CLINICAL STUDY PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF TIVANTINIB (ARQ 197) IN SUBJECTS WITH MET DIAGNOSTIC-HIGH INOPERABLE HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH ONE PRIOR SYSTEMIC THERAPY

ARQ 197-A-U303

EudraCT NUMBER 2012-003308-10

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Version 2.0, 11 JUN 2013

Version 1.0, 21 SEP 2012

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CONFIDENTIALITY STATEMENT

INVESTIGATOR AGREEMENT

A Phase 3, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects with MET Diagnostic-High Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo, Inc and ArQule, Inc representatives listed below.

[redacted]

Print Name	**Signature**
Executive Director,- Clinical Development Oncology, Daiichi Sankyo Pharma Development	
Title	**Date (DD MMM YYYY)**

[redacted]

Print Name	**Signature**
VP Clinical Development, ArQule, Inc	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Daiichi Sankyo Pharma Development (DSPD) or ArQule, Inc. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives, and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

EudraCT/IND Number:	2012-003308-10 / 114642
Protocol Number:	ARQ 197-A-U303
Investigational Product:	Tivantinib (ARQ 197)
Active Ingredient(s)/INN:	(3*R*,4*R*)-3-(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione
Investigational device to prescreen for MET High Status:	LabCorp MET Immunohistochemistry (IHC) Companion Diagnostic Assay
Study Title:	A Phase 3, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects with MET Diagnostic-High Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy
Study Phase:	Phase 3
Indication Under Investigation:	Tivantinib is indicated for the treatment of subjects with inoperable, MET Diagnostic-High hepatocellular carcinoma who progress on or cannot tolerate prior therapy
Study Objectives:	<u>Primary:</u> • Evaluate overall survival (OS) among all subjects in the intent-to-treat (ITT) population compared to placebo. <u>Secondary:</u> • Evaluate progression free survival (PFS) by central, independent radiology review among all subjects in the intent-to-treat (ITT) population compared to placebo. • Evaluate safety of tivantinib in the treated HCC subjects. <u>Exploratory:</u> • Evaluate objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and type of progression, by central, independent radiology review among all subjects in the intent-to-treat (ITT) population compared to placebo.

	• Evaluate pharmacokinetics of tivantinib and its metabolites in HCC subjects and explore the factors, including CYP2C19 genotype, and major strong CYP3A4/CYP2C19 inhibitors which may affect tivantinib pharmacokinetics (PK) in HCC subjects. • Explore the exposure-response relationship of tivantinib to biomarkers and to safety and efficacy endpoints. • Evaluate Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)-based FHSI-3 Pain Score (pain, pain in back, pain/discomfort in stomach); FACT-Hepatobiliary Symptom Index (FHSI-8) score, Emotional Well Being (EWB) score, and the FACT-Hep total score. • Evaluate time-to-hospitalization (all-cause) and time-to-hospitalization (HCC-related).
Study Design:	Global, multi-center, randomized, placebo-controlled, double-blind Phase 3 study designed to compare treatment of tivantinib versus placebo in subjects with MET Diagnostic-High (MET-High) (≥ 50% of tumor cells with a staining intensity of ≥ 2+ for MET as assessed by immunohistochemistry in a central lab) inoperable HCC (where surgery is not indicated due to disease extension, co-morbidities, or other technical reasons). Subjects must have had radiographic disease progression after one sorafenib containing systemic first line therapy or were unable to tolerate sorafenib. Subjects are randomized to receive either tivantinib or placebo in a 2:1 ratio and are stratified based on vascular invasion (present or not), extra-hepatic spread including distant metastasis and/or involved regional (= peri-hepatic, must be ≥20 mm in shortest diameter) or distant lymph nodes (present or not), and Alpha fetoprotein (AFP) (less/equal or greater than 200 ng/mL). In August 2013, following a higher than expected incidence of neutropenia-related adverse events, the study DMC evaluated all available data including preliminary pharmacokinetics, and recommended the reduced starting dose of 120 mg BID. Therefore the 120 mg BID regimen will be the intended dose regimen should marketing approval be granted. The subjects will need to be grouped

	to 2 cohorts: the 120 mg cohort (all subjects who are randomized to a starting dose of 120mg BID versus Placebo) and the 240 mg cohort (all subjects who are randomized to a starting dose of 240mg BID versus Placebo). Data from subjects in the 120 mg cohort will be used for the primary analysis of efficacy regarding potential marketing approval of the 120 mg BID dose regimen. An interim analysis is planned when approximately 154 (~60%) of the 257 OS events are documented. The study may be terminated for superiority at the interim analysis in accordance with the statistical analysis plan. If the study is positive at the prespecified interim or final analysis, the sponsor will allow patients who are receiving placebo treatment to receive active tivantinib treatment, after database lock if the safety parameters in the eligibility criteria are met (see section 4.1). The study will be unblinded after database lock. Data post database lock will be used to capture additional safety information.
Study Duration:	Subjects are to continue therapy with study drug until death or radiographic progressive disease (PD) if confirmed by repeat CT/MRI scan 4 weeks after first suspected radiographic progression (see guidelines in Table 4.1), or until another of the specified criteria is met for stopping therapy. Average estimated duration of subject participation (screening/enrollment through follow-up): 1-7 months. Average estimated duration of subject treatment (from first to last dose of study drug): 1-5 months (some subjects may stay on treatment even less or more). The end of the trial will be defined as the date the last visit in the study is completed for any randomized subject.
Study Sites and Location:	Approximately 120 centers in Europe, the Americas, and Asia Pacific
Planned Sample Size:	Approximately 303 subjects randomized in a 2:1 ratio to either tivantinib (~202 subjects) or placebo (~101 subjects) in 120 mg cohort. The initial 43 subjects who were randomized to the starting dose of 240 mg BID versus Placebo prior to the dose reduction will be analyzed separately as described in statistical analysis section (Section 11.2).

Subject Eligibility Criteria: Inclusion Criteria:

1. Written informed consent granted prior to initiation of any study-specific screening procedures
2. 18 years of age or older
3. Histologically confirmed HCC that is inoperable (where surgery is not indicated due to disease extension, co-morbidities, or other technical reasons) and not eligible for local therapy
4. MET Diagnostic-High tissue reported by the central authorized laboratory using archival or recent biopsy tumor samples (see lab manual and Section 6.1 of protocol for tissue preparation details).
5. Received at least 4 weeks of one prior sorafenib containing systemic therapy and then experienced documented radiographic disease progression; or inability to tolerate prior therapy received for at least a minimum period of time. For the purpose of this study, intolerance to sorafenib is determined as follows:
    - The subject must have tried to take sorafenib for a period of at least 28 days (even intermittently)
    - The subject must have tried to dose reduce sorafenib at ≤50% of the full dose for a period of at least 14 days (even intermittently) and still have a documented Grade ≥2 toxicity
    - A period of even less than 14 days on sorafenib is acceptable in case of:
        i. Uncontrolled Grade 3 - 4 arterial hypertension
        ii. Pancreatitis, cardiac event, encephalopathy related to sorafenib
        iii. ≥ Grade 2 Hand-foot syndrome triggered even at 50% of the sorafenib dose
6. Discontinued prior systemic treatment or any investigational drug for at least 2 weeks (14 days) or for at least 3 weeks for IV anti-cancer drugs, prior to the study randomization
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1 (Appendix 17.2)
8. Local or loco-regional therapy (i.e., surgery, radiation therapy, hepatic arterial embolization,

chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed ≥ 4 weeks prior to randomization and are allowed.

9. Measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Tumor lesions previously treated with local therapy should demonstrate clear dimensional increase by radiographic assessment in order to be selected as target lesion(s) at baseline. Baseline radiographic assessment needs to be done within 21 days prior to randomization.
10. Adequate bone marrow, liver, and renal functions at Screening Visit, defined as: platelet count ≥ 60×10^9/L; hemoglobin ≥ 9.0 g/dL; absolute neutrophil count (ANC) ≥ 1.5×10^9/L; total bilirubin ≤ 2 mg/dL; Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN); serum creatinine ≤ 1.5 × ULN; albumin ≥ 2.8 g/dL; international normalized ratio (INR) 0.8 to ULN or ≤ 3 for subjects receiving anticoagulant such as coumadin or heparin. Subjects who are therapeutically anticoagulated are allowed to participate provided that prior to anticoagulant therapy no evidence of underlying defect in coagulation exists
11. Women of childbearing potential must have a negative serum pregnancy test performed within 14 days prior to the randomization (where demanded by local regulations, test may be required within 72 hours prior to randomization)
12. Male and female subjects of child-bearing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after last study drug dose received
13. Life expectancy of at least 12 weeks

Exclusion Criteria:

1. >1 prior systemic regimen (prior MET inhibitors/antibodies are not allowed; experimental systemic therapy for inoperable HCC given before or after sorafenib counts as separate regimen and is not allowed)

2. Child-Pugh B-C cirrhotic status based on clinical findings and laboratory results during screening period (see Appendix 17.4 for Child-Pugh Classification and interpretation of ascites at physical examination and Prothrombin Time (PT)/ International Normalized Ratio (INR))
3. Previous or concurrent cancer that is distinct from HCC in primary site or histology, EXCEPT cervical carcinoma *in situ*, treated basal cell carcinoma, and superficial bladder tumors (Ta, Tis & T1). Any cancer curatively treated > 3 years prior to enrollment is permitted.
4. History of congestive heart failure defined as Class II to IV per New York Heart Association (NYHA) classification (see Appendix 17.5) within 6 months prior to study entry; active coronary artery disease (CAD); clinically significant bradycardia or other uncontrolled, cardiac arrhythmia defined as ≥ Grade 3 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, or uncontrolled hypertension; myocardial infarction occurring within 6 months prior to study entry (myocardial infarction occurring > 6 months prior to study entry is permitted)
5. Active clinically serious infections defined as ≥ Grade 3 according to NCI CTCAE, version 4.03
6. Any medical, psychological, or social conditions, particularly if unstable, including substance abuse, that may, in the opinion of the Investigator, interfere with the subject's safety or participation in the study, protocol compliance, or evaluation of the study results
7. Known human immunodeficiency virus (HIV) infection
8. Blood or albumin transfusion within 5 days prior to the blood draw being used to confirm eligibility
9. Concomitant interferon therapy or therapies for active Hepatitis C Virus (HCV) infection
10. Pregnancy or breast-feeding
11. History of liver transplant
12. Inability to swallow oral medications
13. Clinically significant gastrointestinal bleeding occurring ≤ 4 weeks prior to randomization
14. Pleural effusion or clinically evident (visible or palpable) ascites

	Patients on the placebo arm being considered for crossover to tivantinib after database lock must meet the safety eligibility criteria at the time of crossover: Inclusion #6, 8, 10, 11, 12, and Exclusion #2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14.
Dosage Form, Dose and Route of Administration:	The investigational drug tivantinib and its matching placebo are supplied as tablets. A dose of 120 mg (1 tablet of 120 mg) of tivantinib will be administered by mouth twice daily (BID), once in the morning and once in the evening with meals, for a total daily dose of 240 mg. After database lock and unblinding, all eligible patients who have been randomized to placebo will be allowed to receive tivantinib.
Study Endpoints:	**Primary:** • Overall survival (OS) in ITT population **Secondary:** • Progression free survival (PFS) by central, independent radiology review • Safety **Exploratory:** • Objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and type of progression, by central, independent radiology review • Population pharmacokinetic (PK) parameters • Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)-based FHSI-3 Pain Score (pain, pain in back, pain/discomfort in stomach); FACT-Hepatobiliary Symptom Index (FHSI-8) score, Emotional Well Being (EWB) score, and the FACT-Hep total score • Time-to-hospitalization (all-cause) and time-to-hospitalization (HCC-related)
Statistical Analyses:	The formal analysis of efficacy endpoints will be performed only for the 120 mg cohort. The final analysis of OS will require 257 events to ensure a 90% power to detect the difference in OS by stratified log-rank test at a 1-sided type 1 error rate of $\alpha = 0.025$, with an underlying true hazard ratio of 0.65 (or 54% improvement

	in median survival from 5 months for the placebo arm to 7.7 months for the tivantinib arm). Approximately 303 total subjects are required to be enrolled in the 120 mg cohort over approximately 28 months of accrual period with 38 months maximum follow-up study period and 10% drop-off rate. An interim analysis is planned when about 60% of the total number of events (i.e., approximately 154 total events) in the 120 mg cohort will be documented. The O'Brien-Fleming alpha spending function will be used to define the stopping boundary for the possible early stopping for superior efficacy. If the interim analysis is based on exactly 154 events, the efficacy boundary would be crossed if the stratified log-rank test to show a 1-sided nominal p-value of 0.0038 or less. If the study meets such criteria at the interim analysis, the Data Monitoring Committee (DMC) and selected representatives from the Sponsor may request a consultation with Health Authorities prior to a final DMC recommendation; the study team will remain blinded during this process. If the DMC does not recommend early termination at the time of the interim analysis, the trial will continue until the final 257 events are documented. The final analysis of OS will require a 1-sided nominal p-value of 0.0238 or less for the study to be positive. It is recognized that the exact number of events at the interim analysis may not be 154. The boundaries will be updated with the actual number of events at the interim analysis. After database lock, additional data will be reviewed via data listings.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AFP	Alpha fetoprotein
ALT	Alanine transaminase
ANC	Absolute neutrophils count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BID	Twice daily
bpm	Beats per minute
BUN	Blood urea nitrogen
CAD	Coronary Artery Disease
CAP	College of American Pathologists
CBC	Complete blood count
CDx	Companion Diagnostic
CDF	Cumulative distribution function
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiologic Health
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum plasma drug concentration
c-Met	c-Met receptor tyrosine kinase
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSPV	Clinical Safety and Pharmacovigilance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAG	Data Analysis Group
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSPD	Daiichi Sankyo Pharma Development
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

ABBREVIATION	DEFINITION
EIU	Exposure in utero
ELISA	Enzyme-linked immunosorbent assay
EQ-5D	EuroQol 5-D
ESA	Erythropoiesis Stimulating Agent
EU	European Union
EWB	Emotional wellbeing
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary
FDA	Food and Drug Administration
FFPE	Formalin Fixed, Paraffin Embedded
FHSI	FACT-Hep Symptom Index
FNA	Fine needle aspirate
FWB	Functional well-being
FWER	Family-wise type I error rate
GCP	Good Clinical Practice (refers to ICH and CFR)
GGT	Gamma-glutamyl transpeptidase
GI_{50}	Drug concentration that inhibits the growth of cancer cells by 50%
HBV	Hepatitis B Virus
HBeAg	Hepatitis B “e” antigen
HBsAg	surface antigen of the hepatitis B virus
HCC	Hepatocellular carcinoma
HCS	Hepatobiliary Additional Concerns Subscale
HCV	Hepatitis C Virus
HCVAb	Hepatitis C antibody
HGB	Hemoglobin
HGF	Hepatocyte Growth Factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IC_{50}	Inhibitor concentration required for 50% inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	International Normalized Ratio
IP	Investigational Product

ABBREVIATION	DEFINITION
IRB	Institutional Review Board
ITT	Intent-to-treat
IXRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
MET	N-Methyl-N'-nitro-N-nitroso-guanidine human steogenic sarcoma cell line transforming protein (gene)
MET-high	≥ 50% of tumor cells with a staining intensity of ≥ 2+ for MET as assessed by immunohistochemistry in a central lab
NBF	Neutral buffered formalin
NCI	National Cancer Institute
NOAEL	No observable adverse effect level
NOEL	No observable effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
NYSDOH	New York State Department of Health
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PO	By mouth
POPPK	Population Pharmacokinetics
PR	Partial Response
PRO	Patient-reported outcomes
PS	Performance Status
PT	Prothrombin time
PWB	Physical well-being
QD	Once per day
QOD	Every other day
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	Stable Disease
SD	Standard deviation

ABBREVIATION	DEFINITION
SOP	Standard Operating Procedure
SWB	Social well-being
TAO	Troleandomycin
TEAE	Treatment-emergent adverse event
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WBC	White blood cell count
WHO	World Health Organization

1. INTRODUCTION AND BACKGROUND INFORMATION

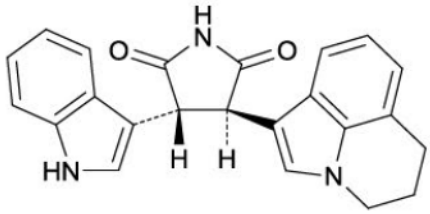
1.1. Investigational Products

1.1.1. Tivantinib

Chemical Name:	(3*R*,4*R*)-3-(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione
Molecular Weight:	369.42
Molecular Formula:	$C_{23}H_{19}N_3O_2$

Tivantinib is a totally synthetic small molecule having the novel bis substituted pyrrolidine-2, 5-dione structure depicted in Figure 1.1.

Figure 1.1 Tivantinib Structural Diagram



1.1.1.2. Description

Tivantinib is a non-ATP-competitive small molecule inhibitor of the tyrosine kinase c-Met, which has been implicated in cancer cell proliferation, migration, invasion, and metastasis.[1,2] The c-Met receptor tyrosine kinase is the only known high-affinity receptor for hepatocyte growth factor (HGF), also known as scatter factor. Binding of HGF to the c-Met extracellular ligand-binding domain results in receptor multimerization and phosphorylation of multiple tyrosine residues in the intracellular portion of c-Met.[3,4] Activation of c-Met results in subsequent activation of signal transducers such as PI3K, PLC-γ, STATs, ERK1 and 2, and FAK. N-Methyl-N'-nitro-N-nitroso-guanidine human steogenic sarcoma cell line transforming protein (gene) (MET) gene amplification and/or mutations are found in many human malignancies.[5,6]

1.1.1.3. Intended Use Under Investigation

Tivantinib is indicated for the treatment of subjects with inoperable, MET Diagnostic-High hepatocellular carcinoma. Phase 1, 2, and 3 studies in solid tumors, prostate, non-small cell lung cancer (NSCLC), pancreatic cancer, colorectal cancer, and hepatocellular cancer are ongoing.

1.1.2 LabCorp MET Immunohistochemistry (IHC) Companion Diagnostic Assay

LabCorp has developed and validated an immunohistochemistry assay for MET in HCC formalin-fixed, paraffin-embedded (FFPE) tissues to meet the requirements of the Clinical Laboratory Improvement Amendments (CLIA), the College of American Pathologists (CAP) Commission on Laboratory Accreditation, and the New York State Department of Health (NYSDOH).

The assay has been reviewed by the US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) under IDE submission #G120183 and is approved for investigational use in this study. CE marking for the assay was obtained in accordance with EU directive 98/79/EC.

It is intended that this LabCorp IHC Assay will be used as a Companion Diagnostic (CDx) to select subjects with high MET expression who would be candidates for therapy with tivantinib.

1.1.2.1 Intended Use

The LabCorp MET IHC Companion Diagnostic Assay is intended for use in the detection of MET protein expression in FFPE tissues.

1.1.2.2 Indications for Use

The indication for use for the LabCorp MET IHC Companion Diagnostic Assay is to select subjects for therapy with tivantinib for the treatment of inoperable MET Diagnostic-High hepatocellular carcinoma who progress on or cannot tolerate prior therapy.

It is intended that this clinical study will support the registration of the assay.

1.1.3. Nonclinical Studies

Tivantinib has demonstrated *in vivo* and *in vitro* anti-tumor activity across a wide range of human tumor cell lines, including those derived from breast, colon, lung, pancreas, and stomach. The potency of tivantinib in cancer cells expressing detectable c-Met in anti-proliferation assays yield inhibitor concentration required for 50% inhibition (IC_{50}) values from 0.1 to 0.6 µM,[7] concentrations lower than the exposures observed in human PK studies. At even lower doses, an *in vivo* study showed inhibition of metastatic activity.[8]

Tivantinib inhibits c-Met activation in a range of tumor cell lines. The drug concentration that inhibits the growth of cancer cells by 50% (GI_{50}) of tivantinib has been evaluated in 12 HCC cell lines by the Sponsor and by academic collaborators. All of the GI_{50} values are below 1.70 µM, with the exception of two cell lines.[9,10]

The compound has demonstrated efficacy in murine xenograft models of human colon, pancreas, and breast cancers. A series of *in vitro* experiments demonstrate that tivantinib is a potent and specific inhibitor of c-Met, which correlates with the ability of tivantinib to kill cancer cells and inhibit metastasis *in vitro*. Single- and repeat-dose toxicology studies have been performed in dogs and rats. In both species, single-dose escalation studies followed by 7- and 28-day repeat-dose studies were performed with doses

administered via oral gavage. In the 28-day repeat-dose studies, a no observable effect level (NOEL) of 10 mg/kg for dogs and a no observable adverse effect level (NOAEL) of 15 mg/kg for rats were identified. Toxicity was observed in a dose-dependent manner in both species. Primary clinical observations included reduced food consumption and loss of body weight at doses > 30 mg/kg/day (rat) and at 45 mg/kg/day (dog) in the 28-day studies; emesis and excessive salivation at doses > 100 mg/kg/day in the dog studies. Non-formed or liquid feces at doses > 100 mg/kg/day were noted in the rat studies.

In both species, toxicokinetic results from the repeat-dose studies showed that exposure to tivantinib generally increased as dose levels increased. However, increases in maximum plasma drug concentration (C_{max}) and area under the time-concentration curve (AUC) values were not consistently dose proportional. Primary clinical pathologic observations consisted of decreased reticulocyte count and lower absolute red cell mass at the maximum doses: 45 mg/kg/day for rats and 30 mg/kg/day for dogs in the 28-day repeat-dose studies. These effects were reversible within a 14-day recovery period. These same effects were observed in both species at higher doses in the single- and 7-day repeat-dose studies. No treatment-related gross or histopathologic effects were observed in the 28-day repeat-dose studies.

Based on these observations, the NOAEL for rats administered tivantinib daily by oral gavage for a 28-day period was 15 mg/kg/day and the NOEL in dogs administered tivantinib daily by capsule for a 28-day period was 10 mg/kg/day

Additional information can be found in the Investigator's Brochure.

1.1.4. Clinical Experience

Tivantinib is currently under joint global clinical development in the United States (US) and European Union (EU) by Daiichi Sankyo, Inc, and ArQule, Inc. Over 780 subjects have been exposed to tivantinib prior to the initiation of this study.[11] Tivantinib is currently being developed as a treatment for a variety of cancers, selected by molecular and biological characteristics, including the presence of the c-Met receptor kinase. Tivantinib has shown promising results in HCC in Phase 1 and 2 studies as monotherapy and in combination with sorafenib. In early Phase 1 studies employing tivantinib capsules, the dose limiting toxicities were found to be leukopenia, neutropenia, thrombocytopenia, vomiting, dehydration, fatigue, mucositis, hand-foot syndrome, and febrile neutropenia.[12, 13] In Phase 1 studies enrolling HCC subjects both with tivantinib capsules as monotherapy and in combination with sorafenib, the tivantinib 360 mg BID dose has produced a manageable safety profile, with higher rate of neutropenia. More extensive discussion of the safety profile in HCC subjects is in Section 1.3 of this protocol. Tivantinib has also been studied in a Phase 3 clinical study in non-squamous NSCLC, employing the tablet formulation.

Further information can be found in the Investigator's Brochure.

1.2. Study Rationale

Expression of c-Met in tumors correlates with aggressive HCC features. Overexpression of the receptor in tumor samples or high level of blood HGF in subjects is related to higher recurrence rate after surgery for HCC, while high c-Met expression correlates with

shorter survival in HCC subjects. In summary, c-Met holds an important prognostic role in the natural history of HCC.[14, 15, 16, 17, 18, 19, 20, 21, 22]

A randomized, controlled Phase 2 study with tivantinib versus placebo in subjects with inoperable HCC who have failed one prior systemic therapy has provided positive results and biological insights on the activity of tivantinib in this disease. This study employed the capsule formulation of tivantinib. While the study met its primary endpoint by improving time to progression (TTP) in the intent-to-treat (ITT) population (6.9 vs 6.0 weeks, hazard ratio (HR) 0.64, 90% Confidence Interval (CI) 0.43-0.94, p=0.04), regardless of the starting dose, the highest benefit was obtained by MET Diagnostic-High subjects. Efficacy analysis by MET status was a pre-planned study endpoint and subjects were defined as "MET Diagnostic-High" if ≥ 50% of tumor cells had a staining intensity of ≥ 2+ for MET as assessed by immunohistochemistry. In MET Diagnostic-High subjects, median TTP was 11.7 versus 6.1 weeks (HR=0.43, 95% CI 0.19-0.97, p=0.03), median progression free survival (PFS) was 9.6 versus 6.0 weeks (HR=0.45, 95% CI 0.21-0.95, p=0.02), and disease control rate (DCR) was 50% versus 20%. In this population, final median overall survival (OS) at the April 2012 update was 7.2 vs 3.8 months, HR=0.38, 95% CI 0.18-0.81, p=0.02). In MET Diagnostic-Low subjects, TTP and OS were statistically similar on tivantinib and placebo. After 57 subjects were enrolled, due to high (21%) incidence of drug-related G ≥ 3 neutropenia, the tivantinib starting dose of 360 mg BID was modified to 240 mg BID and a modified dose reduction schema was implemented. At the latter dose, the rate of G ≥ 3 neutropenia dropped to 6% and a predictable and manageable safety profile emerged. Efficacy was similar in both of the tested dose levels, 360 mg BID and 240 mg BID. Results from the study also showed that c-Met is an independent prognostic factor in the enrolled HCC subjects, since OS for MET Diagnostic-High subjects on placebo appears to be worse than that of MET Diagnostic-Low subjects on placebo (3.8 versus 9.0 months, HR=2.94, 95% CI 1.16-7.43, p=0.02), confirming the prognostic role of MET in HCC. Such results warrant further study in the population selected for this Phase 3 study: MET Diagnostic-High HCC subjects who have failed one prior systemic therapy.

This Phase 3 study in MET Diagnostic-High inoperable HCC subjects has been designed based on the results from the randomized, controlled Phase 2 study conducted by ArQule, Inc. with tivantinib versus placebo in subjects with MET Diagnostic-High inoperable HCC who have failed one prior systemic therapy, mentioned above. The purpose of this study is to confirm the efficacy of tivantinib in MET Diagnostic-High HCC subjects who were previously treated with one systemic therapy, and to further evaluate the safety profile of the experimental drug in this subject population. For manufacturing reasons, this study employs the tablet formulation of tivantinib.

1.3. Risks and Benefits for Study Subjects

A tivantinib tablet dose of 240 mg BID (a total daily dose of 480 mg) was selected for this Phase 3 study on the basis of efficacy and tolerability established in Phase 1 and Phase 2 studies with capsules. In August 2013, following a higher than expected

incidence of neutropenia-related toxicities, the study DMC evaluated all available data including preliminary pharmacokinetics. Based on this review, the DMC recommended the starting dose of 120 mg BID (for a total daily dose of 240 mg). The DMC requested to conduct a detailed safety review of a pre-determined cohort of patients treated at 120 mg BID. By 15 November 2013, 29 subjects were treated at 120 mg BID. Of these, 26 were treated from between 1 and 2½ months and 3 were treated for at least 3 weeks. After reviewing the Absolute Neutrophil Count (ANC) data provided on 15 November 2013, the DMC advised that the study enrollment can continue.

The results of the randomized controlled Phase 2 trial ARQ 197-215 demonstrated that tivantinib offered benefits in TTP, PFS, OS, and DCR, as shown in Section 1.2 of this protocol. The benefits were even more robust in the MET Diagnostic-High subgroup, where the improvement in TTP was 133% and the improvement in OS was 163%. Efficacy was similar in both of the tested dose levels, 360 mg BID and 240 mg BID.

Table 1.1 Most Common (> 5% of all Subjects) Adverse Events and Severe (Grade 3 or higher) Adverse Events Seen in the Randomized-Controlled Phase 2 HCC Study, ARQ 197-215

	Adverse Events		Severe Adverse Events	
Primary System Organ Class Preferred Term	**ARQ 197 240 mg (N=33) n (%)**	**Placebo (N=36) n (%)**	**ARQ 197 240 mg (N=33) n (%)**	**Placebo (N=36) n (%)**
Blood and lymphatic system disorders				
Neutropenia	7 (21.2%)	2 (5.6%)	2 (6.1%)	0
Anaemia	7 (21.2%)	2 (5.6%)	3 (9.1%)	0
Thrombocytopenia	3 (9.1%)	0	2 (6.1%)	0
Leukopenia	2 (6.1%)	1 (2.8%)	1 (3.0%)	0
Cardiac disorders				
Bradycardia	3 (9.1%)	1 (2.8%)		
Gastrointestinal disorders				
Diarrhoea	3 (9.1%)	9 (25.0%)		
Ascites	10 (30.3%)	5 (13.9%)		
Abdominal pain	3 (9.1%)	7 (19.4%)		
Nausea	3 (9.1%)	5 (13.9%)		
Abdominal pain upper	6 (18.2%)	3 (8.3%)		
Constipation	4 (12.1%)	4 (11.1%)		
Dyspepsia	2 (6.1%)	2 (5.6%)		
General disorders and administration site conditions				
Asthenia	14 (42.4%)	7 (19.4%)		
Fatigue	4 (12.1%)	10 (27.8%)	1 (3.0%)	2 (5.6%)
Oedema peripheral	8 (24.2%)	6 (16.7%)		
Pyrexia	3 (9.1%)	5 (13.9%)		
Hepatobiliary disorders				
Hepatic failure *	2 (6.1%)	0	2 (6.1%)	0
Investigations				
Weight decreased	4 (12.1%)	1 (2.8%)		
Metabolism and nutrition disorders				
Decreased appetite	9 (27.3%)	6 (16.7%)		

	Adverse Events		Severe Adverse Events	
Primary System Organ Class Preferred Term	ARQ 197 240 mg (N=33) n (%)	Placebo (N=36) n (%)	ARQ 197 240 mg (N=33) n (%)	Placebo (N=36) n (%)
Respiratory, thoracic and mediastinal disorders				
Cough	4 (12.1%)	5 (13.9%)		
Dyspnoea	2 (6.1%)	3 (8.3%)		
Pleural effusion	1 (3.0%)	3 (8.3%)		

* Not seen in >5% of all subjects.

Protocol ARQ 197-215 was initiated with a tivantinib dose of 360 mg BID. In this study, the safety profile of the experimental drug was manageable, with similar rates of adverse events (AEs) in the treatment and placebo arms; however, the observed rate of ≥ Grade 3 neutropenia at 360 mg BID was 21% compared to < 5% in subjects in other tivantinib studies, and included 3 subjects with neutropenia who died within 30 days of treatment with the study drug. A more aggressive dose reduction schema was then implemented, and the dose was reduced to 240 mg BID for all subjects and both measures are applied in this Phase 3 study. Such measures reduced the incidence of ≥ Grade 3 neutropenia to 6%; however, there was 1 death in a subject associated with neutropenia even at the reduced dose. At the 240 mg BID dose, the most frequent drug-related serious adverse event (AE) in the ARQ 197-215 study was neutropenic sepsis (3%). PK analysis indicated that drug exposure was approximately 3 fold higher in subjects with HCC compared to other cancers. To further manage such risks associated with severe neutropenia (rare, at the 240 mg BID dose), this Phase 3 study mandates more frequent blood counts and treatment with antibiotics and colony-stimulating growth factors in subjects developing Grade 4 neutropenia. Such aggressive prophylaxis of neutropenic sepsis, not in place in the ARQ 197-215 study, is expected to further improve the safety profile of tivantinib in HCC subjects treated with tivantinib.

1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

The study population consists of subjects with MET Diagnostic-High inoperable hepatocellular carcinoma (HCC) treated with one prior systemic therapy. The experimental drug will be given orally, at the starting dose of 120 mg twice a day (BID) once in the morning, once in the evening, with food (240 mg/day), continuously. For administrative reasons, the treatment period is divided into 4-week cycles (28 days).

At the start of each cycle, subjects will receive adequate supplies of tivantinib or placebo tablets for one full cycle of therapy, at a dose of 120 mg BID (i.e., 240 mg per day). See Section 3 for further details. Active tablets will each contain 120 mg of tivantinib.

For individual subjects, treatment will continue until unacceptable toxicity or another discontinuation criterion is met. It is expected that most subjects will receive tivantinib/placebo for at least 1 to 5 treatment months.

1.5. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and the following applicable regulatory requirement(s):

- European Commission Directive (2001/20/EC Apr 2001)
- European Commission Directive (2005/28/EC Apr 2005)
- FDA GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56, and 312 as appropriate
- Other applicable local regulations

1.5.1. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

For EU sites, Daiichi Sankyo and designees will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the Case Report Forms or other documents submitted to Daiichi Sankyo and designees, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to Daiichi Sankyo and designees (i.e., signed Informed Consent Forms [ICF]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

1.5.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IEC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 Code of Federal Regulations (CFR) Part 312.62. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date that informed consent was given should be recorded on the Case Report Form.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested model text for the ICF for the study and any applicable subparts (such as pre-screening, tumor sample collection, pharmacogenomic, pharmacokinetic, and optional tumor biopsy) are provided in the Daiichi Sankyo Pharma Development (DSPD) ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Clinical Study Manager.

For sites in the United States (US), additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

1.5.3. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (i.e., advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IEC or IRB and/ or Sponsor (or designee) for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IEC or IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the Sponsors or Clinical Research Organization (CRO), in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies

obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

Evaluate the overall survival (OS) among all subjects in the intent-to-treat (ITT) population compared to placebo.

2.1.2. Secondary Objectives

Evaluate progression free survival (PFS) by central, independent radiology review among all subjects in the intent-to-treat (ITT) population compared to placebo.

Evaluate the safety of tivantinib in the treated HCC subjects.

2.1.3. Exploratory Objectives

Evaluate the objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and type of progression, by central, independent radiology review among all subjects in the intent-to-treat (ITT) population compared to placebo.

Evaluate the pharmacokinetics of tivantinib and its metabolites in HCC subjects and explore the factors, including CYP2C19 genotype and major strong CYP3A4/CYP2C19 inhibitors, which may affect tivantinib PK in HCC subjects.

Explore the exposure-response relationship of tivantinib to biomarkers and to safety and efficacy endpoints.

Evaluate the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) based FHSI-3 Pain Score (pain, pain in back, pain/discomfort in stomach); FACT-Hepatobiliary Symptom Index (FHSI-8) score, Emotional Well Being (EWB) score, and the FACT-Hep total score.

Evaluate the time-to-hospitalization (all-cause) and the time-to-hospitalization (HCC-related).

2.2. Study Hypothesis

Treatment with tivantinib will improve OS relative to placebo in subjects with MET Diagnostic-High inoperable HCC treated with one prior systemic therapy.

3. STUDY DESIGN

3.1. Overall Plan

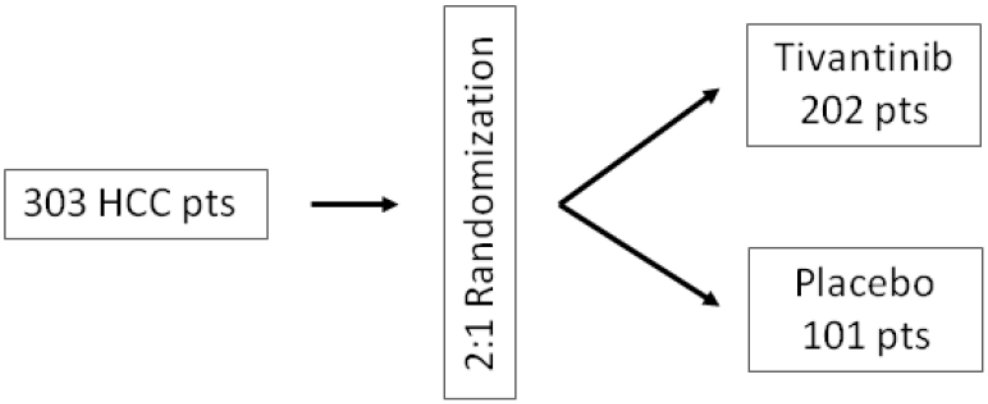
3.1.1. Study Type

This is a Phase 3, global, multicenter, double-blind, randomized, stratified, placebo-controlled study. Subjects are enrolled based on protocol inclusion/exclusion criteria; they are randomized to tivantinib or placebo in a 2:1 ratio; they are stratified based on vascular invasion (present or not), extra-hepatic spread including distant metastasis and/or involved regional or distant lymph nodes (present or not, using RECIST 1.1 criteria, but regional nodes are considered involved if ≥ 20 mm in shortest diameter), and AFP (less/equal or greater than 200 ng/mL). Prior progression or intolerance to sorafenib needs to be documented as per protocol. Over 120 centers will be involved in the study in Europe, the Americas, and Asia Pacific. Approximately 303 adult subjects with MET Diagnostic-High inoperable HCC who progressed or did not tolerate sorafenib (see inclusion/exclusion criteria for detailed information) will be enrolled (approximately 202 on tivantinib and approximately 101 on placebo) in 120 mg cohort. The 43 subjects who were randomized to the starting dose of 240 mg BID versus Placebo prior to the dose reduction will be analyzed separately as described in statistical analysis section (Section 11.2). Crossover from placebo after disease progression is not allowed.

An interim analysis is planned when approximately 154 (~60%) of the 257 OS events are documented. The study may be terminated for superiority at the interim analysis in accordance with the statistical analysis plan. If the study is positive at the prespecified interim or final analysis, the sponsor will allow patients who are receiving placebo treatment to receive active tivantinib treatment after database lock if the safety parameters in the eligibility criteria are met (see section 4.1). The study will be unblinded after database lock.

3.1.2. Treatment Groups

Figure 3.1 Schematic of Treatment Groups



Detailed information on inclusion/exclusion criteria, study procedures, stratification, and schedule of events, are in Sections 4.1.1, 4.1.2, 6, 11.5.1.1, and Appendix 17.1, respectively.

3.1.3. Study Endpoints

3.1.3.1. Primary Endpoint

- Overall survival (OS) in ITT population

3.1.3.2. Secondary Endpoints

- Progression free survival (PFS) by central, independent radiology review
- Safety

3.1.3.3. Exploratory Endpoints

- Objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and type of progression, by central, independent radiology review
- Population pharmacokinetic parameters of tivantinib and its metabolites and explore the factors, including CYP2C19 genotype and major strong CYP3A4/CYP2C19 inhibitors which may affect tivantinib PK
- Evaluate Functional Assessment of Cancer Therapy Hepatobiliary based (FACT-Hep) FHSI-3 Pain Score (pain, pain in back, pain/discomfort in stomach); FACT-Hepatobiliary Symptom Index (FHSI-8) score, FACT-Hep Emotional Well Being (EWB) score, and the FACT-Hep total score
- Evaluate time-to-hospitalization (all-cause) and time-to-hospitalization (HCC-related).

3.1.4. Duration of the Study

This study will last approximately 38 months from First Subject First Visit to Last Subject Last Follow-up.

3.1.5. Duration of Subject Participation

Subjects are to continue therapy with study drug until death, radiographic disease progression (confirmed by repeat CT/MRI scan 4 weeks after radiographic progression first suspected. Refer to section 4.2.1 for details.), or another discontinuation criterion is met. It is expected that most subjects will receive between at least 1 and 5 months (4 to 20 weeks) of treatment.

Once a subject discontinues from the study, they and/or their family will be contacted for long term survival follow up every 3 months until death, lost to follow up, or withdrawal of consent for long term follow up.

3.1.6. Stopping Rules

Stopping rules for individual subjects are specified in Section 4.2. Guidelines for efficacy based on stopping boundaries, with which the Data Monitoring Committee (DMC) will be making their recommendation per the DMC charter taking safety into overall considerations, are specified in Section 11.8. In addition, the study may be terminated at any time at the Sponsor's discretion.

3.2. Selection of Doses

3.2.1. Experimental Treatments

3.2.1.1. Tivantinib Treatment

The tivantinib dosage of 240 mg administered by mouth (PO) once in the morning and once in the evening, with food for a total daily dose of 480 mg, was selected on the basis of efficacy and tolerability established in Phase 1 and Phase 2 studies. In August 2013, following a higher than expected incidence of neutropenia-related toxicities, the study DMC evaluated all available data including preliminary pharmacokinetics. Based on this review, the DMC recommended the starting dose of 120 mg BID (for a total daily dose of 240 mg).

3.2.1.2. Control Treatment

The control arm will receive matching placebo tablets, once in the morning and once in the evening, with food, continuously.

If the study is positive at the interim or final analysis, all eligible patients who have been randomized to placebo will be allowed to receive tivantinib after database lock and unblinding. No placebo will be dispensed by the IXRS system for a subject once that subject receives active treatment.

3.2.1.3. Missed or Vomited Doses

A missed or vomited dose should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time.

3.2.1.4. Dose Modifications

When a drug related toxicity is observed, dose delays and/or reductions in tivantinib/placebo administration are allowed as described below. In the event of a dose reduction, the dose change(s) must be captured in the electronic data capture (EDC) system. If questions or considerations regarding dose modification arise or a specific dose modification is needed, the Sponsor's Medical Monitor or designee should be consulted.

In general, once the dose of tivantinib/placebo has been reduced for a subject, all subsequent cycles should be administered to that subject at the modified dose unless further reduction is required. The reduced dose will be considered the maximum dose for all subsequent cycles for that subject (dose re-escalation is not permitted).

Dose administration may be delayed to allow for recovery from toxicity

Dose reductions are to be made in the following order according to the following dose levels:

- 120 mg once a day (QD), in the morning or in the evening
- 120 mg every other day (QOD) in the morning or in the evening
- 120 mg once every three days in the morning or in the evening (ie: one day of dosing followed by two days off)

If a subject is dosing at the lowest level (i.e., 120 mg once every three days) and has a relevant adverse event (see tables below), this would result in the subject taking pauses in drug administration or being discontinued from the study at the discretion of the Investigator and after discussion with the Medical Monitor of the study.

Further instructions for modifying the tivantinib/placebo dose due to non-hematological or hematological toxicities are listed in the following tables.

Table 3.1 Dose Delays/Reductions for Drug-Related Non-Hematological Toxicity

Event Grade	Action
Grade 1 or 2	Continue current dose level
Grade 3	Withhold tivantinib /placebo until recovery to Grade 1 or baseline. Administer tivantinib /placebo at the next lower dose for subsequent dosing, unless further dose reduction is required.
Grade 4	Withhold tivantinib /placebo until recovery to Grade 1 or baseline. Consult with the Medical Monitor or designee prior to restarting tivantinib /placebo. If the Investigator and Medical Monitor concur, administer tivantinib /placebo at the next lower dose for subsequent dosing, unless further dose reduction is required.

Table 3.2 Dose Delays/Reductions for Drug-Related Hematological Toxicity

Event/severity	Action
Neutropenia (absolute neutrophil count (ANC) < Lower limit of normal (LLN) to ≥ 1.5×10^9/L) **Thrombocytopenia** (Platelets < LLN to ≥ 60×10^9/L) **Anemia** (hemoglobin (Hgb) < LLN to ≥ 9 g/dL)	Continue current dose level
Neutropenia ANC < 1.5 to ≥ 1.0×10^9/L) **Thrombocytopenia** (Platelets < 60 to ≥ 50 $\times10^9$/L) **Anemia** (Hgb < 9 and ≥ 8 g/dL)	Withhold tivantinib/placebo and monitor hematology and/or chemistry weekly (every 2 days in case of ANC <1.5 $\times10^9$/L) until relevant lab value(s) recover to the values outlined below: • In case of neutropenia, resume treatment at the next lower dose once ANC values recover to ≥ 1.5×10^9/L and test hematology twice weekly for the remainder of the cycle. • In case of thrombocytopenia/anemia: o If the relevant lab value recovers within 7 days to ≥ 9 g/dL for hemoglobin, or ≥ 60×10^9/L for platelet, resume tivantinib/placebo treatment at the same dose level. o If the relevant lab value takes more than 7 days to recover to the level described above, restart tivantinib/placebo administration at the next lower dose. o If a second hold is required for the same event, administer tivantinib/placebo at the next lower dose.
Neutropenia (ANC < 1.0 to ≥ 0.5×10^9/L) **Thrombocytopenia** (Platelets < 50×10^9/L) **Anemia** (Hgb < 8 g/dL)	Withhold tivantinib/placebo and monitor hematology and/or chemistry weekly (every 2 days in case of ANC <1.0 $\times10^9$/L) until the relevant lab value(s) recover to the values outlined below. In case of neutropenia, continue to test hematology twice weekly for the remainder of the current cycle and the following (1) cycle. If the relevant lab value recovers to: ≥ 1.5×10^9/L for ANC, 9 g/dL for hemoglobin, or ≥ 60×10^9/L for platelets, resume treatment at the next lower dose once lab values allow doing so, unless further dose reduction is required. Treatment with growth factors is recommended for Grade 3 neutropenia persisting for >7 days.
Neutropenia (ANC < 0.5×10^9/L) Or **Febrile Neutropenia**	Withhold tivantinib/placebo and monitor hematology and/or chemistry every 2 days until relevant lab value(s) recover. Continue to test hematology twice weekly for the remainder of the current cycle and the following (1) cycle. Administer antibiotics and growth factors even if subject is afebrile and asymptomatic. If the relevant lab value recovers to ≥ 1.5×10^9/L for ANC, resume treatment at next lower dose once lab values allow doing so, unless further dose reduction is required.

4. STUDY POPULATION

4.1. Enrollment

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (possibly initials, age, sex) and the date and outcome of screening process (i.e., enrollment in the study, reason for ineligibility, refused to participate).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study, allows the Investigator to reveal the identity of any subject when necessary.

A subject is considered enrolled at the time of randomization. All subjects must personally sign and date (unless incapable of doing so; see Section 1.5.2) the Informed Consent Form provided by the site before pre-screening or screening procedures are performed. For additional information on Informed Consent, see Section 1.5.2.

An interim analysis is planned when approximately 154 (~60%) of the 257 OS events are documented. The study may be terminated for superiority at the interim analysis in accordance with the statistical analysis plan. If the study is positive at the prespecified interim or final analysis, the sponsor will allow patients who are receiving placebo treatment to receive active tivantinib treatment after database lock. The study will be unblinded after database lock. Patients on the placebo arm being considered for crossover must meet the safety eligibility criteria: Inclusion #6, 8, 10, 11, 12, and Exclusion #2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14.

4.1.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Written informed consent granted prior to initiation of any study-specific screening procedures
2. 18 years of age or older
3. Histologically confirmed HCC that is inoperable (where surgery is not indicated due to disease extension, co-morbidities, or other technical reasons), and not eligible for local therapy
4. MET Diagnostic-High tissue reported by the central authorized laboratory using archival or recent biopsy tumor samples; (see the lab manual and Section 6.1 of the protocol for tissue preparation details)
5. Received at least 4 weeks of one prior sorafenib containing systemic therapy and then experienced documented radiographic disease progression; or inability to tolerate prior therapy received for at least a minimum period of time. For the purpose of this study, intolerance to sorafenib is determined as follows:
    - The subject must have tried to take sorafenib for a period of at least 28 days (even intermittently)

- The subject must have tried to dose reduce sorafenib at ≤50% of the full dose for a period of at least 14 days (even intermittently) and still have a documented Grade ≥ 2 toxicity
- A period of even less than 14 days on sorafenib is acceptable in case of:
  i. Uncontrolled Grade 3-4 arterial hypertension
  ii. Pancreatitis, cardiac event, encephalopathy related to sorafenib
  iii. ≥ Grade 2 Hand-foot syndrome triggered even at 50% of the sorafenib dose

6. Discontinued prior systemic treatment or any investigational drug for at least 2 weeks (14 days) or for at least 3 weeks for IV anti-cancer drugs, prior to the study randomization
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1 (see Appendix 17.2)
8. Local or loco-regional therapy (i.e., surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed ≥ 4 weeks prior to randomization
9. Measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Tumor lesions previously treated with local therapy should demonstrate clear dimensional increase by radiographic assessment in order to be selected as target lesion(s) at baseline. Baseline radiographic assessment needs to be done within 21 days prior to randomization.
10. Adequate bone marrow, liver, and renal functions at Screening Visit, defined as: platelet count ≥ 60×10^9/L; hemoglobin ≥ 9.0 g/dL; absolute neutrophil count (ANC) ≥ 1.5×10^9/L; total bilirubin ≤ 2 mg/dL; Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN); serum creatinine ≤ 1.5 × ULN; albumin ≥ 2.8 g/dL; international normalized ratio (INR) 0.8 to ULN or ≤ 3 for subjects receiving anticoagulant such as coumadin or heparin. Subjects who are therapeutically anticoagulated are allowed to participate provided that prior to anticoagulant therapy no evidence of underlying defect in coagulation exists
11. Women of childbearing potential must have a negative serum pregnancy test performed within 14 days prior to the randomization (where demanded by local regulations, test may be required within 72 hours prior to randomization)
12. Male and female subjects of child-bearing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after last investigational drug dose received
13. Life expectancy of at least 12 weeks

4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. >1 prior systemic regimen (prior MET inhibitors/antibodies are not allowed; experimental systemic therapy for inoperable HCC given before or after sorafenib counts as separate regimen and is not allowed)

2. Child-Pugh B-C cirrhotic status based on clinical findings and laboratory results during screening period (see Appendix 17.4 for Child-Pugh Classification and interpretation of ascites at physical examination and PT/INR)
3. Previous or concurrent cancer that is distinct from HCC in primary site or histology, EXCEPT cervical carcinoma *in situ*, treated basal cell carcinoma, and superficial bladder tumors (Ta, Tis, and T1). Any cancer curatively treated > 3 years prior to enrollment is permitted.
4. History of congestive heart failure defined as Class II to IV per New York Heart Association (NYHA) classification (see Appendix 17.5) within 6 months prior to study entry; active coronary artery disease (CAD); clinically significant bradycardia or other uncontrolled, cardiac arrhythmia defined as ≥ Grade 3 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, or uncontrolled hypertension; myocardial infarction occurring within 6 months prior to study entry (myocardial infarction occurring > 6 months prior to study entry is permitted)
5. Active clinically serious infections defined as ≥ Grade 3 according to NCI CTCAE, version 4.03
6. Any medical, psychological, or social conditions, particularly if unstable, including substance abuse, that may, in the opinion of the Investigator, interfere with the subject's safety or participation in the study, protocol compliance, or evaluation of the study results
7. Known human immunodeficiency virus (HIV) infection
8. Blood or albumin transfusion within 5 days prior to the blood draw being used to confirm eligibility
9. Concomitant interferon therapy or therapies for active HCV infection
10. Pregnancy or breast-feeding
11. History of liver transplant
12. Inability to swallow oral medications
13. Clinically significant gastrointestinal bleeding occurring ≤ 4 weeks prior to randomization
14. Pleural effusion or clinically evident (visible or palpable) ascites

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

Subjects may be discontinued prior to randomization but after signing informed consent in case of:

- Screen Failure
- Adverse Event
- Withdrawal by Subject
- Physician Decision
- Lost to follow up

Subjects may be discontinued from treatment after randomization, during the treatment phase of the trial, in cases of:

- Death

- Progressive Disease if confirmed by repeat CT/MRI scan 4 weeks after radiographic progression first suspected(see guidelines in Table 4.1)
- Noncompliance with any part of the study, as evaluated by the Investigator and Sponsor's Medical Monitor or designee
- Clinically unacceptable toxicities
- Withdrawal of consent to treatment
- Lost to Follow-up
- Physician Decision
- Study Terminated by Sponsor

Any subject who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded. Discontinued subjects will still be followed for survival either through direct contacts or collection of public records (i.e., a death certificate) in accordance to local laws.

Unblinding for radiographic progression will not be allowed. Unblinding will only be permitted for medical emergencies where knowing the treatment arm will affect how the physician would treat the subject. Any subject whose treatment has been unblinded before database lock must be discontinued immediately from the treatment. Subjects discontinued from the study because of consent withdrawal will be followed for survival through collection of public records (i.e., a death certificate) unless prohibited by local laws.

Table 4.1 Possible Scenarios and Actions at Radiographic Progression

Scenario:	**Action:**
Radiographic suspicion of tumor progression	Perform confirmatory CT/MRI scan 4 weeks after radiographic progression first suspected. (Any new lesions < 10mm to be confirmed by observation of continued growth or development of a typical HCC pattern). For the purpose of tumor assessment, ascites and/or pleural effusion should not be registered as disease progression unless their malignant origin is proven by pathology.
Radiographic re-assessment confirms tumor progression	Stop the experimental therapy
Radiographic re-assessment does NOT confirm tumor progression	Continue the experimental therapy until new radiographic suspicion of tumor progression (repeat as above)

If a subject withdraws from the study treatment, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal. Subjects who discontinue from the study for reasons other than death will still be followed for survival, either through visits/phone calls or through collection of public records (i.e., death certificate) in accordance with local laws.

If the subject is discontinued due to an adverse event, the Investigator will follow the subject until the adverse event has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures (see Section 4.2.2).

4.2.2. Withdrawal/Discontinuation Procedures

If a subject withdraws from study treatment, the date and reason for withdrawal will be recorded on the electronic Case Report Form (eCRF). The Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment. All procedures and tumor assessment specified for the End of Treatment visit (Section 6.6) will be conducted. See Section 6 for specific follow-up procedures depending on the reason for withdrawal from treatment.

If the subject is discontinued from study treatment due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

Subjects who discontinue from study treatment for reasons other than death will be followed for survival after the End of Treatment visit until death or study closure (i.e., when the pre-specified number of events have occurred), either through visits/phone calls or through collection of public records (i.e., a death certificate) unless they specifically withdraw consent for survival follow up. Survival may still be assessed through collection of public records, in accordance with local laws.

4.2.3. Subject Re-screening Procedures

Subjects can be re-screened if they were deemed a screen failure for technical reasons (i.e., tumor samples were inadequate to determine MET status, or MET status was deemed to be Low and a biopsy needs to be re-done, or performing screening procedures took longer than the allowed window) or due to inadequate lab values that recovered without medical intervention. However, screening procedures must be restarted within 28 days from the screen failure (or the communication of the results to the site, in case of screen failures related to the tissue sample). Such time window does not apply to subjects screen failed because MET status evaluation was not possible. If the originally submitted sample is deemed to be MET-Low, tumor samples from a new biopsy (if safe for the subject) can be submitted for MET evaluation within 28 days from the communication of the results to the site; if the tissue from the new biopsy is found to be MET-High and the subject has progressed or is intolerant to sorafenib, the subject must start screening procedures (e.g. labs, vital signs, etc.) as soon as possible but no later than 14 days from the communication of the MET-High result to the site.

The Principal Investigator will consult with the Sponsors or the CRO before making the re-screen decision.

Re-screened subjects will keep the same identification number they were assigned at first screening.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

Tivantinib is an investigational oral drug supplied as 120 mg red-orange, film-coated tablets. Placebo tablets will be identical in appearance. If the study is positive at the interim or final analysis, all eligible patients who have been randomized to placebo will be allowed to receive tivantinib after database lock and unblinding. No placebo will be dispensed by the IXRS system for a subject once that subject has received active treatment.

5.1.1. Method of Assigning Subjects to Treatments and Blinding

This study will be double blind: the subject, the Investigator, and site staff will be blinded to the treatment administered. If the study is positive at the interim or final analysis, all eligible patients who have been randomized to placebo will be allowed to receive tivantinib after database lock and unblinding.

The randomization schedule will be generated by the Interactive Voice/Web Response System (IXRS) following the randomization specifications before the start of the study.

After obtaining informed consent and confirming eligibility via the Medical Monitor, the Investigator will randomize the subject using the IXRS. The IXRS will randomize the subject to one of the two treatment arms.

Subjects will be stratified by: vascular invasion (present or not), extra-hepatic spread including distant metastasis and/or involved regional or distant lymph nodes (present or not, using RECIST 1.1 criteria but regional nodes are considered involved if ≥ 20 mm in shortest diameter), and AFP (less/equal or greater than 200 ng/mL).

Eligible subjects will be assigned randomly on a 2:1 basis to either tivantinib (120 mg BID) or placebo.

Tivantinib/placebo will be dispensed using the IXRS. The subject should begin treatment as soon as possible after randomization; preferably on the same day.

Emergency unblinding for safety reasons will take place using the IXRS. In case of emergency, the Investigator must make every effort to contact and consult with the Medical Monitor prior to breaking the blind. If the blind is broken without consulting the Medical Monitor, a full explanation for this event must be provided within 24 hours. Contact information is listed in Section 15.2 of the protocol.

5.1.2. Method of Assessing Treatment Compliance

All doses given during the subject's visit with the Investigator will be administered under the supervision of clinical study personnel.

The subjects will be instructed to return all unused study drug at the next visit. Compliance to the study drug regimen will be evaluated by counting unused tablets and may include the use of subjects' diaries:

$$\% \text{ compliance} = \frac{\text{Number of tablets dispensed} - \text{Number of tablets returned}}{\text{Number of tablets prescribed per day}^{a} \times \text{Number of days}^{b} \text{ in the dosing interval}} \times 100$$

a: Number of tablets prescribed (i.e. 2, or as determined per the dose reduction guidelines for toxicity considered related to tivantinib and specified in the eCRF)
b: Number of days during that interval that the subject should have dosed (i.e., excluding any days that the subject was instructed to hold dosing due to an adverse event

During the treatment period, if compliance is not between 80% and 120%, inclusive, the subject will be counseled about the importance of adherence to the mandated regimen. If the subject continues to be non-compliant in terms of dosing, the subject may have to be discontinued from the study treatment.

Administration of Investigational Product (IP) will be recorded in the Drug Accountability Log and eCRF. Subjects must return empty bottles and remaining tablets. Returned tablets must be recorded in the Drug Accountability Log which is supplied to the site. Subjects need to keep record of their daily IP dosing.

At each visit after study treatment is initiated, the Investigator or designee must record the date, interval between visits, quantity and strengths, and any dose changes/interruptions of study drug dispensed/administered.

5.1.3. Labeling and Packaging

The appearance and packaging of tivantinib and placebo are the same. Tivantinib and matching placebo are supplied as tablets in bottles and labeled in the local languages as investigational agent, according to relevant guidelines. The Sponsor will provide tivantinib and placebo required for completion of this study. They will be shipped to the pharmacist/study personnel at the clinical sites during the study through the IXRS.

5.1.4. Preparation

There is no preparation required for tivantinib and matching placebo.

5.1.5. Storage

Drug supplies must be stored in a secure, limited access storage area. Tivantinib tablets and matching placebo are stable when stored at room temperature. The storage requirement applicable to a specific region is reflected in the label.

If storage conditions deviate from the above storage requirements, the Investigator will document the deviation and inform the study monitor within 24 hours of discovery of the deviation. The supplies should be held and not dispensed until the deviation has been reviewed by the Sponsor's Quality Assurance or designee. If it is determined that the product is no longer suitable for use, the bottles must be reported as damaged in the IXRS.

5.1.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, sign the Receipt of Shipment Form provided, and acknowledge receipt of the shipment in IXRS. The Receipt of Shipment Form should be returned as instructed on the form. The original will be retained at the site. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the IP and placebo control

The record must be kept current and should contain the dates and quantities of drug received, subject's identification number (and/or initials or supply number as applicable) for whom the investigational product was dispensed, the date and quantity of IP dispensed and remaining, if from individual subject drug units, as well as the initials of the dispenser.

At the end of the study, or as directed, all study drug (tivantinib and placebo), including unused, partially used, or empty containers, will be returned to a designee as instructed by the Sponsor. Investigational Product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of IP must be documented and the documentation included in the shipment. Dosage form (i.e. tablet) site level accountability documentation is to be included with each drug supply return shipment (or other returning facility, such as another depot). This is required as part of the receiving records for return shipments.

Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition Standard Operation Procedures (SOPs) or equivalent. Dosage form (i.e. tablet) site level accountability documentation is required as part of the disposition records of IP. The dosage form site level accountability documentation should be appended to the Certificate of Destruction.

At the end of the study, a final IP reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor.

All IP inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.2. Concomitant Medications

Treatments permitted before and during study treatment include the following:

- Standard nonsurgical therapies for concurrent medical conditions
- Erythropoiesis stimulating agents (ESAs): Please follow American Society of Clinical Oncology (ASCO) guidelines for the use of ESAs in subjects diagnosed with cancer; see drug labels and FDA alerts.

- Hematopoietic growth factors including filgrastim (Neupogen®), leukine (Sargramostim®), or other colony-stimulating factors as per protocol (See Section 3.2.1.4 on therapies in case of neutropenia)
- Prophylactic antiemetics may be administered according to standard practice
- Appropriate treatment for HBV if necessary (except for interferon)
- Megestrol acetate (Megace®) as supportive care. Use of topical corticosteroids, topical antibiotics, and systemic antibiotics according to institutional guidelines
- Treatment with non-conventional therapies (i.e., herbs or acupuncture), and vitamin/mineral supplements are acceptable, provided that they do not interfere with the study endpoints, in the opinion of the Investigator
- Bisphosphonates for bone metastases
- Palliative radiotherapy for non-hepatic local pain control provided that, in the opinion of the Investigator, the subject does not meet the criteria for exiting the study (i.e. clear progression of disease)
- Prevention of variceal bleeding as per relative guidelines

Prohibited Treatments include the following:

- Any concurrent anti-cancer therapy including chemotherapy, radiotherapy for target lesions, surgery, hormonal therapy (except megestrol acetate as supportive care), or immunotherapy
- Other investigational agents
- Immunosuppressive therapies including interferon and systemic corticosteroids (except up to a 25 mg/day prednisone-equivalent dose or when used intermittently in an antiemetic regimen or premedication for imaging studies)
- Therapies for active HCV infection including interferon, protease and polymerase inhibitors
- Blood or albumin transfusion within 5 days prior to the blood draw being used to confirm eligibility

Caution should be applied when beta-blockers (i.e. atenolol, propranolol, metoprolol, etc) or CYP2C19 inhibitors such as omeprazole, fluvoxamine, moclobemide, fluconazole, ticlopidine, rabeprazole, and fluoxetine or strong CYP3A4 inhibitors such as atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, ciprofloxacin, telithromycin, troleandomycin (TAO), or voriconazole are used as concomitant therapy. Laboratory parameters must be monitored as described in the protocol. Detailed guidelines on dose reduction and/or interruption are provided in Section 3.2.1.4 in regard to any potential hematologic or non-hematologic adverse reaction observed for an individual subject. Additional details may be found in Appendix 17.3.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Appendix 17.1. After written informed consent is obtained, a subject's eligibility for the study and baseline disease status will be assessed. A subject must sign the consent form prior to starting any study related procedures or assessments; but the informed consent can be signed greater than 14 days prior to dosing, and does not have to be re-signed prior to dosing unless specific reasons apply (i.e. a new approved consent version has been issued).

6.1. Pre-Screening Tumor Sample Collection

In order to facilitate transition from the sorafenib treatment to this experimental study, the pre-screening phase can take place even before or while the subject is treated with sorafenib; assessment of MET must be performed by the central authorized laboratory, and the result will be communicated to the Investigator's staff if/when the subject experiences documented tumor progression or intolerance to sorafenib. The following activities and/or assessments will be performed during the pre-screening tumor sample collection phase:

- Archival or recent tumor sample collection (biopsy not older than the maximum time specified in the lab manual; Fine needle aspirate (FNA) is not acceptable unless it can be prepared as per the lab manual; formalin fixed, paraffin embedded (FFPE) tumor tissue block is preferred (specimens should be fixed in 10% neutral buffered formalin (NBF) and should not be stored in fixative for more than 72 hours before processing into paraffin blocks.); if FFPE slides are sent, there must be at least 7 (refer to current lab manual), prepared from FFPE tissue, on positively charged slides; the time between slide preparation and submission for analysis cannot be longer than the timeframe mandated by the lab manual
- Obtain written informed consent from the subject or the subject's legal representative to analyze archival samples for the purpose of the study
- If a tumor biopsy is needed, obtain written informed consent to perform the biopsy and analyze samples for the purpose of the study
  Medical history (including Primary Cancer History)
- Record any serious adverse events (SAEs) directly related to a pre-screening procedure (i.e., a tumor biopsy). Do not record AEs or unrelated SAEs unless this is mandated by local laws.

If the tumor tissue is found to be MET-High and the subject has progressed or is intolerant to sorafenib, the subject must start screening procedures (e.g. labs, vital signs, etc.) as soon as possible but no later than 14 days from the communication of the MET-High result to the site. If the tumor tissue is not adequate for testing or is found to be MET Low please refer to section 4.2.3.

6.2. Screening Visit (Days -14 to 0)

The following activities and/or assessments will be performed at/during Screening:

- If not already provided, obtain written informed consent from the subject or the subject's legal representative (subjects must sign the consent form prior to starting any study related procedures or assessments, but the informed consent can be signed greater than 14 days prior to enrollment and does not have to be re-signed prior to dosing unless specific reasons apply)
- Medical history (including Primary Cancer History)
- Physical examination including height
- ECOG PS
- Vital signs and weight, including temperature
- Blood sample for Surface antigen of the hepatitis B virus (HBsAg), Hepatitis B "e" antigen (HBeAg), HBV Deoxyribonucleic acid (DNA)*, delta virus; Hepatitis C antibody (HCVAb)
- Hematology
- Coagulation tests
- Blood chemistry
- Blood sample for AFP testing
- Serum pregnancy test, if applicable**
- Child-Pugh status assessment
- 12-lead electrocardiograms (Triplicate ECGs approximately 2 minutes apart)
- Prior and Concomitant medications (including Previous Cancer Therapy)
- Tumor assessment by CT or MRI scan (can be up to -21 days before randomization) reporting also vascular invasion status.
- Tumor sample collection (biopsy if necessary), if not done at pre-screening. Can be performed even earlier than 14 days prior to enrollment***
- Record any SAEs directly related to a screening procedure (e.g. a tumor biopsy). Do not record AEs or SAEs that are unrelated to a screening procedure unless this is mandated by local laws.

* If active HBV replication is discovered, the subject must be immediately treated with conventional anti-viral therapy (not including interferon) as per standard of care

** Where demanded by local regulations, a pregnancy test may be required within 72 hours prior to randomization

*** Archival or recent tumor sample collection (biopsy not older than the maximum time specified in the lab manual; FNA is not acceptable unless it can be prepared as per the lab manual; formalin fixed, paraffin embedded (FFPE) tumor tissue block is preferred (specimens should be fixed in 10% neutral buffered formalin (NBF) and should not be stored in fixative for more than 72 hours before processing into paraffin blocks.); if FFPE slides are sent, there must be at least 7 (refer to current lab manual), prepared from FFPE tissue, on positively charged slides; the time between slide preparation and submission for analysis cannot be longer than the timeframe mandated by the lab manual

6.3. Randomization

The randomization schedule will be generated by an IXRS per randomization specifications before the start of the study. After all screening procedures are performed and results of screening tests are available (i.e., between the screening visit and the Cycle 1, Day 1 visit), eligible subjects will be assigned randomly on a 2:1 ratio to the tivantinib or placebo treatment groups.

Randomization will be performed by the IXRS. Subjects will be stratified based on vascular invasion (present or not), extra-hepatic spread including distant metastasis and/or involved distant or regional lymph nodes (present or not, per RECIST 1.1 criteria, but regional nodes are considered involved if ≥ 20 mm in shortest diameter), and AFP (less/equal or greater than 200 ng/mL).

Study treatment should be initiated as soon as possible after randomization, preferably on the same day, no later than 2 days from randomization.

6.4. Cycle 1 Day 1 Visit

The following activities and/or assessments will be performed at/during Randomization/Cycle 1 Day 1, and, other than AEs and PK sampling, will be done prior to the first dose of study drug:

- Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and EuroQol-5D (EQ-5D) questionnaires (before meeting with the physician or having any other assessment performed)
- Physical examination
- ECOG PS
- Vital signs and weight, including temperature
- Hematology
- Coagulation tests
- Blood chemistry
- If not restricted by local regulation, collect a blood sample for pharmacogenomic (CYP 2C19) analysis from all subjects. If permitted and the subject consents, some of this sample may be banked for future pharmacogenomic analysis (see Section 8.4.3)
- Blood sample for HGF testing
- Child-Pugh status assessment
- Concomitant medications (any medication the subject took within 30 days from randomization)
- Dispense study drug (to be taken with meals)
- AEs
- 12-lead electrocardiograms (Triplicate ECGs approximately 2 minutes apart) at the same time as each of the blood draws for pharmacokinetics (PK). ECGs to be performed ±30 minutes from the time of each PK collection.
- Blood samples for pharmacokinetics between 1 and 3 hours post first dose and between 4 and 8 hours post first dose (as described in Appendix 17.6). Dose and PK sampling time should be recorded.

6.5. Treatment Period

All visits are based on the date of the first dose at Cycle 1 Day 1 regardless of drug holds. If a subject visit deviates from the protocol permitted window, the next visit must be done at the correct time based on the date of Cycle 1 Day 1.

6.5.1. Cycle 1, Days 5, 9, 13, 17, and 25 (±1 day)

- Hematology
- AEs
- Concomitant Medications

6.5.2. Cycle 1, Day 21 (±1 day)

- Hematology
- 12-lead electrocardiograms (Triplicate ECGs approximately 2 minutes apart) at the same time as the blood draw for pre-dose pharmacokinetics (PK). ECGs to be performed ±30 minutes from the time of the pre-dose PK collection.
- Blood samples for pharmacokinetics before the morning dose and at least one hour after the morning dose (as described in Appendix 17.6). The morning dose (to be taken with a meal) should be administered at the clinic. Dose and PK sampling time should be recorded. Time for the two preceding doses must also be recorded.
- Vital signs and weight, including temperature
- AEs
- Concomitant Medications
- Optional core needle tumor biopsy (after Day 22 and preferably before Day 30). See Section 6.1 for details on tissue preparation.

6.5.3. Cycles 2+, Day 1 (±2 days)

- Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) and EQ-5D questionnaires (before meeting with the physician or having any other assessment performed)
- Physical examination
- ECOG PS
- Vital signs and weight, including temperature
- Hematology
- Coagulation tests
- Blood chemistry[1]
- Where monthly pregnancy testing is required by local regulations for subjects of child bearing potential, a pregnancy test will be performed
- Blood samples for HGF and AFP testing (at cycles 2, 3, and 4)

[1] If a remarkable sudden increase in AST/ALT values is found, and subject is HBV positive, HBV replication must be assessed; if active HBV replication is discovered, subject must be immediately treated with conventional anti-viral therapy (not including interferon) as per standard of care

- Blood sample(s) for pharmacokinetics as described in Section 8 and Appendix 17.6. The morning dose should be administered at the clinic (experimental drug is taken with a meal). Dose and PK sampling times, and the time when the two preceding doses were taken, must be recorded.
- Child-Pugh status assessment
- Tumor assessment (as per frequency outlined in section 6.5.5)
- ECG – single ECG (at Cycle 2 ONLY. If heart rate during first cycle is ≤ 50 beats per minute (bpm) then ECG will also be performed on Day 1 of every cycle thereafter)
- AEs
- Concomitant medications
- Dispense Drug
- Collect returned drug/Assess treatment compliance

6.5.4. Cycle 2, Days 8, 15 and 22 (±2 days)

- Hematology: samples can be tested locally (close to the subject's home) and results need to be reviewed rapidly by the hospital study team
- AEs
- Concomitant medications

6.5.5. Cycle 3+, Day 15 (±2 days)

- Hematology: samples can be tested locally (close to the subject's home) and results need to be reviewed rapidly by the hospital study team
- AEs
- Concomitant medications

6.5.6. Tumor Assessment Scans

During the study, tumor assessment will be performed in 8-week intervals (±3 days) from the date of first dose. Dates of all post dose scans are based on the date of first dose. If for any reason a scan is performed out of window, the subsequent scan must be performed at the correct time. The same imaging modality (e.g. CT or MRI) must be used throughout the study to follow lesions for each subject, unless contraindicated for safety reasons (e.g. development of allergy to contrast medium).

Note: Subjects who discontinue their assigned treatment for a reason other than confirmed radiographic disease progression, withdrawal of consent, death, or loss to follow-up should continue tumor evaluation visits at 8-week intervals if possible until they start another anti-cancer therapy, disease progression, withdrawal of consent, death, or are lost to follow-up.

6.5.7. Crossover Visits (positive study and post database lock)

If the study is positive at the prespecified interim or final analysis, the sponsor will allow patients who are receiving placebo treatment to crossover to the active tivantinib treatment arm after database lock if the safety parameters in the eligibility criteria are met (see section 4.1).

For the first month on tivantinib, hematology will be tested every 4 days and for the second month, hematology will be tested weekly. A single ECG must be performed prior to the first dose of tivantinib and again on Day 1 of the following cycle (one month after starting dosing with tivantinib). If heart rate is ≤ 50 beats per minute (bpm) then an ECG will also be performed on Day 1 of every cycle thereafter.

6.6. End of Treatment

Subjects who stop any assigned treatment should be seen within 7 days after last dose of tivantinib/placebo for the following assessments:

- Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-Hep) and EQ-5D questionnaires (before meeting with the physician or having any other assessment performed)
- Physical examination
- ECOG performance status
- Vital signs and weight, including temperature
- Serum pregnancy test (if applicable)
- Hematology
- Blood chemistry[2] and coagulation
- Blood samples for HGF and AFP testing
- Child-Pugh assessment
- Tumor assessment (if not done within 14 days)
- ECG (single ECG)
- Record concomitant medications
- Assess adverse events
- Collect returned drug/Assess treatment compliance
- Deactivate the subject in the IXRS
- Optional core needle tumor biopsy. See Section 6.1 for details on tissue preparation.

6.7. 30-Day Safety Follow-up

All subjects must have a follow-up visit or phone call 30 days following their last dose of assigned treatment. Subjects with unresolved protocol-therapy related AEs at the time of treatment discontinuation or that occur within 30 days after discontinuation of assigned treatment will be followed for a minimum of 30 days following the last dose of protocol designated therapy or until all study related toxicities have, in opinion of the Investigator, resolved to baseline, stabilized, or are deemed to be irreversible. If a subject receives other anti-cancer therapy within the 30-day follow-up period, the follow-up and recording for AEs will cease beginning the first day of the new therapy.

[2] If a remarkable sudden increase in AST/ALT values is found, and subject is HBV positive, HBV replication must be assessed; if active HBV replication is discovered, subject must be immediately treated with conventional anti-viral therapy (not including interferon) as per standard of care

6.8. Survival Follow up (every 3 months ±14 days)

Survival follow-up will start the day of the End of Treatment visit. All subjects and/or family will be contacted at 3-month intervals (±2 weeks) and record the subject status as Alive (date); Dead (date); Alive, but withdrew consent; Lost to Follow Up. The survival follow-up period will continue until at least the required number of events have been reported. Survival follow-up will also continue with subjects who withdraw from treatment, unless specifically notified, in writing, by the subject. In that case, public records (i.e., death certificates) will be used for survival analysis.

6.9. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by the Sponsors and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

A deviation to any protocol procedure, or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsors must be notified of all intended or unintended deviations to the protocol (i.e., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or designee should document all protocol deviations and explain (if possible) any deviation from the approved protocol.

Any data recorded on the study Case Report Form will be collected and included in the database according to Clinical Data Interchange Standards Consortium (CDISC) standards and subjected to the same procedures as other data. If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

The Investigator should notify the IEC or IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

7.1. Primary Variable(s)

- Overall survival (OS) in the ITT population

7.2. Secondary Variable(s)

- Progression free survival (PFS)

7.3. Exploratory Variable(s)

- Time to progression (TTP), type of progression, overall response rate (ORR), and disease control rate (DCR) evaluated by independent radiology review
- FACT-Hep-based FHSI-3 pain score, FACT-Hepatobiliary Symptom Index (FHSI-8) score, FACT-Hep Emotional Well Being (EWB) score, FACT-Hep total score, EQ-5D
- Time-to-hospitalization (all-cause) and time-to-hospitalization (HCC-related)

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Variable(s)

Blood samples will be collected on Day 1 and Day 21 of Cycle 1 and Day 1 of Cycles 2 and 3 to further evaluate pharmacokinetics of tivantinib and its metabolites and their correlation with biomarkers and clinical endpoints. Such analysis will be conducted using a population pharmacokinetic/pharmacodynamic approach.

Dose and PK sampling times must be recorded. The date and time that the 2 preceding doses were taken must also be recorded.

Blood samples for pharmacokinetic analysis will be collected as per the following time points:

- Cycle 1, Day 1: two samples
  - One blood draw between 1 and 3 hours after the first dose of tivantinib/placebo
  - One blood draw between 4 and 8 hours after the first dose of tivantinib/placebo
- Cycle 1, Day 21: two samples
  - One blood draw before the morning dose of tivantinib/placebo
  - One blood draw at least 1 hour after the morning dose of tivantinib/placebo
- Cycle 2, Day 1: one sample
  - One blood draw before the morning dose of tivantinib/placebo
- Cycle 3, Day 1: one sample
  - One blood draw at any time after the morning dose of tivantinib/placebo

If the subject starts receiving a CYP2C19 and/or CYP3A4 inhibitor/inducer at any cycle after Cycle 3, 2 blood samples *should* be collected, if possible, while the subject is on the concurrent medication:

- One blood draw before the morning dose of tivantinib/placebo
- One blood draw at least 1 hour after the morning dose of tivantinib/placebo

If a subject experiences Grade ≥ 2 neutropenia, if possible, collect 1 pharmacokinetic blood sample at anytime during the dosing period but before any dose suspension or reduction is applied. Do not delay dose suspension or reduction.

8.2. Pharmacodynamic (PD) Variable(s)

Blood samples will be collected at pre-dose on Day 1 of Cycles 1, 2, 3, and 4 and at the end of treatment for the analysis of dynamic changes in hepatocyte growth factor (HGF). Blood samples will be collected at pre-dose at Screening and on Day 1 of Cycles 2, 3, and 4 and at the end of treatment for the analysis of dynamic changes in AFP. HGF and AFP will be measured using an approved enzyme-linked immunosorbent assay (ELISA) kit.

Additional biomarkers may also be evaluated on blood samples as new data may suggest.

8.3. Biomarker and Exploratory Variable(s)

Tumor samples of archival or recent biopsy must be collected at baseline for all subjects (formalin fixed, paraffin-embedded blocks or at least 7 (refer to current lab manual) formalin fixed, paraffin embedded unstained, unbaked, positively charged slides of 4 to 5 micron thickness; specimens should be fixed in 10% neutral buffered formalin (NBF) and should not be stored in fixative for more than 72 hours before processing into paraffin block) as described in the related lab manual. If slides are sent, they must have been prepared from formalin-fixed paraffin-embedded tissue; the time between slide preparation and submission for analysis cannot be longer than the timeframe mandated by the lab manual. Recent biopsy (also providing formalin fixed, paraffin-embedded blocks or at least 7 (refer to current lab manual) unstained slides) is preferred. Fine Needle Aspirate (FNA) is not acceptable unless it can be prepared as per the lab manual. Biopsy samples collected within 30 days before the first day of treatment are considered recent.

Collected samples will be evaluated primarily for the expression of total MET by immunohistochemistry. The samples will be shipped to a designated central laboratory where they will be tested. Tissue samples will be considered MET Diagnostic-High when $\geq$ 50% of tumor cells have a staining intensity of $\geq$ 2+ for MET in a single slide as assessed by immunohistochemistry using a single validated assay.

If an archival sample is deemed to be MET Diagnostic-Low, tumor samples from a new biopsy can be submitted for MET evaluation, if safe for the subject; re-screening procedures must be started within 28 days from the communication of the results to the site. If the new baseline biopsy provides a MET Diagnostic-High sample, the subject will be eligible for the study. Shipment of pre-screening samples will be allowed upon signature of informed consent.

In addition, if deemed safe for the subjects and with their consent, optional tumor biopsies will be performed at baseline, post-treatment (after Day 22 and preferably before Day 30 of Cycle 1), and at the end of treatment. Collected samples may be evaluated, if possible, for the expression of MET, p-MET, downstream markers of MET signaling, cell proliferation, and additional (non genetic) biomarkers may also be evaluated on tumor samples as new data may suggest.

Samples will be labeled by personnel from the institution with the subjects' study ID and their identity will not be made known to employees from the company, additional collaborators, or other Investigators. Samples will only be used for the purposes of the protocol and will only be used by Sponsors' personnel or by an external laboratory chosen by the Sponsors to outsource the analysis according to internal guidelines. Tissue samples collected for the purpose of this study will be utilized to complete all necessary analyses to support the regulatory approval for the indication. Additional analysis may be performed to gain a better understanding of the target (MET) and/or effect of the study drug unless restricted by local regulations. These samples will be stored for the period required by the analyzing lab, unless otherwise specified by applicable local regulations. After completion of the protocol-related analyses, unused or remaining tissue samples will be destroyed per the Laboratory standard practice unless the sites/subjects requested the samples to be returned.

8.4. Pharmacogenomics and Optional Pharmacogenomic Sample Banking

8.4.1. Pharmacogenomic Testing

If not restricted by local regulations, after signature of informed consent, a blood sample will be collected from each subject on Day 1 of Cycle 1 as part of this study, primarily for genotyping of commonly known variants in CYP2C19.

CYP2C19 is the cytochrome P_{450} enzyme primarily responsible for the metabolism of tivantinib. Subjects carrying common genetic variants in CYP2C19 have altered pharmacokinetics and suboptimal outcomes following treatment with clopidogrel,[23] another drug primarily metabolized by CYP2C19.

These results may provide information on how different individuals metabolize and react to the study drug.

If the subject has also provided a specific consent for pharmacogenomic banking, and if not restricted by local regulations, then the sample will be stored for future analysis. Samples for those subjects who do not consent to genetic banking will be destroyed after all the assessments have been performed.

8.4.2. Pharmacogenomic Sample Collection

On Day 1 of Cycle 1, if not restricted by local regulation, a blood sample should be collected and frozen as soon as it is possible. Sample volumes and handling procedures are provided in the laboratory manual.

To ensure subject confidentiality, each sample tube will be identified only by a barcode. This barcode will be linked to the subject's study identification number.

The samples will be shipped to designated central laboratory. Sample collection, handling, storage, and shipping instructions are described in the lab manual.

8.4.3. Optional Pharmacogenomic Sample Banking

The remainder of the pharmacogenomic samples from each consenting subject, if not restricted by local regulation and if the subject consents, may be retained for possible future research as new information regarding the safety and efficacy of tivantinib may emerge.

All subjects should be provided with the opportunity to consent separately to pharmacogenomic sample banking at enrollment. Participation in this portion of the study is optional for all subjects. Thus, a subject who chooses not to allow retention of his/her pharmacogenomic sample beyond the initial testing may still participate in the main portion of the study. Pharmacogenomic samples from all subjects who choose not to participate in the banking portion of the study will be destroyed at the end of the study.

Because it is impossible to know what new scientific information may arise in the future, no analysis plan exists for these samples. However, the scope of the analysis will be limited to genes suspected to contribute to the safety and efficacy of tivantinib. Samples will be retained until the DNA has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures).

The retention period will not exceed 10 years. During the period of storage, the DNA sample will not be immortalized or sold to anyone.

Subjects will have the right to withdraw consent and have their samples destroyed at any time.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

Adverse events (AEs) will be collected from the date of randomization until the end of the treatment with the study drug. Serious adverse events (SAEs) related to study-specific procedures will be reported from the date of signing the informed consent; all SAEs will be reported from the date of randomization to 30 days after the last dose of study drug. If mandated by local law, AEs and/or SAEs as appropriate will be recorded for time of consent. If a subject receives any other anti-cancer therapy within the 30-day follow-up period, the follow-up and recording for AEs will cease beginning the first day of the new therapy.

Any findings noted during baseline assessment will be recorded as part of medical history. All serious adverse events (SAEs) are to be reported according to the procedures in Section 9.2 SAE Reporting-Procedure for Investigators. Report the diagnosis as the AE or SAE term; when the diagnosis is unavailable, report signs and symptoms as individual entries of the AE or SAE until the diagnosis becomes available. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.1.1 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate causes, “disease progression” should be reported as an SAE. In addition, any untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an AE.

At each visit, the Investigator will determine whether any adverse events have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All laboratory values must be appraised by the Investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the Investigator must be recorded in the adverse event page of the Case Report Form (CRF), and if serious, report as an SAE following the procedures in Section 9.2.

The Investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. Subjects with unresolved protocol-therapy related AEs at the time of treatment discontinuation or that occur within 30 days after discontinuation of assigned treatment will be followed for a minimum of 30 days following the last dose of protocol designated therapy or until all study related toxicities have, in opinion of the Investigator, resolved to baseline, stabilized, or are deemed to be irreversible.

9.1.1. Definitions

9.1.1.1. Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal lab findings which should be considered adverse events.

9.1.1.2. Serious Adverse Event (SAE)

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event 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 (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE
- Pre-planned (prior to signing the Informed Consent Form) surgeries or hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs

9.1.1.3. AE Severity

All AEs will be graded (1 to 5; see below) by the Investigator, according to the NCI CTCAE, Version 4.03, (publish date: 14 Jun 2010).[24]

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI CTCAE Grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

9.1.1.4. Causality Assessment

The relationship between an adverse event and the study product will be determined by the Investigator on the basis of his/her clinical judgment and the following definitions:

- 1 = Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (i.e., disease under study, concurrent diseases, and concomitant medications)
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (i.e., disease under study, concurrent diseases, and concomitant medications).

9.1.1.5. Action Taken Regarding the Study Product

- 1 = None
  - No change in study drug dosage was made
- 2 = Discontinued Permanently
  - The study product was permanently stopped
- 3 = Reduced
  - The dosage of study product was reduced (including if drug was interrupted and reduced)
- 4 = Interrupted
  - The study product was held temporarily

9.1.1.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable
  - Identify sequelae/residual effects
- 3 = Not Recovered/Not Resolved
  - The adverse event itself is still present and observable
- 4 = Fatal
- 5 = Unknown

9.1.1.7. Other Action Taken for Event

- 1 = None
  - No treatment was required
- 2 = Medication was required
  - Prescription and/or over-the-counter (OTC) medication was required to treat the adverse event
- 3 = Hospitalization or prolongation of hospitalization was required
  - Hospitalization was required or prolonged due to the adverse event, whether or not medication was required
- 4 = Other

9.2. Serious Adverse Event Reporting–Procedure for Investigators

9.2.1. Initial Reports

Within 24 hours of receiving an SAE report:

- Complete a Daiichi Sankyo Serious Adverse Event Report (SAVER) form, sign and fax the form to Covance using the designated fax transmittal form. Covance will review and forward the SAVER form to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV)
- Call the Covance SAE Hotline for any questions regarding SAE reporting
- Covance SAE Hot Line telephone number and fax:
  [redacted]
- Place the initial version of the SAE Report Form in the subject's file

9.2.2. Follow-up Reports

This is NEW information received on a previously reported SAE.

Within 24 hours of the receipt of new information for a reported SAE:

- Complete a Daiichi Sankyo Serious Adverse Event Report (SAVER) form with the new information. Please complete Sections 1 through 3 even if they contain no new information. For Sections 4 through 10, provide only the new information. Sign and fax the form to Covance using the fax transmittal form.
- Fax, e-mail, or send by express mail, copies of supporting documents (i.e., hospital discharge summaries, lab test results with normal ranges, autopsy or biopsy reports) to Covance
- The CRO will review and forward the follow-up SAVER form and supporting documents to Daiichi Sankyo Clinical Safety and Pharmacovigilance [redacted]
- Place the follow-up version of the SAVER form and all supporting documentation in the subject's file

9.2.3. Notifying Investigators or Ethics Committee/Institutional Review Board

Daiichi Sankyo and/or CRO will undertake to inform Investigators of any serious, unexpected (not listed in the Investigator's Brochure) and related AEs occurring in other study sites or other Daiichi Sankyo studies of the investigational product, as appropriate.

Depending on the country/region, either Daiichi Sankyo or the Investigator will inform the Ethics Committee/Institutional Review Board of serious unexpected and related AEs reported with Daiichi Sankyo's investigational product.

9.2.4 Events of Special Interest

9.2.4.1 Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the criteria of a potential Hy's Law case [TBL ≥ 2 x ULN with simultaneous ALT or AST ≥ 3 x ULN for subjects starting from a baseline normal value, or with simultaneous ALT or AST ≥ 5 × ULN for subjects starting with a higher than ULN baseline value] should always be reported to the Sponsor using a SAVER form, with the Investigator's assessment of seriousness, causality, and a detailed narrative. (FDA's Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation; July 2009; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072278.pdf). These events should be reported as soon as possible following the procedures outlined in Section 9.2 for SAE reporting.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject must perform all the evaluations included in the end of treatment per the Schedule of Events in Appendix 17.1. In addition, if the subject is HBV positive, HBV replication must be

tested and if active replication is discovered the subject must be treated per standard guidelines (not including interferon).

9.3. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 30 days of discontinuing the investigational product. Although pregnancy is not technically an adverse event, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs.

9.4. Clinical Laboratory Evaluations

Laboratory assessments will include hematology, blood chemistry, coagulation, HGF, and AFP. All testing other than hematology will be performed by a central lab. In case coagulation results from the central lab are altered due to shipment-related issues, local coagulation results may be used to determine a subject's eligibility. Hematology will be tested at the study site laboratory. For subjects living more than approximately 1 hour from the study site, a lab local to the subject's location can be considered for Cycle 1, Days 5, 9, 13, 17, and 25, for Cycle 2, Days 8 and 22, for Cycle 2+ Day 15 and for unscheduled visit hematology testing. A lab local to the subject's location can also be considered for any placebo patients who crossover to tivantinib following database lock for the extra hematology testing required during their first two months on tivantinib (see section 6.5.7).

Each local lab must be approved in advance of being used for this study by providing to the CRO **all** applicable regulatory documents (including lab normal ranges and lab certification at minimum).

- Hematology: complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count (WBC) with 5-part differential, red blood cell count (RBC), and platelet count
  The results of unscheduled hematology tests performed at a local laboratory ordered by the Investigator in order to manage a subjects' condition will be collected as a part of the safety laboratory assessment of the subject.
- Coagulation: prothrombin time, international normalized ratio, and partial thromboplastin time
- Blood chemistry: calcium, phosphorus, magnesium, albumin, sodium, potassium, chloride, glucose, serum creatinine, uric acid, total protein, and blood urea nitrogen (BUN), AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin, and gamma-glutamyl transpeptidase (GGT)

- Serum pregnancy test for female subjects of childbearing potential
- AFP blood sample
- HGF blood sample
- HBsAg, HBeAg, HBV DNA, delta virus, HCVAb

9.5. Vital Signs

Height (on screening visit only), weight, vital signs (to include blood pressure, heart rate, respiratory rate, and temperature [oral, axillary or tympanic]) and ECOG Performance Status (Appendix 17.2). Subject is to be in the same position each time vital signs are assessed (i.e., supine, etc) over the course of the study.

9.6. Electrocardiograms

Triplicate ECGs should be conducted at the screening visit, at Cycle 1 Day 1 and at Cycle 1 Day 21. A 12-lead ECG (single) should be conducted at Cycle 2 Day 1, and the end of treatment visit. Additional ECG(s) may be conducted if clinically indicated. Bradycardic subjects with a heart rate ≤ 50 beats per minute during the first cycle should have an ECG done on Day 1 of every cycle.

For patients that were crossed from placebo to tivantinib following database lock, a single ECG must be performed prior to the first dose of tivantinib and again on Day 1 of the following cycle (one month after starting dosing with tivantinib). If heart rate is ≤ 50 beats per minute (bpm) then an ECG will also be performed on Day 1 of every cycle thereafter.

9.7. Physical Findings

Complete physical examination of the major body systems.

9.8. Other Safety Assessments

Not applicable.

10. OTHER ASSESSMENTS

10.1. Patient-Reported Outcomes (PROs)

Patient-reported outcomes (PROs) will be evaluated based on the administration of:

a) The Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) scale

b) The EuroQol 5-D

10.1.1. Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep)

The FACT-Hep contains 4 general subscales (total 27 items) measuring physical well-being (PWB), functional well-being (FWB), social well-being (SWB), emotional well-being (EWB), and a hepatobiliary-cancer symptom-specific subscale – the 18-item Hepatobiliary Additional Concerns Subscale (HCS). Further, within the overall 45-item FACT-Hep, combining 3 pain-related items – "I have pain" (PWB item 4), "I have pain in my back" (Additional Concerns item 8), and "I have discomfort/pain in my stomach area" (Additional Concerns item 18) – yields a 3-item FACT Hepatobiliary Pain Symptom Index (FHSI-3). Also, within the 45-item FACT-Hep, combining 8 items that measure specific symptoms and side effects yields the 8-item FHSI-8.[24] All questions have 5 possible scores for responses, ranging from 0 = not at all to 4 = very much; higher scores represent more favorable patient-reported outcomes.

Specifically, 4 specific summary scores will be evaluated based on the FACT-Hep scale

- FHSI-3 pain subscale score
- FHSI-8 symptom index score
- EWB score
- FACT-Hep total score

10.1.2. EUROQOL 5-D (EQ-5D)

The EQ-5D, a generic measure of standardized health status, consists of:

(i) The EQ-5D descriptive system which contains 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

(ii) The EQ-5D Visual Analog Scale (VAS)[25]

For the former, each of the 5 dimensions has 3 responses: no problem, some problems, and severe problems. The set of responses to each of the 5 dimensions will yield a 5-digit number which represents a unique health state (for example, 11111 represents the best possible response to all 5 dimensions); these will be converted into a single summary weighted index based upon the EQ-5D algorithm[25] (further details will be provided in the SAP). Based upon the EQ-5D VAS assessment, a measure of overall self-rated health status[25] will be generated. Finally, the distribution of responses on the EQ-5D descriptive system will be used to generate a health profile,[25] in particular, the proportion of subjects

with “extreme problems” on each dimension. All of the EQ-5D analyses will be conducted independent of treatment group, i.e., on pooled data, without any comparison across treatment groups, by baseline, on-study, and end of treatment assessment only (further details will be provided in the SAP).

10.1.3. Hospitalization (all-cause and HCC-related)

Time-to-hospitalization, for any cause and for reasons related to HCC, will be evaluated. Additional details including length of stay (based on dates of admission and discharge), primary reason for hospitalization, and subject discharge status (death, nursing home, home, or other facility) will be captured on an electronic CRF. Further details will be provided in the SAP.

10.1.4. Analgesic, Diuretic, and Antibiotic Use

Based on concomitant medication records and a pre-specified list of analgesics, diuretics, and antibiotic use will be captured including dates of use. The use of analgesics, diuretics, and antibiotics (for the one week preceding each scheduled visit) will be compared across treatment groups in order to ensure that the patient-reported pain endpoint is not confounded by differential use of analgesics, diuretics, and antibiotics across treatment groups. Details will be provided in the SAP.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set will include all randomized subjects.

11.1.2. Per-Protocol Analysis Set

The Per-Protocol Analysis Set will include all subjects in the ITT analysis set who meet all of the following criteria:

- No major violation occurs in the eligibility criteria for randomization
- Completion of at least one cycle of treatment

Major violations of eligibility criteria will be defined and documented in a memo prior to the unblinding of the database.

11.1.3. Safety Analysis Set

The Safety Analysis Set will include all subjects who received any amount of study drug.

11.1.4. Patient-Reported Outcome (PRO) Analysis Set

The PRO Analysis Set will include all subjects in the ITT analysis set who complete the relevant PRO assessment at screening, at least partially in a manner that permits imputation of missing responses. Further details will be provided in the SAP.

11.1.5. Biomarker Analysis Set

The Biomarker Analysis Set will include all subjects who received at least one dose of study drug and had at least one pre-dose and at least one post-dose biomarker assessment.

11.1.6. Pharmacogenomic Analysis Set

The Pharmacogenomic Analysis Set will include all subjects for whom CYP2C19 genotyping was done at the central genotyping designated laboratory.

11.2. General Statistical Considerations

The randomization will be stratified by vascular invasion (present or not), extra-hepatic spread including distant metastasis and/or involved regional or distant lymph nodes (present or not, using RECIST 1.1 criteria, but regional nodes are considered involved if $\geq$ 20 mm in shortest diameter), and AFP (less/equal or greater than 200 ng/mL).

Summary statistics will be presented as follows. For continuous variables, number of available observations (n), mean, standard deviation (SD), median, and range will be provided. The distribution by a clinically relevant discretization also will be provided. For categorical variables, the number and percentage in each category will be displayed.

In August 2013, following a higher than expected incidence of neutropenia-related adverse events, the study DMC evaluated all available data including preliminary pharmacokinetics, and recommended the reduced starting dose of 120 mg BID. Therefore the 120 mg BID regimen will be the intended dose regimen should marketing approval be granted.

The subjects will need to be grouped to 2 cohorts: the 120 mg cohort (all subjects who are randomized to a starting dose of 120mg BID versus Placebo) and the 240 mg cohort (all subjects who are randomized to a starting dose of 240mg BID versus Placebo). Data from subjects in the 120 mg cohort will be used for the primary analysis of efficacy regarding the potential marketing approval of the 120 mg BID dose regimen.

Formal efficacy analyses will be performed using only the 120 mg cohort. The primary analysis will use the ITT Analysis Set, while some of the descriptive analysis will use the Per-Protocol Analysis Set. Safety analysis will be performed using the Safety Analysis Set. The data from the 240 mg cohort will be viewed as a pilot study where all analyses of those data will be descriptive.

The primary analysis of the primary efficacy endpoint of OS will be based on the ITT Analysis Set for the 120 mg cohort. Comparison of OS between treatment groups will be based on the stratified log-rank test and the hazard ratio (HR). The HR will be estimated using the stratified Cox proportional hazards regression model.

The efficacy analyses will be performed according to the treatment groups assigned at randomization. For safety analyses, subjects will be analyzed according to actual treatment received. As with efficacy, the evaluation of safety will be performed separately for the 120 mg cohort and the 240 mg cohort.

Assessments of change from baseline to post-baseline or the ratio of post-baseline to baseline will include only those subjects with both baseline and post-baseline measurements. The last assessment taken before the first dose of study drug will be used as the baseline, unless otherwise specified.

In general, missing or drop out data will not be imputed for the purpose of data analysis. Since any statistical approach for handling missing data would rely on untestable assumptions that likely would be invalid, the focus will be to implement creative approaches to prevent missingness[27].

11.3. Study Population Data

Subject disposition will be summarized by dose cohort for each randomized treatment group and in total for the different Analysis Sets. The ITT Analysis Set will be used for the summary.

The demographic and baseline characteristics such as baseline ECOG disease status will be summarized descriptively by dose cohort and treatment group for the ITT, Per-Protocol, and Safety Analysis Sets.

Study drug exposure (amount and duration) will be summarized using descriptive statistics by dose cohort and treatment group for the Safety Analysis Set.

11.4. Efficacy Analyses

As stated in section 11.2, formal analyses of efficacy endpoints will be performed only for the 120 mg cohort as this is now the intended dose regimen should marketing approval granted.

11.4.1. Primary Efficacy Analyses

The overall survival (OS) will be the primary efficacy endpoint for this study. OS is defined as the time from the date of randomization to the date of death from any cause. If there is no death reported for a subject before the cut-off date for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

The analyses for OS will be based on the ITT analysis set. The distribution of OS will be compared between the two treatment groups using a stratified log-rank test adjusting for vascular invasion, extra-hepatic spread and AFP at one-sided 2.5% significance level.

The distribution function of OS will be estimated using the Kaplan-Meier method. The median OS along with the 95% confidence intervals by Brookmeyer and Crowley will be presented by treatment group. The stratified Cox proportional hazards regression model in which the treatment group is included as model factor will be used to estimate the hazard ratio (HR) of OS, along with the 95% confidence interval. SAS PROC LIFETEST and PROC PHREQ will be used in the analysis.

Two analyses are planned for OS as follows:

1) An interim analysis at the time when at least 154 (64% of the 257) deaths are documented in the 120 mg cohort
2) The final analysis for OS when at least 257 deaths have been recorded in the 120 mg cohort (expected around 38.0 months from the date of the first subject randomized to the 120 mg cohort), if the trial continues after the interim analysis

The type I error rate for these analyses in the 120 mg cohort will be controlled by using a one-sided 2-look group-sequential design. Specifically, Lan DeMets method (Lan 1983) with O'Brien-Fleming type stopping boundary (as implemented in EAST 5.0) will be used to maintain the cumulative type-I error rate at 2.5%.

11.4.2. Secondary Efficacy Analyses

The secondary efficacy endpoints include PFS in the ITT population in the 120 mg cohort.

PFS is defined as the time from the randomization date to the date of first objective documentation of disease progression via central review per RECIST, Version 1.1, or death resulting from any cause, whichever comes first. Objective documentation of disease progression is based upon tumor assessments recorded as "progressive disease" for "overall tumor assessment".

The rules for censored cases of PFS are defined as follows:

- Subjects who are alive and progression-free at the time of the analyses will be censored at the date of the last tumor evaluation

- Subjects who discontinue from the study prior to the first post-baseline tumor evaluation for a reason other than disease progression or death will be censored at the date of randomization
- Subjects who discontinue from the study due to reasons other than disease progression or death (i.e. considered not to have died or progressed) will be censored at the date of the last tumor evaluation
- Subjects who start other anti-cancer therapy prior to disease progression will be censored at the date of the last tumor evaluation prior to starting new anti-cancer therapy
- Subjects who progress or die after missing ≥2 consecutive scheduled tumor assessments will be censored at the date of the last tumor evaluation prior to progression or death
- Subjects who have surgical intervention for curative reason without confirmation of progression will be censored at the date of the last tumor evaluation prior to their surgical intervention
- Subjects without baseline tumor assessment will be censored at the date of randomization

Similarly to the primary efficacy analysis, comparisons of PFS between treatment groups will be made using the stratified log-rank test based on the ITT Analysis Set in the 120 mg cohort. The median PFS will be calculated based on Kaplan-Meier estimates and the corresponding 95% confidence interval (CI) will be calculated using the method provided by Brookmeyer and Crowley. These statistics will be calculated using PROC LIFETEST in SAS software. In addition, the stratified Cox proportional hazards regression model with the treatment group as the only factor will be performed to obtain point estimates of hazard ratios and two-sided 95% CI based on the ITT Analysis Set.

To control for the family-wise type I error rate (FWER) for primary and secondary efficacy endpoints, the stagewise hierarchical group-sequential testing strategy is implemented (the details are specified in the Statistical Analysis Plan). The primary assessment of OS in the ITT population will be evaluated first, and if significant at a one-sided alpha of 0.025, a statistical evaluation of PFS in the ITT population will be performed.

11.5. Exploratory Analyses

Exploratory analyses in the 120 mg cohort include exploratory efficacy analyses and patient reported outcome (PRO) analysis.

11.5.1. Exploratory Efficacy Analyses

The exploratory efficacy analyses for the 120 mg cohort include additional supportive analyses and subgroup analyses of the primary and secondary endpoints, and analyses of exploratory efficacy endpoints.

11.5.1.1. Additional Supportive Analyses

As a sensitivity analysis, unstratified log-rank test and unstratified Cox proportional hazards regression analysis without adjusting for stratification factors will be performed only for the 120 mg cohort using the ITT Analysis Set for time-to event endpoints OS, PFS and TTP. Any additional analysis will be added to the Statistical Analysis Plan.

All primary and secondary analyses, including the supportive analyses specified above, will also be repeated for the Per-Protocol Set.

11.5.1.2. Subgroup Analyses

The analyses specified in Sections 11.4.1 and 11.4.2 will be performed by the following subgroups:

- Vascular invasion: Present, Not
- Reason of discontinuation of prior systemic therapy: PD, Other
- Prior systemic therapy duration: ≤ 60 days, > 60 days
- Extra-hepatic spread at baseline: Present, Not
- ECOG at baseline: 0, 1
- AFP at baseline: less/equal to 200 ng/mL, greater than 200 ng/mL
- Hepatitis: HBV positive, HCV positive (excluding HBV positive), HBV negative and HCV negative
- AST/ALT at baseline: below ULN, Between ULN and 3xULN, above 3xULN
- Platelets at baseline: $<100 \times 10^9$/L, $\geq 100 \times 10^9$/L
- Best response to prior sorafenib therapy: PD, Other
- Age group: less than 65 yrs, greater than/equal to 65 yrs
- Race: Caucasian, Black, Asian, American Indian or Alaskan Native, Native Hawaiian/Pacific Islander, Other
- Sex: Female, Male
- CYP2C19 inhibitor use: Yes, No
- CYP3A4 inhibitor use: Yes, No
- Region: Asia, US/Canada/Australia/West Europe, Rest of World

11.5.1.3. Analysis of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and type of progression, by central, independent radiology review among all subjects treated with tivantinib compared to placebo.

ORR is defined as the proportion of subjects whose post-baseline tumor responses include at least one complete response (CR) or partial response (PR).

The ORR for each treatment group will be estimated based on binomial distribution. The asymptotic 95% confidence intervals for the ORRs will be calculated based on normal approximation. The comparison of ORRs between treatment groups and the odds ratio estimate will be based on logistic regression model with logit link function. The Wald statistic will be used to obtain the p-value of the test and the 95% confidence limit of the odds ratio. The analyses will be performed using PROC LOGISTIC in SAS software.

DCR is defined as the proportion of subjects whose post baseline tumor responses include at least one CR, PR, or SD.

The DCR for each treatment group will be estimated based on binomial distribution. The asymptotic 95% confidence intervals for the DCRs will be calculated based on normal approximation. The comparison of DCRs between treatment groups and the odds ratio estimate will be based on logistic regression model with logit link function. The Wald statistic will be used to obtain the p-value of the test and the 95% confidence limit of the odds ratio. The analyses will be performed using PROC LOGISTIC in SAS software.

TTP is defined as the time from the date of randomization to the date of the first objective documentation of disease progression per RECIST, Version 1.1, criteria. The rules for censored cases are defined as follows:

- Subjects who are alive and progression-free at the time of the TTP analyses will be censored at the date of the last tumor evaluation
- Subjects who died or discontinue from the study due to reasons other than disease progression will be censored (i.e., considered not to have progressed) at the date of the last tumor evaluation
- Subjects who died or discontinue from the study prior to the first post-baseline tumor evaluation for a reason other than disease progression will be censored at the date of randomization
- Subjects who start other anti-cancer therapy prior to progression will be censored at the date of the last tumor evaluation prior to starting new anti-cancer therapy
- Subjects who progress after ≥ 2 consecutive missed visits will be censored at the date of the last tumor evaluation prior to progression
- Subjects who have surgical intervention for curative reason without confirmation of progression will be censored at the date of the last tumor evaluation
- Subjects with no baseline tumor assessment will be censored at the date of randomization

Similarly to the primary efficacy analysis, comparisons of TTP between treatment groups will be made using the stratified log-rank test based on the ITT Analysis Set in the 120 mg cohort. The median TTP will be calculated based on Kaplan-Meier estimates and the corresponding 95% confidence interval (CI) will be calculated using the method provided by Brookmeyer and Crowley. These statistics will be calculated using PROC LIFETEST

in SAS software. In addition, the stratified Cox proportional hazards regression model with the treatment group as the only factor will be performed to obtain point estimates of hazard ratios and two-sided 95% CI based on the ITT Analysis Set.

Type of progression will analyze reasons for progression (including clinical, radiographic due to new lesions or new vascular invasion or increase in tumor dimensions) in the ITT.

11.5.2. Other Assessments

11.5.2.1 Patient Reported Outcomes: FACT-Hep

The FACT-Hep Total Score is the sum of the scores of 45 items on the questionnaire.

The FACT-Hep Total Score ranges from 0-180. The Emotional Well-Being (EWB) Subscale is the sum of the scores of GE1, GE2, GE3, GE4, GE5, and GE6. The Emotional Well-Being Score ranges from 0-24. The FHSI-8 score is the sum of 8 items (within the FACT-Hep) representing various symptoms and side effects; the FHSI-8 score ranges from 0-32. The FHSI-3 Pain Subscale Score is the sum of 3 pain items (within the FACT-Hep) and its score ranges from 0-12. The FACT-Hep total score, Emotional Well Being score, FHSI-8 score, and the FHSI-3 Pain scores will be analyzed as exploratory endpoints.

All analyses on the FACT-Hep total score, the FACT-Hep EWB score, the FACT-Hep FHSI-3 score, and the FACT-Hep FHSI-8 score will be conducted in the 120 mg cohort separately for (i) all subjects, (ii) subjects with score < median of the corresponding subscales, and (iii) subjects with a score ≥ median of the corresponding subscales, compared across treatment groups, in all analyses (i) to (iii).

For each evaluation of treatment group differences on the FHSI-3 Pain scores, appropriate statistical adjustment for measured use of concomitant analgesics, diuretics, and antibiotics will be applied; details will be provided in the SAP.

The study and control arms will be compared as follows:

1. Frequency distribution of change from baseline to each visit, for each of the FACT-Hep total score, the FACT-Hep EWB score, the FACT-Hep FHSI-3 score, and the FACT-Hep FHSI-8 score.
2. In terms of time-to-deterioration from baseline, where subject-level deterioration for each score is defined as follows:
   - FHSI-3 pain subscale score decrease ≥ 2
   - FHSI-8 symptom index score decrease ≥ 4[26]
   - EWB score decrease ≥ 3
   - FACT-Hep total score decrease ≥ 10

   Note: Kaplan-Meier analysis and stratified Cox proportional hazards regression analyses will be performed for each of the time-to-deterioration analyses noted above. Further details including alternative rules for censoring, will be provided in the SAP.

3. In terms of the cumulative distribution function (CDF) of change from baseline, for each visit (where at least 25% of randomized subjects have non-missing observations) by treatment group, for the FACT-Hep total score, the FACT-Hep Emotional Well Being (EWB) score, the FACT-Hep Pain Symptom Index (FHSI-3) score, and the FACT-Hep FHSI-8 score. Further details on appropriate statistical tests for comparisons of the CDF curves across treatment groups will be provided in the SAP.

For relevant analyses on the FHSI-3 pain subscale, analgesic use, diuretic use, and antibiotic use in the one-week preceding the assessment of the FACT-Hep will be treated as covariates in comparison of treatment groups, using stratified Cox Proportional Hazard modeling (as in [i] above). Further details of all analyses, including handling of missing data, will be provided in the SAP.

11.5.2.2. Patient Reported Outcomes: EQ-5D

The EQ-5D analyses will be conducted independent of treatment group, i.e., on pooled data, without any comparison across treatment groups, by baseline, on-study, and end of treatment assessment only. If data warrants, the EQ-5D health status will be summarized overall (i.e. for combined treatment groups, without any comparisons across treatment groups), by disease state (baseline, pre-progression, post-progression, and during Grade 2 - 4 adverse events). Specifically, EQ-5D will be summarized for all subjects for each of the above disease states defined as follows:

- For baseline, the Cycle 1 Day 1 assessment will be used
- For the pre-progression disease state, the worst EQ-5D score (over potential multiple assessments of EQ-5D prior to progression, and not including any assessments attributable to grade 2-4 AEs, see below) will be summarized
- For the post-progression disease state, the end-of-treatment visit-based assessment (where end of treatment is attributable to progression) will be summarized
- For the disease state representing Grade 2 - 4 adverse events, the worst assessment following the AE will be summarized
- In the case of multiple Grade 2 - 4 AEs, the worst EQ-5D score immediately following the event will be selected.

Repeated or unscheduled tests will not be summarized for each scheduled visit, but will be included for summaries of maximum and minimum post-treatment values. All scheduled visits having a minimum of 5% of the total number of randomized subjects with non-missing observations will be summarized. Further details will be provided in the SAP.

11.5.2.3. Health Care Utilization Analyses

Spontaneous utilization of health care services unrelated to protocol-mandated visits: emergency room use, outpatient clinic use, laboratory tests (unscheduled), and hospitalization will be assessed. A separate case report form (CRF) has been developed

for this purpose. In the 120 mg cohort, the treatment groups will be compared in terms of time-to-hospitalization (all-cause and HCC-related), using Kaplan-Meier and stratified Cox proportional hazard model approaches. The median time-to-hospitalization (all-cause and HCC-related) along with the 95% confidence intervals by Brookmeyer and Crowley will be presented by treatment group. The stratified Cox proportional hazards regression model in which the treatment group is included as model factor will be used to estimate the hazard ratio (HR) of time-to-hospitalization (all-cause and HCC-related), along with the 95% confidence interval. Further details will be provided in the SAP.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

11.6.1. Pharmacokinetic Analyses

Pharmacokinetics of tivantinib and its four major metabolites will be evaluated using the respective plasma concentrations by using Population pharmacokinetic analysis. This will be conducted separately in the 120 mg cohort, with possible pooling of data from other clinical studies of tivantinib. This analysis will not be part of the statistical analysis plan for this study. The results will be provided in a separate pharmacokinetics report outside the clinical study report (CSR) for this study. For the CSR, purpose concentration of tivantinib and its metabolites will be listed.

11.6.2. Pharmacodynamic/Biomarker Analyses

If possible, exploratory analysis may be conducted to examine relationships of tivantinib exposure to circulating levels of HGF and clinical outcome measures. These analyses may be presented in a separate report. Additionally, the relationship between exposure and response may be explored as a part of the population pharmacokinetic/ pharmacodynamic analysis. These analyses may be provided in a separate report.

Additionally, for biomarkers, HGF and AFP change from baseline at each visit will be calculated and will be summarized by visit and treatment arm. Maximum change from baseline will also be calculated for individual subjects and will be summarized by treatment arms. Descriptive statistics including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be computed by evaluation time for biomarkers.

11.6.3. Pharmacogenomic Analyses

The relationship between common genetic variants in CYP2C19 (i.e., extensive metabolizers vs poor metabolizers) on select safety endpoints will be explored. Details of these analyses will be provided in the SAP. Additionally, the relationship between CYP2C19 genotype and exposure and response may be explored as a part of the population pharmacokinetic/pharmacodynamic analysis.

11.7. Safety Analyses

Safety analysis will be performed by dose cohort and treatment group within dose cohort.

11.7.1. Adverse Event Analyses

Treatment-emergent AEs (TEAEs) are defined as those AEs that occur, having been absent before the study, or worsen in severity after the initiation of study treatment administration and start no later than 30 days after the end of treatment.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and assigned grades based on NCI CTCAE, Version 4.03.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst CTCAE grade, system organ class, and preferred term, with a breakdown by dose cohort and treatment group. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study drugs.

A by-subject AE (including treatment-emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, CTCAE grade, and relationship to study drug will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study drugs, will be listed.

11.7.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results, as well as for the change from baseline, by scheduled time of evaluation and by dose cohort and treatment group using the Safety Analysis Set. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the End of Treatment visit. Abnormal laboratory results will be graded according to NCI CTCAE version 4.03, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by-treatment group the two-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.7.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements, as well as for the change from baseline, by scheduled time of evaluation and by dose cohort and treatment group using the Safety Analysis Set. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the End of Treatment visit.

11.7.4. Electrocardiogram Analyses

The ECG findings (normal/abnormal and outliers) will be summarized by dose cohort and treatment group and visit/timepoints. A listing of ECG examination data will also be provided.

11.7.5. Physical Finding Analyses

The abnormal findings from the physical examinations at baseline will be summarized by dose cohort and treatment group. A listing of new or worsening abnormalities found at physical examination will also be provided.

11.7.6. Other Safety Analyses

Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (most recent version). Number and percentage of subjects taking concomitant medications will be summarized by dose cohort and treatment group.

Subgroup analyses of adverse events will also be performed using subgroups based on sex, age, ECOG status, CYP2C19 genotyping, and CYP3A4 inhibitor usage.

11.8. Interim Analyses

A single interim efficacy analysis will be performed for the 120 mg cohort when about 60% of the planned number of events (i.e., 154 events) are observed in that cohort. The primary intent of the interim analysis is to stop early for superior efficacy. The stopping criteria for efficacy will be based on the α- spending function methodology of Lan-DeMets family with O'Brien-Fleming parameters as shown in Table 11.1 below. At the interim analysis of OS, the trial would be stopped to reject null hypothesis if an observed z-statistic is greater than 2.669 if the interim analysis is based on exactly 154 events. The probability of stopping for superior efficacy is approximately 0.4% under the null hypothesis (i.e., no difference in relative risk between the two treatment arms, and approximately 44.1% under the alternative hypothesis that the true hazard ratio is 0.65). If the study meets criteria of superior efficacy at the interim analysis and, the Data Monitoring Committee (DMC) recommends termination of the trial, then selected representatives from the Sponsor may request a consultation with Health Authorities prior to reaching their final decision about whether to accept the DMC recommendation; the study team will remain blinded during this process. A dedicated Data Analysis Group (DAG) at an independent CRO (separate CRO from the one for the final data analysis) will perform the interim analysis. The composition of the DAG will be described in a Data Monitoring Committee (DMC) charter. The actual identities of the treatment assignments will only be revealed to the DMC and to this group, which supports the DMC. This group will store all files that are potentially unblinded in nature in a secure directory on a file server. The access to this directory will be limited to this group and a network administrator. Data stored in this directory would include, but not be limited to, SAS programs, SAS datasets, output produced by SAS programs, and summary documents/correspondence describing the unblinded results. The security and access to this directory will be maintained by a network administrator.

Table 11.1 Statistical Guidelines for Stopping Boundaries

Analysis Time	# of Events (OS)	Expected Time of Analysis (months)	Expected Accrual	Efficacy	
				P-value (one-sided)	Crossing Boundary (Z-score)
Interim	154	24	260	0.0038	2.669
Final	257	38	303	0.0238	1.981

It is recognized that the exact number of events at the interim analysis may not be 154. The boundaries will be updated with the actual number of events at the interim analysis.

Additionally, the interim analysis will also include analysis to explore the effects of CYP2C19 genotype and concomitant medications such as CYP2C19 inhibitors and strong CYP3A4 inhibitors on neutropenia, and also exposure response (neutropenia and neutropenia- related toxicity) relationships using population pharmacokinetics (POPPK)/PD.

11.9. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established for periodic review of unblinded safety and/or efficacy data in this study. The DMC will review all data relevant to safety (i.e., AEs, SAEs, clinical laboratory values, exposure, genotyping, and concomitant medication information on inhibitors of CYP2C19 and CYP3A4) as well as data relevant to efficacy and quality of trial conduct. The composition and tasks of the DMC are described in detail in the DMC Charter for this study.

11.10. Sample Size Determination

The efficacy analysis will be performed only for the 120 mg cohort, and thus the sample size determination is for the 120 mg cohort.

The primary endpoint of this trial is OS in the ITT. OS is defined as the time from date of randomization to the date of death due to any cause. The final analysis of OS will require 257 OS events, which is the number of OS events needed for a one-sided stratified log-rank test at 0.025 significance level to have 90% power to achieve a statistically significant difference in OS distribution when the true hazard ratio is 0.65 (i.e., when the median OS in tivantinib is 7.7 months and the median OS in placebo is 5 months, corresponding to a 54% improvement).

Approximately 303 subjects will be randomized in a 2:1 ratio into the 2 treatment arms (202 subjects in the tivantinib treatment arm and 101 subjects in the control arm) in approximately 28 months. The 257 OS events are expected to have occurred by approximately 38 months from the randomization date of the first subject in the 120 mg cohort, assuming 8 subjects/month enrollment for the first 6 months and 12 subjects/month enrollment thereafter.

The design accounts for one interim look under a 2-look group sequential design. The primary intent of the interim analysis is to address potential early termination for superior efficacy. An α-spending function according to Lan-DeMets group sequential design with

an O'Brien-Fleming type stopping boundary (as implemented in EAST version 5.3) is used to construct the stopping boundaries. The interim analysis is planned when approximately 154 (about 60%) of the 257 OS events are documented. If the interim analysis of OS is based on exactly 154 events, the efficacy boundary would be crossed if the z-statistics are greater than 2.669, according to a 1-sided nominal p-value of 0.0038 or less. The probability of termination for superiority at interim analysis is approximately 44.1% under the alternative hypothesis (i.e., HR = 0.65) and less than 0.4% under the null hypothesis. The sample size derivation is based on the following method: Survival Superiority Trials: Two Sample Test – Logrank Test: Given Accrual Duration and Enrollment Rate in the EAST version 5.3, assuming an accrual period of 28 months, enrollment rates of 8 subjects per month for the first 6 months and of 12 subjects per month thereafter, and a drop-out rate of 10%. If the DMC does not recommend early termination at time of the interim analysis, the trial will continue until the final 257 OS events are documented. The final analysis of OS will require a 1-sided nominal p-value of 0.0238 or less for the study to be positive.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The monitors and designee and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (i.e., case report forms, source data, and other pertinent documents).

The monitors are responsible for visiting sites at regular intervals throughout the study to verify adherence to the protocol (as defined in the monitoring plan); completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitors are responsible for inspecting the case report forms and ensuring completeness of the study essential documents. The monitors should have access to subject source medical records and other study-related records needed to verify the entries on the case report forms.

The monitor will communicate deviations from the protocol, SOPs, ICH GCP, and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from DSPD. Inspection of site facilities (i.e., pharmacy, drug storage areas, laboratories, etc) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Computer Systems

Appropriately validated standard computer systems will be used by the CRO involved in this study.

12.3. Data Collection

All data collected during the study will be recorded in the individual, subject specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software's "audit trail".

The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. There will be DMC reviews during the conduct of this study. The information should be entered into the eCRF within 48 hours of the visit

for the generation of the report for DMC review, and should be completed, reviewed and signed off by the Investigator.

An eCRF must be completed for each subject who signs an ICF, and undergoes any pre-screening or screening procedures. If a subject is not treated, the reason must be recorded on the eCRF.

All data generated from external sources (i.e., central laboratory, pharmacokinetic processing, pharmacodynamic processing, and genotyping laboratory) will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

The Investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications and agrees with the content.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.4. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

All adverse events (AEs) will be coded using the current MedDRA (Medical Dictionary for Regulatory Activities).

Prior and concomitant medication will be coded by WHO (World Health Organization) Drug Dictionary. AEs and concomitant medications will be coded in the latest version of both dictionaries at the time of final protocol.

12.4.1. Data Validation

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to the CRO. Data will be vetted both electronically and manually for eCRFs and the data will be electronically vetted by programmed data rules within the application, as described in the Data Management Plan. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies.

12.5. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from DSPD and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation (if kept)
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IEC/IRB and DSPD
- Records related to the Investigational Product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

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

No study document should be destroyed without prior written agreement between DSPD and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify DSPD in writing of the new responsible person and/or the new location.

12.6. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, Case Report Forms (CRFs), inventory of study product, regulatory documents (i.e., protocol and amendments, IRB/EC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records DSPD must be notified in writing and be given the opportunity to further store such records.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with DSPD and/or designee. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that ArQule and Daiichi Sankyo have had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of ArQule and Daiichi Sankyo Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by DSPD. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within five working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsors

ArQule, Inc.
One Wall Street
Burlington, MA 01803
[redacted]

Daiichi Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837
[redacted]

Daiichi Sankyo Development Limited
Chiltern Place, Chalfont Park
Gerrards Cross, Buckinghamshire SL9 0BG
United Kingdom

15.2.2. Global Medical Monitor

[redacted]
Vice President, Clinical Development
ArQule, Inc
Burlington, MA, USA
[redacted]

15.2.3. Drug Safety

Covance Safety Medical Monitor
[redacted]

15.2.4. Safety Reporting:

For sites in USA and Canada:
[redacted]

[redacted]

For sites in the European Union:

[redacted]

For sites in Asia-Pacific:

[redacted]

15.2.5. Principal Investigators

[redacted]

[redacted]

16. REFERENCES

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17. APPENDICES

17.1. Schedule of Events

Phase		Pre-Screening	Screening	Treatment							Follow-up		
Visit		Tumor Sample Collection[1]	Screening	Cycle 1			Cycle 2		Cycle 3+		End of Treatment	30-Day Safety FU	Survival FU
				D1[2]	D5, 9, 13, 17, 25	D21	D1	D8, 15, 22	D1	D15			
Tests and Procedures[3]	Window (days)		-14 to 0		±1 day		±2 days		±2 days		Within 7 days of last dose		every 3 Months ±14 days
Written informed consent		X[4]	X[5]										
Tumor sample collection (biopsy if necessary)[6]		X	X										
Medical history		X	X										
Physical examination			X[7]	X			X		X		X		
ECOG performance status			X	X			X		X		X		
Vital signs and weight, including Temperature			X	X		X	X		X		X		
HBsAg, HBeAg, HBV DNA, delta virus; HCVAb			X										
Serum pregnancy test (if applies)[8]			X								X		
Hematology[8, 9, 23]			X	X	------X------		X	X	X	X	X		
Blood chemistry and coagulation[8]			X	X			X		X		X		
Blood sample for CYP2C19[10]				X									
Blood sample for AFP analysis			X				X[11]		X[11]		X		

Phase		Pre-Screening	Screening	Treatment								Follow-up		
Visit		Tumor Sample Collection[1]	Screening	Cycle 1			Cycle 2		Cycle 3+			End of Treatment	30-Day Safety FU	Survival FU
				D1[2]	D5, 9, 13, 17, 25	D21	D1	D8, 15, 22	D1	D15				
Tests and Procedures[3]	**Window (days)**		-14 to 0		±1 day		±2 days		±2 days			Within 7 days of last dose		every 3 Months ±14 days
Blood sample for HGF analysis				X			X[11]		X[11]			X		
Blood sample(s) for PK				X		X	X[12]		X[12]					
Optional blood sample for PK when subjects are on strong CYP2C19/ CYP3A4 inhibitors or experienced grade ≥2 neutropenia			X[13]											
Child-Pugh assessment			X	X			X		X			X		
Patient-Reported Outcomes: FACT-Hep and EQ-5D				X			X		X			X		
12-Lead electrocardiogram (ECG) - triplicate			X	X[14]		X[14]								
12-Lead electrocardiogram (ECG) - single							X[15]		X[15]			X		
Tumor Assessment			X[16]	X[17]								X[18]		
Optional Tumor sample collection[19]						X						X		
Concomitant medications			X[20]	----------X----------								X		
Adverse events				----------X----------								X	X[21]	
SAEs (relating to pre-screening or screening procedure)		X	X											

Phase		Pre-Screening	Screening	Treatment								Follow-up		
Visit		Tumor Sample Collection[1]	Screening	Cycle 1			Cycle 2		Cycle 3+		End of Treatment	30-Day Safety FU	Survival FU
				D1[2]	D5, 9, 13, 17, 25	D21	D1	D8, 15, 22	D1	D15			
Tests and Procedures[3]	**Window (days)**		**-14 to 0**		**±1 day**		**±2 days**		**±2 days**		**Within 7 days of last dose**		**every 3 Months ±14 days**
Drug dispensing / administration approval[22]				X			X		X				
Drug collection/Treatment Compliance							X		X		X		
Randomize (R) /Deactivate (D) Subject				R							D		
Telephone call													X

1. Tumor biopsy, or collection of existing tumor samples, takes place before screening (even while or before the subject is on sorafenib) and requires specific consent. Assessment of MET must be performed by the central authorized laboratory, and the result will be communicated to the Investigator's staff if/when the subject experiences documented tumor progression or intolerance to sorafenib
2. Calculated from the first day of dosing of the assigned treatment. All assessments on C1D1 to be done prior to first dose (other than the PK and AE)
3. Unscheduled procedures performed because of clinical considerations are to be recorded
4. The pre-screening consent portion is only for the purpose of collecting the biopsy/tumor samples and medical history; signature of the full consent will be needed if subject is deemed eligible by the MET status
5. Must be obtained before any study related procedures (even earlier than 14 days prior to enrollment; does not have to be repeated unless ICF is updated)
6. MET expression results will be communicated to the Investigator's staff if/when the subject experiences documented tumor progression or intolerance to sorafenib. If sample is deemed to be MET-Low, tumor samples from a new biopsy (if safe for the subject) can be submitted for MET evaluation within 28 days from the communication of the results to the site. If biopsy provides a MET-High sample, the subject will be eligible for the study and must start screening procedures (e.g. labs, vital signs, etc.) as soon as possible but no later than 14 days from the communication of the MET-High result to the site. There is no need to re-do at screening if biopsy/tumor sample collection was done at pre-screening and resulted in MET High. Screening biopsy can be performed even earlier than 14 days prior to dosing
7. Height will be recorded at screening visit only
8. Refer to Section 9.4 for description of laboratory assessments. Where demanded by local regulations, pregnancy test may be required within 72 hours from randomization.

9. Hematology samples will be tested locally (either at site or at lab near the subject's location) with results reviewed by the site study team. For the first 2 cycles, results must be reviewed the same day the test is done and prior to the subject continuing to dose.
10. If not restricted by local regulation; may include optional banking of samples (per informed consent)
11. Day 1 of Cycles 2, 3, and 4
12. Day 1 of Cycles 2 and 3
13. Refer to Section 8.1. No additional sample needed if coincides with scheduled PK sampling

14 Performed at ±30 minutes from time of 1-3 hours and 4-8 hours post dose PK samples on C1D1 and at ±30 minutes from time of predose PK sample on C1D21.

15. At Cycle 2 only. However, subjects with heart rate $\leq$ 50 bpm during the first cycle will also have ECG tested at every cycle thereafter. If after database lock and study unblinding a patient originally randomized to placebo crosses over to tivantinib, they will have an ECG prior to the first dose and again on Day 1 of the following cycle. Such subjects with heart rate $\leq$ 50 bpm during the first month on tivantinib will also have ECG tested at every cycle thereafter
16. Within 21 days of randomization
17. In 8-week intervals from C1D1 until confirmed radiographic progressive disease (- refer to Section 4.2.1), subject death, or loss to follow-up. Window of ± 3 days permitted for the tumor assessment scans.
18. If not done within 14 days. Subjects who discontinue their assigned treatment for a reason other than disease progression, withdrawal of consent, death, or loss to follow-up should continue tumor evaluation visits at 8-week intervals if possible until disease progression, withdrawal of consent, death, start of subsequent anti-cancer therapy, or loss to follow-up.
19. Optional Biopsy after Day 22 and preferably before Day 30 and again at End of Treatment. FNA is not acceptable unless it can be prepared as per the lab manual.
20. Any medication the subject took within 30 days from randomization
21. Can be done either in person or over the phone
22. Hematology results must be verified prior to dispensing study drug to subject
23. If after database lock and study unblinding a patient originally randomized to placebo crosses over to tivantinib, hematology will be tested every 4 days for the first month and weekly for the second month after starting tivantinib

17.2. ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

17.3. Examples of in vivo Substrates, Inhibitors, and Inducers for specific CYP enzymes for study

CYP	Substrate	Inhibitor	Inducer
2C19	omeprazole, esoprazole, lansoprazole, pantoprazole	omeprazole, fluvoxamine, moclobemide, fluconazole, ticlopidine, rabeprazole, fluoxetine	rifampin
3A4/ 3A5	midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	rifampin, carbamazepine

*Note that this is not an exhaustive list (created May 1, 2006).

Adopted from: http://www.fda.gov/Cder/drug/drugInteractions/tableSubstrates.htm#classInhibit

Substrates for any particular CYP enzyme listed in this table are those with plasma AUC values increased by 2-fold or higher when co-administered with inhibitors of that CYP enzyme; for CYP3A, only those with plasma AUC increased by 5-fold or higher are listed. Inhibitors listed are those that increase plasma AUC values of substrates for that CYP enzyme by 2-fold or higher. For CYP3A inhibitors, only those that increase AUC of CYP3A substrates by 5-fold or higher are listed. Inducers listed are those that decrease plasma AUC values of substrates for that CYP enzyme by 30% or higher.

17.4. Liver Status – Child-Pugh Classification

Parameter	Points assigned		
	1	2	3
Ascites*	Absent	Slight	Moderate
Bilirubin, mg/dL	< 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prolonged prothrombin time, seconds ** (or INR)	1-3 (<1.7)	4-6 (1.7-2.3)	>6 (>2.3)
Encephalopathy***	None	Grade 1-2	Grade 3-4

* Ascites as per physical examination assessment (must be palpable), not per radiographic assessment, in a subject taking no more than 100 mg spironolactone (or equivalent diuretic) per day; subjects who need more than 100 mg spironolactone (or equivalent diuretic) per day to control ascites must be assigned 1 extra point.
** For subjects on anticoagulant therapy such as warfarin/heparin use the PT value and detract one point from the PT score if PT is prolonged by more than 3 seconds above the upper limit of normal.
*** Encephalopathy grades:

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Assessment as good operative risk (A) if 5 or 6 points; moderate risk (B) if 7 to 9 points, and poor operative risk (C) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics).

17.5. The Criteria Committee of the New York Heart Association.

Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

17.6. Pharmacokinetics

- Cycle 1, Day 1: two samples
  - One blood draw between 1 and 3 hours after the first dose of tivantinib/placebo
  - One blood draw between 4 and 8 hours after the first dose of tivantinib/placebo
- Cycle 1, Day 21: two samples
  - One blood draw before the morning dose of tivantinib/placebo
  - One blood draw at least one hour after the morning dose of tivantinib/placebo
- Cycle 2, Day 1: one sample
  - One blood draw before the morning dose of tivantinib/placebo
- Cycle 3, Day 1: one sample
  - One blood draw at any time after the morning dose of tivantinib/placebo

If the subject starts receiving a CYP2C19 and/or CYP3A4 inhibitor/inducer at any cycle after cycle 3, 2 blood samples *should* be collected, if possible, while the subject is on the concurrent study drug:

- One blood draw before the morning dose of tivantinib/placebo
- One blood draw at least 1 hour after the morning dose of tivantinib/placebo

If a subject experiences Grade ≥ 2 neutropenia, if possible, collect 1 pharmacokinetic blood sample at anytime during the dosing period but before any dose suspension or reduction is applied. Do not delay dose suspension or reduction.

17.7. Patient reported outcomes questionnaires information sheet – FACT-Hep and EQ-5D

Functional Assessment of Cancer Therapy Hepatobiliary (FACT-Hep) Questionnaire - Guidelines for Administration[3]

These guidelines assume that an appropriate person has been designated to facilitate the self-administration of the questionnaire.

When and how should the questionnaire be administered?

The FACT-Hep should be completed by the subject without assistance during his or her scheduled visits at the clinic. The FACT-Hep should be administered at the start of the visit, before the subject sees the physician, so that any interaction between the subject and physician will not influence the subject's responses to the questionnaire. The questionnaires should also be administered before the subject is asked about adverse experiences and concurrent illnesses, again so that any discussions of health problems do not influence the subject's responses. The FACT-Hep is to be administered on Day 1 of every cycle and at End of Treatment.

A quiet place should be provided for the subject to complete the questionnaire. It is important that the subject completes the questionnaire alone, without any advice from family members or friends who may accompany them. On average, it takes less than 10 minutes to complete the questionnaire.

Subjects must have basic fluency in the language of their country in order to complete the FACT-Hep. If a subject is not able to speak/read the language of his/her country, check if the subject has basic fluency in any of the languages in which the questionnaire is currently available and which has been approved by the sites IRB/IEC.

How should the questionnaire be introduced?

A sample script for introducing the questionnaire is given below.

"Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, please complete this questionnaire about your health. The questionnaire is easy to fill out. The instructions are on the front cover (point to them). You should read each question and then circle the appropriate number that matches your answer. Remember that this is not a test and there are no right or wrong answers. Choose the answer that best describes the way you feel. I will quickly review the questionnaire when you are finished to make sure that all of the questions have been answered. You should answer these questions by yourself. Your spouse or other family members should not help you when you answer the questionnaire. I will be nearby in case you want to ask me any questions. Please return the questionnaire to me when you have finished."

[3] These guidelines are adapted from questionnaire administration guidelines developed by the Department of Quality Assessment, New England Medical Center Hospitals

What to do if the subject asks for clarification?

Some subjects may ask the meaning of specific questions. If this happens, the staff member can assist the subject by re-reading the question for them verbatim. If the subject asks what something means, do not try to explain what the question means, but tactfully suggest that the subject use his/her own interpretation of the question. All subjects should answer the questions based on what they think the questions mean, or the study results may be biased.

Questionnaire completion:

When the subject returns the questionnaire, check that all of the questions have been answered. If the questionnaire is not complete, point out to the subject that some of the questions were not answered. If the subject does not quickly volunteer to answer these items, ask him/her whether she had any difficulty completing the questionnaire. If the subject says that he/she had trouble understanding a question, ask him/her why he/she had difficulty with that item. Re-read the question for him/her verbatim, but do not attempt to explain or reword the question, as explained before. If the subject is still unable to answer the question, accept the questionnaire as is.

Some subjects may be confused by the response choices. They may want to respond with "I don't know" or some other response choice that is not available. If this happens, try to help the subject choose one of the response categories by saying something like: "I know that it may be difficult for you to choose an answer, but which of these answers do you think comes closest to the way that you are thinking or feeling?" If the subject still cannot select an answer, accept the questionnaire as is.

Occasionally, subjects may not report having difficulty with a question or the response choices, but still may hesitate or refuse to answer an item or items. If this happens, accept the questionnaire as is.

If a subject asks for interpretation of his/her responses or asks for his/her scores on the questionnaire, tell him/her that you are not trained to score or interpret the questionnaire. Emphasize that their answers will be kept confidential.

Completed questionnaire:

Thank the subject once he/she has completed the questionnaire and you have checked it for completeness.

FACT-Hep (version 4) Questionnaire

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐						
GS7	I am satisfied with my sex life	0	1	2	3	4	

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

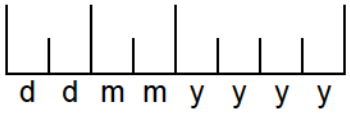
	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C1	I have swelling or cramps in my stomach	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
Hep 1	I am unhappy about a change in my	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued.....	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills.....	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach	0	1	2	3	4

Patient Reported Outcomes (PRO) Questionnaire Information Sheet – FACT-Hep

Instructions:
- This information sheet is to be completed by the study nurse/investigator.
- This information sheet must be completed for all subjects at each visit in which the protocol requires Patient-Reported Outcome assessment, whether or not the questionnaire has been completed by the subject.
- When the subject returns the questionnaire
  - Complete the information sheet.
  - Please check that the subject has answered all questions and no question has more than one answer.

1. Was the questionnaire provided to the subject at this visit? ☐1 No ☐2 Yes
   If YES, continue and answer Q. 2-4
   If NO, go to Q. 5

2. Date questionnaire answered



3. Was the questionnaire answered prior to clinical examination? ☐1 No ☐2 Yes

4. Were all questions answered? ☐1 No ☐2 Yes
   If YES, stop
   If NO, continue

5. If No, specify reason questionnaire was not answered:

☐ Subject was on-site but felt too ill

☐ Subject refused to complete questionnaire for reason other than illness

☐ Subject did not keep appointment- If this is the reason and the visit was rescheduled, answer Q.6

☐ Questionnaire not administered (although the subject was on-site) due to institution error- If this is the reason. Note that if the questionnaire was not administered due to institution error, no attempt can be made to subsequently administer the questionnaire via telephone, email, direct mail or other means, once the subject has left the site, on that visit.

☐ Other, please specify: _____

6. If subject did not keep his/her appointment or questionnaire not administered due to institutional error:

	No	Yes
Was the questionnaire completed at a rescheduled visit that occurred within 7 days of the originally scheduled visit day? If NO, stop If YES, continue Note: the questionnaire must be completed in person at the re-scheduled visit	☐	☐

Date questionnaire was completed at the rescheduled visit: | | | | | | | | |
d d m m y y y y

Patient Reported Outcomes (PRO) Questionnaire Information Sheet – EQ-5D

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

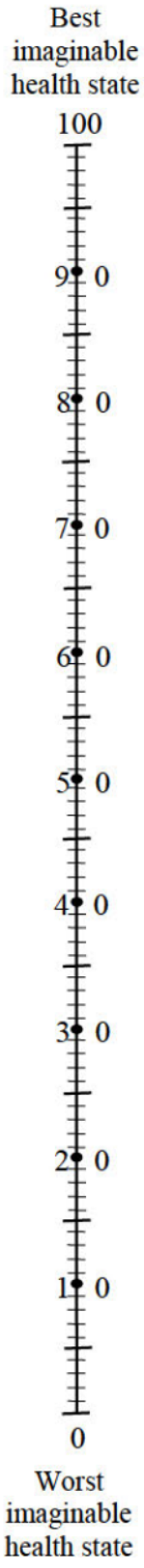
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



17.8. Hospitalization Sub-Form

	Hospitalization #1	**Hospitalization # 2**	**Hospitalization # 3**
Date and Time of Admission	Date: DD/MM/YYYY	Date: DD/MM/YYYY	Date: DD/MM/YYYY
Final Adjudicated Reason for Hospitalization	Check ONE: - Grade ≥ 3 neutropenia/fever - Rash/Hand-foot syndrome - New/metastatic malignancy (specify site) - Spontaneous Bacterial Peritonitis/other infection (specify) - Uncontrolled ascites - Other (specify)____		
Nature of hospitalization	Check ONE - Urgent/Emergency - Scheduled/Planned - Prolongation of existing hospitalization		
Date of Discharge	Date: DD/MM/YYYY	Date: DD/MM/YYYY	Date: DD/MM/YYYY
Subject Discharged to:	Check ONE: - Home w/out supportive nursing care - Home with supportive nursing care - Hospice - Long term care facility - Another acute care hospital - Dead - Other, specify_____	Check ONE: - Home w/out supportive nursing care - Home with supportive nursing care - Hospice - Long term care facility - Another acute care hospital - Dead - Other, specify_____	Check ONE: - Home w/out supportive nursing care - Home with supportive nursing care - Hospice - Long term care facility - Another acute care hospital - Dead - Other, specify_____

1) Was the primary reason for hospitalization related to a serious adverse event (if so, complete the appropriate SAE form).

17.8.1. Outpatient Sub-Form

1) Did the subject have any unscheduled (not related to study protocol) outpatient evaluations since the last visit?

YES (check all that apply):

(i) Emergency room visits NOT resulting in hospitalization

Number of visits _____

(ii) Outpatient physician visits NOT related to study protocol

Number of visits_____

(iii) Skilled nursing facility – Number of days in skilled nursing facility/nursing home _____

(iv) Home health nursing care – Number of days of home health care_____

(v) Hospice care – Number of days of hospice care _____

(vi) Diagnostic tests (NOT related to study protocol):

List tests conducted_____

(vii) Other outpatient evaluations (please specify): number of visits_____