale which records the respondent's self-rated health between 100 ('the best health you can imagine') and 0 ('the worst health you can imagine') and serves as a quantitative measure of health by the individual respondents.

The first assessments will be performed on Week 1 Day 1 prior to dosing. After Week 1 Day 1, the HRQOL assessments will be collected every 4 weeks (±2 days) up to Week 9 Day 1, and every 4 weeks (±7 days) thereafter through 6 months on study. Upon completion of 6 months on study, the HRQOL assessments will be collected every 8 weeks (±7 days) thereafter until last tumor assessment. The HRQOL questionnaires should be completed by the patient before any other study procedures are performed or study drug is administered on scheduled visits. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the day of the last tumor imaging assessment as described in Section 9.4.15.

Every effort should be made by the study site to retrieve all completed HRQOL questionnaires including the assessment following radiographic progression or discontinuation of study treatment, and kept at the site as source documentation.

The Japanese versions of the EQ-5D-5L questionnaire and instructions for filling them out will be provided to each study site.

9.4.21 Child-Pugh Scoring

Child-Pugh score will be based on the Modified Child-Pugh classification of severity of liver disease [40,41] according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. The Child-Pugh scoring system is located in Appendix E.

The Child-Pugh score to confirm study eligibility will be derived locally by the site within 10 days before Week 1 Day 1. Laboratory parameters required for the scoring must be evaluated within 10 days before Week 1 Day 1. If possible, the results of central laboratory tests to establish eligibility may be used for Child-Pugh assessment. Child-Pugh assessments should be performed on Week 1 Day 1, Week 9 Day 1, and every 8 weeks (±7 days) thereafter. These assessments will continue regardless of whether study treatment is given, reduced, held, or discontinued until last tumor assessment. Determination of severity of ascites and encephalopathy will be made by clinical assessment.

9.4.22 Survival Status and Subsequent Anticancer Therapy

Overall survival will be assessed every 8 weeks (±7 days) after the 30-day posttreatment followup visit. Subjects will be followed until death, consent withdrawn, or the sponsor decision to no longer collect these data. Receipt of subsequent nonprotocol anticancer therapy will also be collected during followup contacts.

9.5 Completion of Study Treatment (for Individual Subjects)

Not applicable for this study.

9.6 Completion of Study (for Individual Subjects)

Not applicable for this study.

9.7 Discontinuation of Treatment With Study Drug and Subject Replacement

Treatment with study drug may be discontinued for any of the following reasons. However, subjects may discontinue study treatment at any time without prejudice. If treatment is interrupted for more than 6 weeks for study treatment-related TEAEs it should be permanently discontinued, unless continuation of treatment is approved by the sponsor for interruptions which are not due to AEs (see Section 8.2.1).

- AE (excluding AEs of disease progression).
- Clinical deterioration (AEs or SAEs related to disease progression).
- Protocol deviation.
- PD.
- Lack of efficacy.

Subject no longer experiences clinical benefit as determined by the investigator. If study treatment is discontinued for this reason, the date of this decision is to be recorded and every effort should be made to continue safety evaluations, tumor assessments, and collection of subsequent anticancer treatment information and followup information for survival.

- Death
- Study terminated by sponsor.
- Pregnancy.
- Withdrawal by subject (with or without concurrent withdrawal of informed consent).
- Lost to followup.
- Physician decision.

  The investigator feels it is not in the best interest of the subject to continue on study.
- Other.

The sponsor should be notified of all discontinuations of study treatment as soon as possible (see the subjects' enrollment/discontinuation manual). The reason for treatment discontinuation and the date of the last known dose of study treatment will be recorded in the eCRF. Subjects who discontinue treatment with study drug will not be replaced.

Once study drug has been discontinued, all study procedures outlined for the 30-day posttreatment followup visit will be completed as specified in the Schedule of Events (Appendix A). For subjects who withdraw or are withdrawn from study treatment, every effort must be made to continue protocol-specified evaluations and procedures unless consent to participate in the study is also withdrawn. All subjects will be followed until death, unless consent to do so is specifically withdrawn by the subject or until a decision by the sponsor is made to stop collection of these data.

If a subject withdraws from study treatment, AEs are to be documented and/or followed as described in Section 10.2 and Section 10.3.

If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at a minimum, a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the study site.

9.8 Withdrawal of Subjects From Study

A subject may be withdrawn from the study for any of the following reasons. However, subjects may withdraw their consent to participate in the study at any time without prejudice.

- Study terminated by sponsor.
- Withdrawal by subject (with or without concurrent withdrawal of informed consent).
- Lost to followup.

- Death.
- Other.

The sponsor should be notified of all subject withdrawals from the study as soon as possible. No further study procedures or assessments will be performed or study data collected for this subject.

The consequence of study withdrawal is that no new information will be collected from the withdrawn subject and added to the existing data or any database. However, every effort will be made to follow all subjects for safety.

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

9.10 Posttreatment Followup Assessments

A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug or until the start of subsequent systemic anticancer treatment, whichever occurs first. Radiographic tumor assessments, Child-Pugh assessments, AFP assessments, and HRQOL assessments will continue regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment as described in Section 9.4.15. Consequently these assessments may be required in the Posttreatment period for some subjects. All subsequent antineoplastic therapies will be recorded, regardless if they are initiated before or after PD.

In addition, subjects will be contacted every 8 weeks (±7 days) after the 30-day posttreatment followup visit to assess survival status and document receipt of subsequent anticancer therapy. Subjects will be followed until death, withdrawal of consent, or the sponsor decision to discontinue collection of these data in the study. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, e-mail, or mail. In addition, the start of another anticancer therapy for the disease under study will be collected. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study and data collection is withdrawn.

Note: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study treatment that occur during the posttreatment followup. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

This includes any newly occurring event, or a previous condition that has increased in severity or frequency after signing the ICF.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.2 Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the subject, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle

(eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [42]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on subject/event outcome or action criteria described above, and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided in the protocol annex). This should be done by faxing an SAE form, by telephone or by e-mail within 24 hours after becoming aware of the event. Followup information on the SAE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [42].

If a subject is noted to have ALT and/or AST elevated >3 ×ULN and total bilirubin >2 ×ULN, the abnormality should be recorded as an SAE. The SAE form should be completed and reported as described above. The investigator must contact the monitor or the sponsor's designee for discussion of the relevant subject details and possible alternative etiologies, such as acute viral

hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Followup laboratory tests as described in Section 9.4.14 must also be performed.

Causality of the event to study drug administration will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of ICF through 30 days after the last dose of study drug or the start of subsequent systemic anticancer treatment whichever occurs first, and recorded in the eCRFs.
- SAEs (related and unrelated) will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF through 30 days after administration of the last dose of study drug or the start of subsequent systemic anticancer treatment whichever occurs first, and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

All SAEs that are ongoing 30 days after the last dose of study drug, and AEs assessed Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the last dose of study drug, are to be followed until either:

- the AE has resolved.
- the AE has improved to Grade 2 or lower.
- the investigator determines that the event has become stable or irreversible.

This requirement also applies to related SAEs that occur >30 days after the day of the last dose of study drug.

The status of all other AEs that are ongoing at the 30-day posttreatment followup visit will be documented as of the 30-day posttreatment followup visit.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form

to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

10.5.1 Procedures for Reporting Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Investigators who identify a potential product complaint situation should immediately report this to the study monitors.

If a product complaint results in an SAE, an SAE form should be completed and sent to BI Medical, Inc (contact information is provided in the protocol annex).

10.5.2 Procedures for Reporting Medication Errors (Including Overdose)

A medication error is a preventable event that involves an identifiable subject and that leads to inappropriate medication use, which may result in subject harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a subject do not.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on the AE page of the eCRF.

If a medication error results in an SAE, an SAE form should be completed and sent to BI Medical, Inc (contact information is provided in the protocol annex).

10.6 Safety Reporting to Investigators, IRBs and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs and/or the head of each study site. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent Radiology Committee

An IRC will be established to evaluate tumor scans and prior radiation history data of trial subjects in a central, blinded, and independent fashion (see also Section 9.4.15.2). The IRC will be comprised of board certified radiologists who will determine radiographic response and progression following enrollment. Additional imaging results may be requested by the sponsor for IRC review.

Additional details regarding IRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the IRC Charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, medical history including concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will allow the study sites to have access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs, including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original

in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 3 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 3 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) for the CSR and for the CSR efficacy and safety addendum will be prepared separately, and finalized prior to database lock for each analysis. These documents will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to database lock for each analysis. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, 2 kinds of analysis sets are defined: full analysis set (FAS) and safety analysis set. Both FAS and safety analysis set will be defined as "all subjects who received at least one dose of study drug."

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for each Cohort and overall using the FAS.

13.1.3 Efficacy Analysis

Efficacy analyses will be performed using the FAS unless otherwise specified.

13.1.3.1 Primary Endpoint and Analytical Methods

The primary endpoint is 24-week PFSR, per RECIST 1.1 by IRC. PFS is defined as time from the first day of study drug administration to the earlier of PD per RECIST 1.1 or death due to any cause. 24-week PFSR is defined as PFS proportion at Study Day of Week 25 Day 1 + 7 days.

Only adequate tumor assessments will be considered in the determination of progression and censoring date. General censoring rules for the analysis of PFS will be as follows:

- Subjects who have not experienced an event at the time of data cutoff will be censored at the date of the last adequate tumor assessment.
- Subjects who receive subsequent systemic or liver directed local anticancer therapy or radiation therapy (other than to bone) before experiencing an event will be censored at the date of the last adequate tumor assessment on or prior to the date of initiation of the subsequent treatment.
- Subjects who receive tumor resection surgery after enrollment before experiencing an event will be censored at the date of the last adequate tumor assessment on or prior to the date of the surgery.

- Subjects who miss 2 or more consecutive adequate scheduled tumor assessments immediately followed by an event will be censored at the date of the last adequate tumor assessment prior to the missing/inadequate assessments.
  - If the 2 or more consecutive missing adequate assessments are immediately followed by an adequate assessment with an overall response assignment of SD, PR, or CR, this will be deemed sufficient clinical evidence that progression did not occur during the period of missing data and the missing evaluations will be ignored.

Primary Analysis

For 24-week PFSR by IRC, Kaplan-Meier estimate will be provided and the corresponding 2-sided 90% CI will be calculated for Cohort A using the Greenwood's formula and the complementary log-log transformation.

Other Analysis

The same analysis as that in the primary analysis will be conducted for Cohort B and overall (ie, Cohort A + Cohort B).

13.1.3.2 Secondary Endpoints and Analytical Methods

PFS, per RECIST 1.1, by IRC

For PFS by IRC, median PFS will be estimated using the Kaplan-Meier method, and the Kaplan-Meier plot will be presented for each Cohort and overall.

ORR, per RECIST 1.1, by IRC

ORR is defined as proportion of subjects whose best overall response is CR or PR per RECIST 1.1, which is confirmed by a subsequent evaluation conducted ≥28 days later.

Only the results of tumor assessment conducted on or prior to the earlier of the date of PFS event or date of censoring for PFS, described in the analytical method for 24-week PFSR above, will be used in order to determine the best overall response.

For ORR by IRC, point estimate and the 2-sided 95% exact CI will be calculated for each Cohort and overall.

DCR, per RECIST 1.1, by IRC

DCR is defined as proportion of subjects whose best overall response is CR, PR or SD per RECIST 1.1. CR and PR require confirmation by a subsequent evaluation conducted ≥28 days later, and SD have to be maintained for at least 8 weeks (51 days) after the first day of study drug administration.

DCR will be determined using the same data as those used in the determination of ORR.

For DCR by IRC, point estimate and the 2-sided 95% exact CI will be calculated for each Cohort and overall.

OS

OS is defined as time from the first day of study drug administration to death due to any cause.

Subjects who have not experienced an event at the time of data cutoff will be censored at the earlier of the data cutoff or the last date when the subjects are known to be alive.

For OS, the same analyses as those for PFS will be performed.

13.1.3.3 Additional Endpoints

Analytical methods for the additional endpoints will be described in the SAP.

13.1.3.4 Confidence Coefficient

- Analyses for primary endpoint: 90% (2-sided).
- Other analyses: 95% (2-sided).

13.1.4 PK Analysis

The plasma concentration of cabozantinib will be analyzed by the designee using a validated bioanalytical method. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to describe the concentration-time data. Where appropriate, these data may be analyzed using PopPK models and/or combined with data from other studies as part of a meta-analysis. The influence of exposure on biomarkers, clinical safety parameters (eg, selected AEs) or clinical response may also be explored.

13.1.5 Biomarker Analysis

A retrospective correlative study of candidate biomarkers (protein expression in signal pathway, metabolic signature, etc) in relation to clinical response to cabozantinib in patients with advanced HCC may be performed using descriptive statistics, graphical methods, and statistical modeling as appropriate. Biomarker analysis data from this study may be combined with data from other studies. Results of pooled analyses may be summarized in a separate report.

13.1.6 Pharmacogenomic Analysis

Genotyping of polymorphisms in genes encoding drug-metabolizing enzymes and/or transporters will be performed. Individual germline genotype will be listed for each of the polymorphisms evaluated, if applicable. Descriptive and graphical methods may be used to explore the relationship between genotype and PK, safety, tolerability, and/or response to study treatment. Pharmacogenomic data from this study may be combined with data from other studies. Results of pooled analyses may be summarized in a separate report.

13.1.7 Safety Analysis

Safety analyses will be performed using the safety analysis set.

13.1.7.1 Safety Endpoints and Analytical Methods

TEAEs

- TEAEs.
- Grade 3 or higher TEAEs.
- Serious TEAEs.
- Permanent discontinuation by TEAEs.
- Dose modification (dose reduction or interruption) by TEAEs.

TEAE is defined as an AE whose date of onset occurs on or after the start of study drug and within 30 days after the last dose of study drug. TEAEs will be coded using the MedDRA dictionary.

The frequency distribution will be provided for each Cohort and overall for each summary using the system organ class and the PT. The same analyses will be provided including only TEAEs which are considered related to the study drug.

Laboratory Values and Vital Sign Measurements

- Clinically significant abnormal laboratory values.
- Clinically significant abnormal vital sign measurements.

The frequency distribution of maximum grade for laboratory abnormalities, and the frequency distribution of clinically significant abnormal vital sign measurements will be provided for each Cohort and overall.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A study with 17 subjects will provide at least 80% probability that the lower limit of the two-sided 90% CI for the 24-week PFSR by Kaplan-Meier method results in ≥11.1% when assuming the true 24-week PFSR ≥38.4%.

In Study XL184-309 in subjects with advanced HCC who have received prior sorafenib, the 24-week PFSR by investigator was 38.4% (95% CI: [33.5, 43.3]%) and 11.1% (95% CI: [7.2, 15.8]%) in cabozantinib and placebo group, respectively. In reference to the above results, a 24-week PFSR of 38.4% is assumed and the threshold is set at 11.1% in this study.

This study will enroll at least 17 subjects who have received prior sorafenib in Cohort A. In addition, for better understanding of the efficacy and safety profile of cabozantinib in Japanese patients, similar number of subjects who have received prior sorafenib in Cohort A and who have not received prior sorafenib in Cohort B will be enrolled, resulting in approximately 32 subjects in total.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required).

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification, no protocol activities including assignment of patients may occur.

Study sites must adhere to all requirements stipulated by their respective IRBs. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and

benefits, as well as the date that informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The principal investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF must be approved by both the IRB and the sponsor prior to use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the ICF must be signed and dated by the subject, at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF at the time of consent and prior to subject entering into the study.

Once signed, the original ICF will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility name, investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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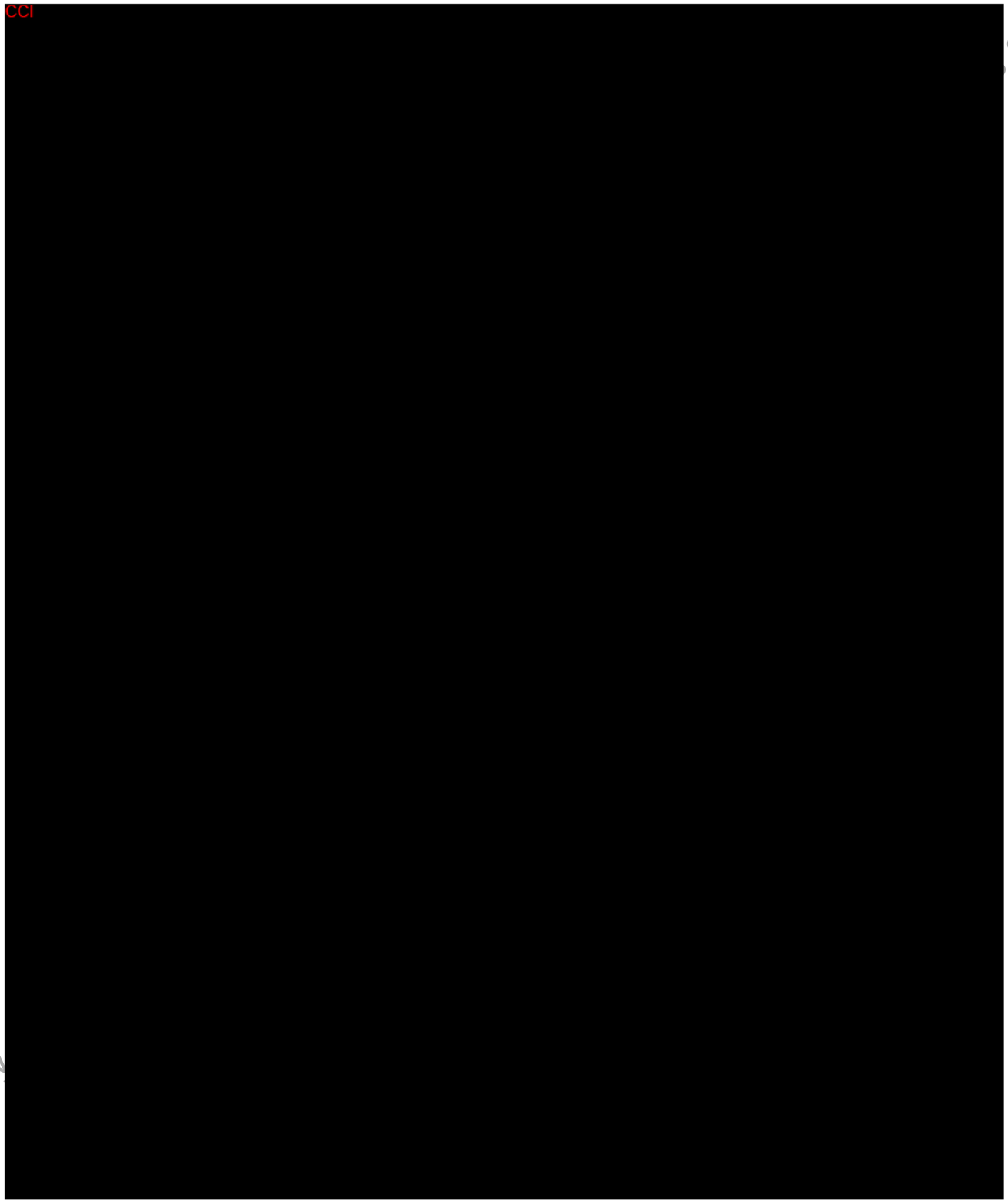

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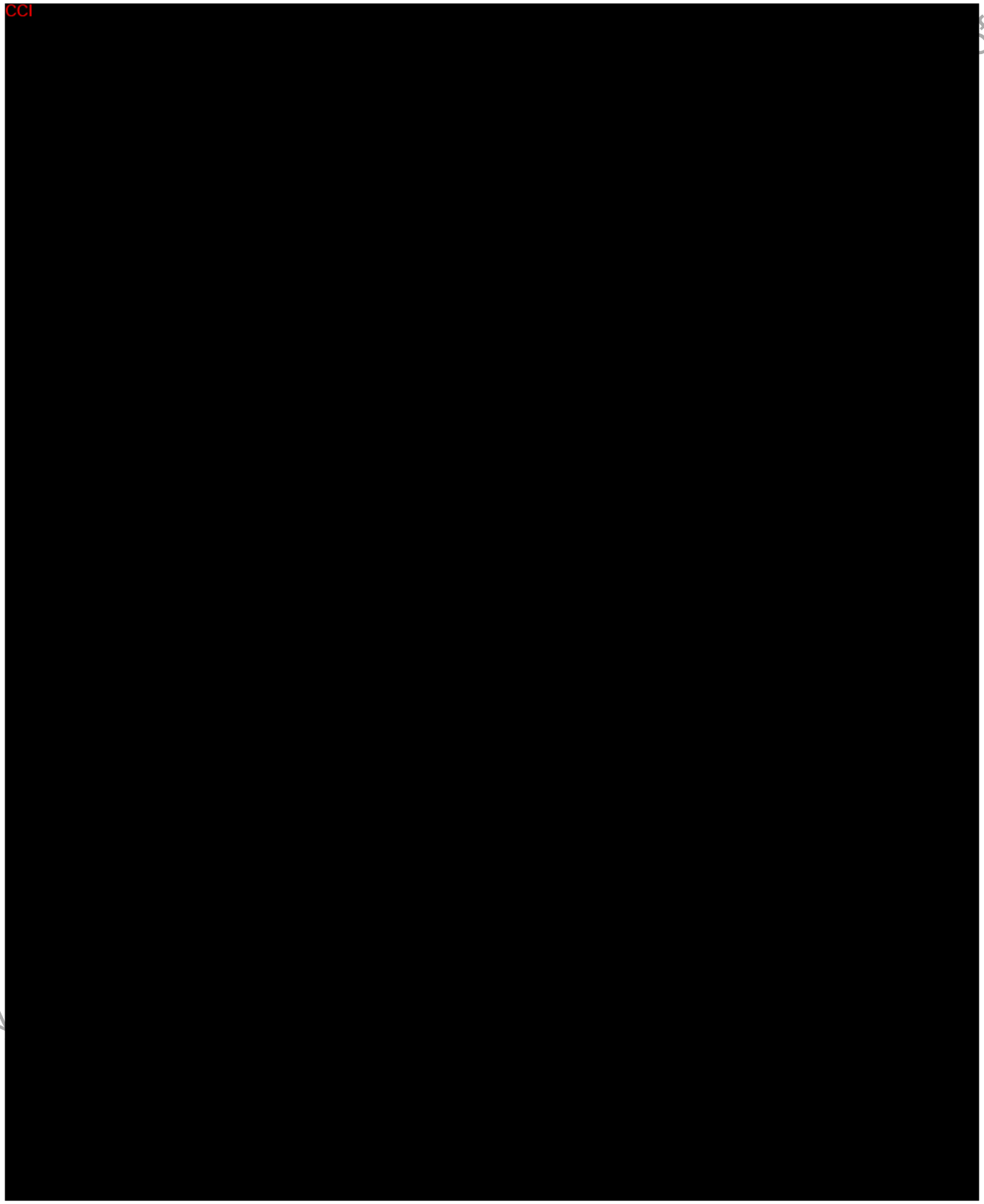

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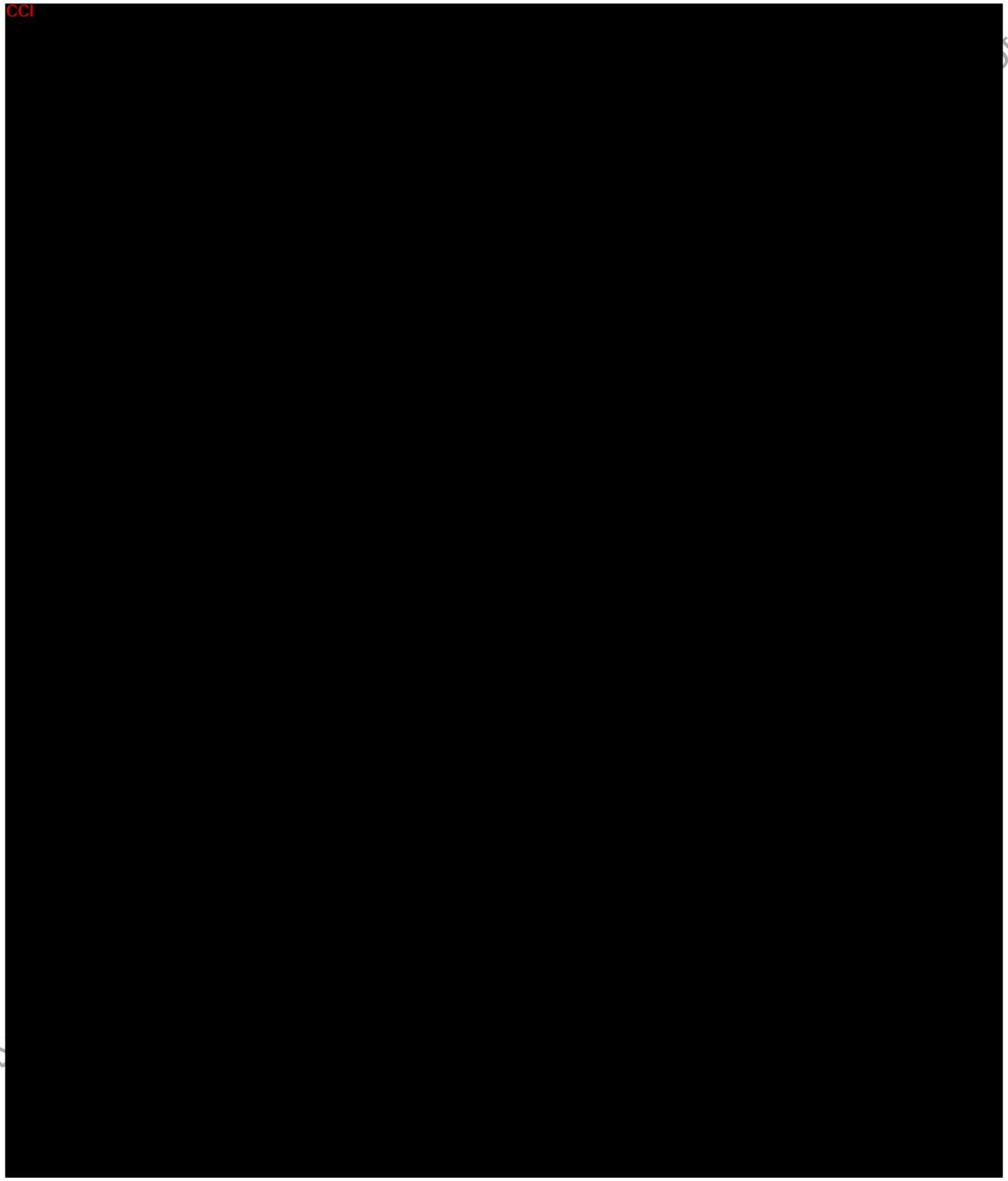

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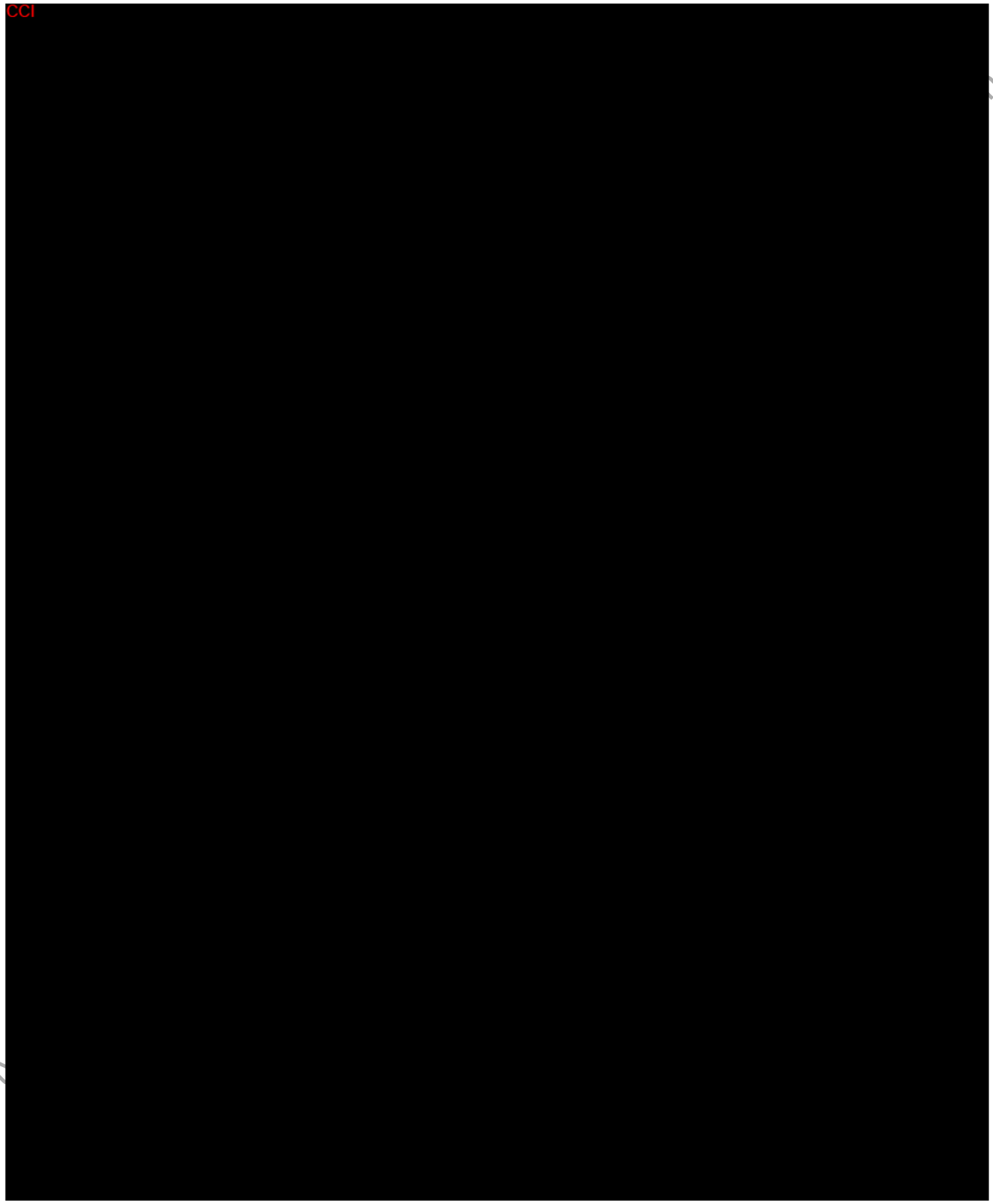

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Appendix J Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 01.

The text that was deleted or revised in Amendment No. 01 is indicated using italics and underline font. New or revised text adopted in Amendment No.01 is shown in bold font.

Page 11, Section 2.0 STUDY SUMMARY (Treatment Period) / Page 38, Section 6.1 Overview of Study Design (Treatment Period) / Page 41, Section 6.3.1 Duration of an Individual Patient's Study Participation

Existing Text

Treatment may continue after radiographic RCC progression per Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks.

Revised Text

Treatment may continue after radiographic RCC progression per Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks. **However the subject should discontinue study treatment after the second determination of disease progression.**

Rationale for Amendment

Revised to clarify the duration of the study treatment tolerable in subjects with disease progression. The subject should discontinue study treatment after the second determination of disease progression to consider any other treatment opportunity.

Page 11, Section 2.0 STUDY SUMMARY (Posttreatment Period) / Page 38, Section 6.1 Overview of Study Design (Posttreatment Period) / Page 41, Section 6.3.1 Duration of an Individual Patient's Study Participation / Page 83, Section 9.10 Posttreatment Followup Assessments

Existing Text

A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug.

Revised Text

A 30-day posttreatment followup visit for safety will occur 30 (+14) days after the last dose of study drug **or until the start of subsequent systemic anticancer treatment, whichever occurs first**.

Rationale for Amendment

Revised the posttreatment followup period. Considering that the subsequent systemic anticancer treatment may modify the safety profile of Cabozantinib, if the subsequent systemic anticancer treatment is conducted within 30 days after the last dose of study drug, posttreatment followup is to be completed at that time.

Page 24, Section 4.1.2 Study Drug

Existing Text

Cabometyx *is also currently under review by the European Medicines Agency (EMA) for previously untreated patients with advanced RCC, and the Committee for Medicinal Products for Human Use adopted a positive opinion recommending a change to the terms of the marketing authorization on 22 March 2018.*

Revised Text

Cabometyx **was also approved by FDA on 19 December 2017 for patients with previously untreated advanced RCC, and by European Commission on 17 May 2018 for the previously untreated adults patients with intermediate-or poor-risk advanced RCC.**

Rationale for Amendment

Updated information. This information is also reflected in Section 4.2 Rationale for the Proposed Study.

Page 50, Section 8.2.1 Dose Reductions, Interruptions and Discontinuation / Page 73 Section 9.4.14 Clinical Laboratory Evaluations / Page 75 Table 9.a.

Existing Text

The following parameters must be included in local laboratory assessment for dose modification: *complete blood count with differential leucocyte count, ALP, ALT, AST, and bilirubin (total bilirubin, conjugated and unconjugated bilirubin) .*

Revised Text

The following parameters must be included in local laboratory assessment for dose modification: **WBC count with differential and platelets , ALP, ALT, AST, and total bilirubin.**

Rationale for Amendment

Modified to clarify that local laboratory assessment for dose modification.

Page 50, Section 8.2.1 Concomitant Medications and Procedures

Existing Text

- Dose interruptions for reason(s) other than AEs (eg, surgical procedures) *can be longer than 6 weeks but require sponsor approval.* The acceptable length of interruption will depend on agreement between investigator and the sponsor.

Revised Text

- **Following cases require sponsor approval;**
  - **Keeping same level of dose despite the toxicity meet the status in the modification guideline that require dose reduction or interruption.**
  - **Dose re-escalation or dose reinstitution at the same level after dose interruption due to the toxicity.**
  - Dose interruptions for reason(s) other than AEs (eg, surgical procedures) **for more than 6 weeks.** The acceptable length of interruption will depend on agreement between investigator and the sponsor.

Rationale for Amendment

Added the cases that require sponsor approval in dose modifications.

Page 72, Section 9.4.10 Concomitant Medications and Procedures

Existing Text

Medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) and therapeutic procedures completed by the subject and their outcomes will be recorded in the electronic case report form (eCRF) from the time of the signing of the ICF through 30 days after the last dose of study drug.

Revised Text

Medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) and therapeutic procedures completed by the subject and their outcomes will be recorded in the electronic case report form (eCRF) from the time of the signing of the ICF through 30 days after the last dose of study drug **or the start of subsequent systemic anticancer treatment, whichever occurs first**.

Rationale for Amendment

Revised the collection period of concomitant medications and procedures to adapt it to the revised posttreatment followup period.

Page 73, Section 9.4.14 Clinical Laboratory Evaluations

Existing Text

Local laboratory tests for dose modification consideration will be performed at each study visit as well as central laboratory tests.

Revised Text

Local laboratory tests for dose modification consideration will be performed at each study visit as well as central laboratory tests. **On Week 1 Day 1, the results of local laboratory tests at the most recent or Week 1 Day 1 that consideration will be used to start of treatment.**

Rationale for Amendment

Added the results of local laboratory tests at the most recent or Week 1 Day 1 that consideration will be used to start of treatment on Week 1 Day 1.

Page 76, Section 9.4.15.1General

Existing Text

1. Chest/Abdomen/Pelvis: CT (or MRI) of CAP will be performed in all subjects at Screening. CT (or MRI) will be performed on Week 9 Day 1 and every 8 weeks (±7 days) thereafter. If MRI of the CAP study is performed at Screening, then a noncontrast CT of the chest should be performed as well.

…

Duration of Radiographic Tumor Assessments

- For subjects who discontinue study treatment before radiographic disease progression or within 8 weeks after radiographic disease progression, final radiographic tumor assessments are to be performed 8 weeks after radiographic disease progression. For subjects who discontinued study treatment and commenced a subsequent anticancer therapy (other than radiation therapy to bone), radiographic tumor assessments are *no longer necessary to be performed.*

…

Tumor assessment by investigator

…

For the purpose of subject management and treatment decisions, radiographic response and disease progression will be assessed by investigators using RECIST 1.1 (Appendix F). The sponsor should be notified of all disease progression as soon as possible. If any doubt or ambiguities exist about radiographic progression, investigators are encouraged to continue study therapy if the subject is tolerating it acceptably, repeat radiographic studies at the next scheduled time, and delay determination of progression until the findings indicating radiographic progression

are unequivocal. Radiographic progression determined by the investigator does not warrant discontinuation of tumor assessments or study treatment (see Section 9.7).

Revised Text

1. Chest/Abdomen/Pelvis: CT (or MRI) of CAP will be performed in all subjects at Screening. CT (or MRI) will be performed on Week 9 Day 1 and every 8 weeks (±7 days) thereafter. If MRI of the CAP study is **used** at Screening, **MRI of abdomen and pelvis will be required and** noncontrast CT of the chest should be performed as well.

…

Duration of Radiographic Tumor Assessments

- For subjects who discontinue study treatment before radiographic disease progression or within 8 weeks after radiographic disease progression, final radiographic tumor assessments are to be performed 8 weeks after radiographic disease progression. For subjects who discontinued study treatment and commenced a subsequent anticancer therapy (other than radiation therapy to bone), **radiographic tumor assessments should be performed prior to the subsequent therapy. No further** radiographic tumor assessments are **necessary to be performed.**

…

Tumor assessment by investigator

…

For the purpose of subject management and treatment decisions, radiographic response and disease progression will be assessed by investigators using RECIST 1.1 (Appendix F). The sponsor should be notified of all disease progression as soon as possible. If any doubt or ambiguities exist about radiographic progression, investigators are encouraged to continue study therapy if the subject is tolerating it acceptably, repeat radiographic studies at the next scheduled time, and delay determination of progression until the findings indicating radiographic progression are unequivocal. Radiographic progression determined by the investigator does not warrant discontinuation of tumor assessments or study treatment (see Section 9.7). **If the study treatment is continued even after determination of disease progression, the time of disease progression determined by the investigator will be considered "baseline" and tumor assessment will be continued based on the RECIST 1.1 criteria. If a new lesion is identified and determined to be disease progression by the investigator, this lesion will be assessed as a nontarget lesion and tumor assessment will be continued. No radiographic assessment is necessary after the second determination of disease progression.**

Rationale for Amendment

Added the requirements of the MRI. This change is also included in the same section Imaging Guidelines. Clarified the radiographic tumor assessments period of the subjects who commenced a subsequent anticancer therapy. Clarified the study treatment continued procedures of after determination of disease progression.

Page 84, Section 10.1.1 Adverse Event Definition

Existing Text

This includes any newly occurring event, or a previous condition that has increased in severity or frequency *since the administration of study drug.*

Revised Text

This includes any newly occurring event, or a previous condition that has increased in severity or frequency **after signing the ICF.**

Rationale for Amendment

Modified to make consistent with the collection period of adverse event.

Page 86, Section 10.3 Monitoring of Adverse Events and Period of Observation

Existing Text

- AEs will be reported from the signing of ICF through 30 days after the last dose of study drug and recorded in the eCRFs.
- SAEs (related and unrelated) will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

All SAEs that are ongoing 30 days after the last dose of study drug, and AEs assessed Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the last dose of study drug, are to be followed until either:

- the AE has resolved.
- the AE has improved to Grade 2 or lower.
- the investigator determines that the event has become stable or irreversible.

This requirement also applies to related SAEs that occur >30 days after the day of the last dose of study drug.

The status of all other AEs that are ongoing *30 days after the day of the last dose of study drug* will be documented as of the 30-day posttreatment followup visit.

Revised Text

- AEs will be reported from the signing of ICF through 30 days after the last dose of study drug **or the start of subsequent systemic anticancer treatment whichever occurs first,** and recorded in the eCRFs.

- SAEs (related and unrelated) will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF through 30 days after administration of the last dose of study drug **or the start of subsequent systemic anticancer treatment whichever occurs first,** and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

All SAEs that are ongoing 30 days after the last dose of study drug, and AEs assessed Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the last dose of study drug, are to be followed until either:

- the AE has resolved.
- the AE has improved to Grade 2 or lower.
- the investigator determines that the event has become stable or irreversible.

This requirement also applies to related SAEs that occur >30 days after the day of the last dose of study drug.

The status of all other AEs that are ongoing **at the 30-day posttreatment followup visit** will be documented as of the 30-day posttreatment followup visit.

Rationale for Amendment

Revised the posttreatment AEs followup period. Considering that the subsequent systemic anticancer treatment may modify the safety profile of Cabozantinib, if the subsequent systemic anticancer treatment is conducted within 30 days after the last dose of study drug, AEs collection and recording in the eCRF are to be completed at that time.

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Overall

Clarified the Baseline. Correct typographical errors, punctuation, grammar, and formatting. These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	01-Nov-2018 04:24 UTC
PPD	Clinical Pharmacology Approval	01-Nov-2018 04:59 UTC
PPD	Clinical Approval	01-Nov-2018 05:53 UTC