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TITLE:	**An Extension Protocol for Subjects Who Were Previously Enrolled in Other Tivantinib (ARQ 197) Protocols**
PROTOCOL NUMBER:	**ARQ 197-299**
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SYNOPSIS

Study Title	An Extension Protocol for Subjects Who Were Previously Enrolled in Other Tivantinib (ARQ 197) Protocols
Study Number	ARQ 197-299
Study Phase	Phase 1/2/3, depending on the phase of the study into which subjects were originally enrolled.
Primary Objective	To provide subjects who participated in previous tivantinib studies that have reached their designated end-dates and who may have benefited from the treatment with access to the study drug(s).
Secondary Objective	To collect additional safety, tolerability, and efficacy information for tivantinib.
Study Design	Open label extension protocol for subjects who have participated in previous tivantinib studies. Subjects enrolled in this extension protocol will receive study drug(s) at the dose(s) and schedule(s) of the original protocols in which they were enrolled. Subjects who were previously treated with tivantinib as a single agent and who, in the opinion of the Investigator, may benefit from combination therapy will be allowed to receive combination therapy with the Sponsor's approval. The combination therapy(ies) considered must have been evaluated in prior tivantinib combination studies. The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials. Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.
Study Population	Subjects who have been treated under other tivantinib protocols that have reached their designated end-dates.
Test Product, Dose, and Mode of Administration	Subjects will receive treatment with either tivantinib (monotherapy) or tivantinib in combination with other drug(s) (combination therapy) at the same dose(s) and same schedule(s) as in the original study protocol into which they were enrolled. Subjects who were previously treated with tivantinib only and who in the opinion of the Investigator and with the Sponsor's approval may benefit from combination therapy will be allowed to receive combination therapy. Subjects who were previously enrolled in tivantinib studies but did

	not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials. The combination therapy(ies) considered must have been evaluated in prior tivantinib combination studies. The tivantinib monotherapy and combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials. Tivantinib will be administered orally, twice a day, with meals (regardless of original protocol requirements).
Duration of Treatment	For an individual subject, treatment will continue until the discontinuation criteria are reached.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophils count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ATP	adenosine triphospate
AUC	area under the time-concentration curve
BID	twice daily
bpm	beats per minute
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
C_{max}	maximum plasma drug concentration
c-MET	circulating mesenchymal-epithelial transition factor
CNS	central nervous system
CRF/eCRF	case report form/electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EM	extensive metabolizers
EP	erlotinib + placebo
ESA	erythropoietin stimulating agents
ET	erlotinib + tivantinib
FDA	Food and Drug Administration
GCP	Good Clinical Practice

ABBREVIATION	DEFINITION
G-CSF	colony stimulating factors
HCC	hepatocellular carcinoma
HGF	hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
IC_{50}	inhibitor concentration required for 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
ILD	interstitial lung disease
INR	international normalized ratio
IRB	institutional review board
Ki	inhibition constant
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
PFS	progression free survival
PK	pharmacokinetics
PM	poor metabolizers
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WBC	white blood cells

1 INTRODUCTION

Tivantinib is the most advanced representative of a newly discovered class of trans 3,4 disubstituted pyrrolidine-2,5-diones having the potential to treat cancer.[1] Tivantinib is a novel, small molecule inhibitor of c-MET receptor tyrosine kinase. The expression of c-MET is dysregulated in many types of human malignancies with overexpression of c-MET kinase, c-*MET*-activating genetic mutations, c-*MET* amplifications, and increased expression of the c-MET ligand hepatocyte growth factor (HGF). This dysregulation is implicated with a poor prognosis with greater tumor proliferation and increased angiogenesis with migration and invasion.[2,3]

The c-MET receptor tyrosine kinase is the only known high-affinity receptor for HGF, also known as scatter factor. The 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.[4,5]

Activation of c-MET results in the binding and phosphorylation of adaptor proteins such as growth factor receptor-bound-associated binder-1 (Gab-1), growth factor receptor-bound protein 2 (Grb-2), Src homology 2 domain-containing and Casitas B-lineage lymphoma progene (c-Cbl), and subsequent activation of signaling pathways, including phosphatidylinositol-3-kinase/activated protein kinase B (PI3K/Akt), focal adhesion kinase-1 (FAK), signal transducers and activators of transcription protein (STAT), and mitogen-activated protein kinase/ERK (Ras/MEK/Erk) pathways. Mesenchymal-epithelial transition factor and HGF are expressed in numerous tissues and their expression is normally confined predominantly to cells of epithelial and mesenchymal origin, respectively.[6,7] Mesenchymal-epithelial transition factor and HGF are deregulated in human cancers and may contribute to dysregulation of cell growth, tumor cell dissemination, and tumor invasion during disease progression and metastasis. Mesenchymal-epithelial transition factor and HGF are highly expressed relative to surrounding tissue in numerous cancers, and this expression correlates with poor subject prognosis.[8,9,10,11] Mesenchymal-epithelial transition factor and HGF may protect tumors against cell death induced by deoxyribonucleic acid (DNA)-damaging agents and, as such, may contribute to chemoresistance and radioresistance of tumors. Therefore, inhibitors of c-MET may be useful as therapeutic agents in the treatment of proliferative disorders.

Tivantinib selectively inhibits the inactive or unphosphorylated form of human c-MET and shows *in vitro* biochemical activity against recombinant c-MET with an inhibition constant (Ki) of approximately 355 nM. The potency of tivantinib inhibition of c-MET activity is independent of adenosine triphosphate (ATP) concentration, which suggests that tivantinib's inhibition is of noncompetitive nature. Tivantinib was profiled against 230 protein kinases, and while tivantinib inhibits c-MET kinase activity, it is not a promiscuous kinase inhibitor.

In nonclinical studies, tivantinib showed broad-spectrum *in vitro* anti-cancer activity against human tumor cell lines, including breast, colon, lung, pancreas, and gastric cancer cell lines. The potency of tivantinib in cancer cells expressing detectable c-MET in anti-proliferative assays yield IC_{50} values from 0.1 mM to 0.6 mM. The ability of tivantinib to inhibit c-MET phosphorylation correlated with its ability to inhibit growth in c-MET expressing cancer cells, thereby indicating its anti-cancer activity. In single-agent *in vivo* studies, tivantinib was

shown to be efficacious against multiple human cancer xenograft models and was well tolerated without drug-related clinical signs or deaths.

The tivantinib development program is predicated on the hypothesis that tivantinib-mediated inhibition of the c-MET pathway, either alone or in combination with other anti-cancer compounds, will be beneficial in treating malignancies.

Detailed information of the nonclinical and clinical studies is provided in the tivantinib Investigator's Brochure (IB).[12]

1.1 Overview of Clinical Experience

As of 23 Aug 2013, 30 Phase 1 and Phase 2 studies (completed and ongoing) have been conducted; refer to the IB for additional information on these studies.[12–27] One Phase 3 study in subjects with non-small cell lung cancer (NSCLC) is ongoing (ARQ 197-006) and one is completed (ARQ 197-A-U302). A Phase 3 study in subjects with hepatocellular carcinoma (HCC) is ongoing (ARQ 197-A-U303). Completed and ongoing studies have included subjects with colorectal cancer, gastric cancer, HCC, microphthalmia transcription factor associated tumors, non-central nervous system germ cell tumors, NSCLC, and pancreatic adenocarcinoma. Approximately 127 healthy subjects have received tivantinib in completed Phase 1 studies. Another 2691 subjects with cancer have been randomized in ongoing or completed Phase 1, 2, and 3 studies of tivantinib. Phase 1 and Phase 2 studies demonstrated early clinical activity of tivantinib as monotherapy and in combination with other anticancer agents (including erlotinib, sorafenib, gemcitabine, irinotecan, and cetuximab).

In all studies, subjects have been treated with assigned therapy until unacceptable toxicity, documented progression of disease, or another criterion for discontinuation has been met.

Clinical pharmacokinetic (PK) studies of tivantinib have been conducted in 14 Phase 1 studies that include 127 healthy subjects and 426 subjects with cancer. In general, AUC and C_{max} increased with an increasing dose of tivantinib, although this increase was not dose proportional.

Following human oral administration with a meal, tivantinib is rapidly and almost completely absorbed. The drug is extensively metabolized by CYP3A4 and CYP2C19 isozymes with no parent compound being detected in the urine and only traces of parent compound being detected in the feces. Tivantinib exposure is affected by the following factors: CYP2C19 genotype, history of hepatocellular carcinoma, coadministration of a CYP3A4 inhibitor, dosage form (i.e., crystalline vs. amorphous), formulation (capsule vs. tablet), and fed status during tivantinib administration.

1.1.1 Safety in Clinical Studies

Tivantinib demonstrated a manageable safety profile with adverse drug reactions of myelosuppression (including anemia, neutropenia, febrile neutropenia, thrombocytopenia, leukopenia, pancytopenia, and neutropenic sepsis) and bradycardia. The majority of drug-related adverse events (AEs) have been mild to moderate with manageable toxicities.

Myelosuppression

Myelosuppression (including anemia, neutropenia, febrile neutropenia, thrombocytopenia, leukopenia, pancytopenia, and neutropenic sepsis) has been reported in single agent and combination therapy clinical studies of tivantinib. There have been fatal outcomes for some neutropenic events. Complete blood count should be performed as advised in the protocols. Caution is advised when any CYP2C19 inhibitors and/or strong CYP3A4 inhibitors are used as concomitant therapy, and in subjects with known CYP2C19 poor metabolizer status. Dose modifications were made in the HCC studies because of higher incidences of neutropenia and febrile neutropenia, which were associated with higher drug levels in these subjects. Subjects who experience severe myelosuppression including neutropenia should be monitored more closely throughout the study, and dose modifications or interruptions should be made as specified in the original protocols. For subjects with severe neutropenia, febrile neutropenia, or neutropenic sepsis, supportive care, including use of haematopoietic growth factors and antibiotics should be considered.

Bradycardia

Bradycardia has been reported in single agent and combination therapy clinical studies of tivantinib. In general, bradycardia was most commonly reported as a nonserious adverse event. Most of these events were mild to moderate in severity (Grade 1–2.) Most subjects were asymptomatic and recovered without additional therapy, though the bradycardic effect may be prolonged. However, cases of bradycardia requiring hospitalization have been reported, and some subjects received placement of permanent pacemakers.

Subjects who appear to be at a greater risk for severe bradycardia are those with pre-existing bradycardia or sick sinus syndrome or those patients receiving beta-blocker therapy. In these patients, tivantinib should be used with caution.

Electrocardiogram (ECG) monitoring is recommended prior to initiation of tivantinib therapy and is to be repeated at any visit when a subject has a heart rate ≤50 beats per minute (bpm), or as clinically indicated. In general, heart rate and ECG should be monitored as specified in the original protocol, and dose reduction should be considered for subjects with persistent bradycardia and symptomatic hypotension.

Interstitial Lung Disease

There have been reports of interstitial lung disease (ILD) or similar events in subjects enrolled in tivantinib studies. The reported events included ILD, pneumonitis, acute respiratory distress syndrome, acute lung injury, and diffuse alveolar damage.

In the majority of the reports, tivantinib was given in combination with agents with known association with ILD, including erlotinib and gemcitabine. An association of tivantinib and ILD has not been established. However, it is recommended to investigate the cause for a marked increase in respiratory symptoms in subjects participating in tivantinib studies, particularly in Asian patients.

MONOTHERAPY STUDIES

ARQ 197-101

ARQ 197-101 was an open-label study of tivantinib in subjects with metastatic solid tumors, including renal cell carcinoma (RCC) and other c-MET-expressing tumors, that were refractory to available systemic therapies or for whom no standard effective systemic therapy existed. A total of 79 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment were disease progression (59.5%), symptomatic deterioration without evidence of progression (19.0%), and subject request (10.1%). The most common (≥ 10%) AEs were fatigue (40.5%), nausea and vomiting (27.8% each), anemia/hemoglobin decreased (24.0%), and diarrhea (21.5%). One subject had an AE (neutropenia) that led to a dose reduction, which was considered drug-related. A total of 28 of 79 (35.4%) subjects reported serious adverse events (SAEs). The most common SAEs were disease progression and dehydration, each experienced by 5 (6.3%) subjects. There were eight deaths within 30 days of the last dose of study drugs; five of the deaths resulted from disease progression. The other deaths, one each, were due to the following: cardio-pulmonary arrest, pancytopenia, and respiratory failure.

ARQ 197-103

ARQ 197-103 was an open-label study of tivantinib in subjects with advanced solid tumors who were refractory to available therapy or for whom no standard effective systemic therapy existed, including subjects with advanced prostate cancer. A total of 51 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment were progressive disease (74.5%), AE (13.7%), and symptomatic deterioration without evidence of progression (5.9%). The most common AEs were fatigue (49.0%), nausea (29.4%), anemia (27.5%), vomiting (25.5%), anorexia and constipation (23.5% each), and back pain and weight decreased (21.6% each). Seven (13.7%) subjects experienced AEs that led to treatment discontinuation. Two subjects discontinued treatment due to hyperbilirubinaemia and one subject each discontinued treatment due to chest infection, infection, fatigue, palmar-plantar erythrodysesthesia syndrome, febrile neutropenia, and nausea. Serious adverse events were reported in 22 (43.1%) subjects. Serious adverse events reported at a ≥ 5% incidence (more than one subject) were febrile neutropenia (5.9%) and disease progression (9.8%). There were five deaths during treatment or within 30 days of the last dose of study drug. All deaths were due to disease progression and were judged to be not related to study drug.

ARQ 197-114

ARQ 197-114 was an open-label study of tivantinib in cirrhotic subjects with HCC who had received not more than two prior systemic regimens. A total of 21 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment were progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST) (61.9%), clinically unacceptable toxicities (19.0%), and clinical disease progression (9.5%). The most common AEs were asthenia and neutropenia (57.1% each), anemia (52.4%), anorexia (47.6%), leukopenia (38.1%), and fatigue, edema peripheral, and diarrhea (33.3% each). In this study, AEs leading to dose reduction occurred in 4 of 21 (19.0%) subjects and all were considered

to be drug-related. One subject had a dose reduction due to neutropenia and anemia. A second subject had dose reduction due to bradycardia and dyspnea. A third subject had dose reduction due to anemia. The fourth subject had a dose reduction due to asthenia. Serious adverse events reported for more than one subject were neutropenia (three subjects), and anemia, leukopenia, and disease progression (two subjects each). Five subjects died during treatment or within 30 days of the last dose of study drug. The cause of death in one subject (septic shock) was considered related to study drug. Other deaths were considered unrelated to study drug and were the result of the following causes: disease progression (two subjects), peritoneal hemorrhage (one subject), and pneumonia (one subject).

ARQ 197-A-U157

ARQ 197-A-U157 was an open-label, randomized, two-treatment, two-period, two-way crossover, relative bioavailability study of a capsule and a tablet formulation of tivantinib in subjects with advanced solid tumors. A total of 26 subjects were enrolled in the study and 25 (96.2%) completed the 14-day crossover study phase. One subject withdrew from the 14-day crossover study phase due to disease progression, and 25 (96.2%) subjects continued in the extension phase. Bradycardia was reported for 6 of 26 (23.1%) subjects and 6 of 25 (24.0%) subjects in the cross-over and extension phases, respectively; the majority of the events of bradycardia were considered related to study treatment. Neutropenia was reported for 4 of 25 (16.0%) subjects in the extension phase; 2 subjects had neutropenia that was considered to be study-drug related. Most of the AEs were Grade 1 or Grade 2. Grade ≥3 events in the extension phase of the study included anemia, neutropenia, pneumonia, failure to thrive, haemoptysis, respiratory failure (Grade 5), lactic acidosis, and bone pain, which were experienced by 1 subject (4.0%) each, and Grade ≥3 dyspnoea, experienced by 2 subjects (8.0%). There were no SAEs reported during the crossover phase of the study. During the extension phase of the study, four subjects had SAEs considered unrelated to study treatment and three of these subjects died due to the SAEs, which included progressive disease (fatal), respiratory failure (fatal), and metastatic NSCLC (fatal). None of the deaths were considered related to study treatment.

ARQ 197-0701

ARQ 197-0701 was an open-label study of tivantinib in Japanese subjects with advanced or recurrent solid tumors who had been classified as extensive metabolizers (EM) or poor metabolizers (PM) based on CYP2C19 genotype, including 25 subjects with NSCLC, and who were refractory to available therapy or for whom no standard therapy existed. A total of 47 subjects were enrolled and treated in the study. The most common reason for discontinuing treatment was disease progression (43 subjects). Sixteen SAEs were reported in 11 subjects. Two SAEs were reported more than once: neutrophil count decreased (2 subjects) and white blood cell count decreased (2 subjects). No subjects died during the study or within 30 days of the last dose of study drug.

ARQ 197-A-U158

ARQ 197-A-U158 was a Phase 1, open-label, single-sequence, crossover study to determine the effect of multiple doses of tivantinib on the single-dose PK of omeprazole/S-warfarin/caffeine/midazolam and digoxin when co-administered with tivantinib in cancer

subjects. A total of 28 subjects were enrolled into the study. All 28 subjects completed Probe Reference Treatment and initiated tivantinib. Twenty-two (78.6%) subjects completed the Primary Objective Phase. Of the six (21.4%) subjects who discontinued from the Primary Objective Phase, three (10.7%) discontinued due to an AE, two (7.1%) due to other reasons, and one (3.6%) due to progressive disease. The most commonly reported AEs were fatigue (7 [25.0%] subjects), constipation (5 [17.9%] subjects), and vomiting (5 [17.9%] subjects). Twenty-four SAEs were reported in 13 subjects. Disease progression was reported in 4 subjects, anemia was reported in 3 subjects, and neutropenia, nausea, vomiting, and white blood cell count decreased were each reported in 2 subjects. No subject died due to an adverse event during the Primary Objective Phase of the study or during the Extension Phase. Three subjects died after completing the Primary Objective Phase and one subject died before completing the Primary Objective Phase, all due to disease progression.

ARQ 197-A-U159

ARQ 197-A-U159 was a single-blind, single-sequence study assessing the effect of tivantinib on the QTc interval in subjects with cancer. A total of 38 subjects were enrolled in the study; 1 subject was discontinued from the study prior to dosing with tivantinib. The remaining 37 (97.4%) subjects all completed the Primary Objective Phase. All of the 37 subjects entered the Extension Phase. Of these, 30 received tivantinib in combination with one or two other drugs while 7 continued on tivantinib monotherapy. Adverse events were reported in 37 (97.4%) subjects during the study. During the Primary Objective Phase, the most commonly (≥ 5%) reported AEs occurring after tivantinib dosing were fatigue (6 [16.2%] subjects), nausea (3 [8.1%] subjects), vomiting (2 [5.4%] subjects), and headache (2 [5.4%] subjects). During the Extension Phase, AEs reported by ≥ 10% of subjects included neutropenia (11 [29.7%] subjects); nausea, fatigue (9 [24.3%] subjects each); diarrhea (8 [21.6%] subjects); constipation, dyspnea (7 [18.9%] subjects each); anemia, dermatitis acneiform (6 [16.2%] subjects each); and decreased appetite, tumor pain, and alopecia (5 [13.5%] subjects each). No subject had an SAE during the Primary Objective Phase, and 4 (10.8%) subjects experienced SAEs during the Extension Phase. No subject was discontinued due to AEs during any phase of the study. No subject died during the study due to an AE. One subject died during the Extension Phase due to disease progression.

ARQ 197-004

ARQ 197-004 was an open-label study of tivantinib in gastric cancer subjects following gastrectomy, to determine exposure and progression free survival (PFS) rate in gastric cancer. A total of 31 subjects were enrolled and treated in this study. The most common reason for discontinuing treatment was progressive disease (27 [87.1%] subjects). The most common AEs were anorexia (33.3%), nausea (30.0%), alkaline phosphatase increased, anemia, and fatigue (each 23.3%), and abdominal pain, aspartate aminotransferase (AST) increased, and constipation (each 20.0%). There were no deaths during study treatment or within 30 days after the last dose of study drug.

ARQ 197-204

ARQ 197-204 was an open-label study of tivantinib in subjects 13 years of age or older with histologically or cytologically confirmed MiT tumors (alveolar soft part sarcoma, clear cell

sarcoma, or translocation associated RCC). A total of 47 subjects were enrolled and treated in the study. The most common reason for discontinuing treatment was disease progression (31 [66.0%] subjects discontinued due to progressive disease by RECIST and 7 [14.9%] subjects discontinued due to clinical progression). Of the 47 enrolled subjects, 18 received tivantinib 120 mg twice daily (BID) (capsule formulation), 21 received tivantinib 360 mg BID (capsule formulation), and 8 initiated treatment with tivantinib 120 mg BID and had their dose escalated to 360 mg BID. The most common (≥ 10%) AEs were the following: fatigue (66.0%), nausea (51.1%), vomiting (38.3%), anemia (25.5%), cough (25.5%), and bradycardia/sinus bradycardia, diarrhea, and headache (21.3% for each). Seven subjects (14.9%) experienced neutropenia. Six subjects (12.8%) experienced leukopenia. One additional event of febrile neutropenia was reported as an SAE. In this study, 2 of 47 (4.3%) subjects discontinued treatment due to an AE. One subject in the 360 mg BID treatment group experienced thrombocytopenia, and one subject in the 120 mg BID treatment group experienced diarrhea, fatigue, headache, and cough. In this study, AEs leading to dose reduction (neutropenia, leukopenia, and febrile neutropenia) occurred in 3 of 47 (6.4%) subjects. Disease progression was reported in two subjects during the treatment phase of the study. Three subjects had SAEs (febrile neutropenia, thrombocytopenia, and deep vein thrombosis) that were considered possibly related to study treatment; all three of these events resolved (the deep vein thrombosis resolved with sequelae). There were two deaths during the study or within 30 days of the last dose of study drug. Both deaths resulted from disease progression and were not attributed to study drug.

ARQ 197-205

ARQ 197-205 was an open-label study comparing tivantinib to gemcitabine in treatment-naïve subjects with unresectable locally advanced or metastatic pancreatic adenocarcinoma. A total of 43 subjects were enrolled and randomized in this study and 40 subjects received study drug. All subjects in the tivantinib group received 120 mg BID (capsule formulation) in the fasted state. The most common reason for discontinuation was progressive disease (12 [63.2%] and 13 [61.9%] subjects in the tivantinib and gemcitabine groups, respectively). Three subjects (15.8%) and 2 subjects (9.5%) in the tivantinib and gemcitabine groups, respectively, discontinued treatment due to AEs. The most common (≥ 10%) AEs were fatigue (42.1%), edema peripheral, anorexia, and ascites (26.3% for each), and nausea, abdominal pain, and blood alkaline phosphatase increased (21.1% for each). Five subjects in the gemcitabine group (23.8%) experienced neutropenia and two subjects in the gemcitabine group (9.5%) experienced leukopenia. There were no events of neutropenia or leukopenia in the tivantinib group. There were no events of bradycardia reported in this study. There were 13 subjects (32.5%), 5 (26.3%) in the tivantinib treatment arm and 8 (38.1%) in the gemcitabine treatment arm, who discontinued treatment due to an AE. Adverse events leading to treatment discontinuation in the tivantinib arm included ascites (2 subjects), vomiting (1 subject), malignant neoplasm progression (1 subject), and cholangitis (1 subject). Adverse events leading to treatment discontinuation in the gemcitabine arm included abdominal pain upper (1 subject), fatigue (3 subjects), malignant neoplasm progression (2 subjects), pneumonia (1 subject), and hip fracture (1 subject). Malignant neoplasm progression was the most common SAE, occurring in 13 (32.5%) subjects; anemia and fatigue were the second most common SAEs, occurring in 3 (7.5%) subjects each. Thirteen (32.5%) subjects died during study treatment or within 30 days of the last dose of study drug,

including 9 subjects who received tivantinib and 4 subjects who received gemcitabine. None of the AEs leading to death was considered related to treatment. Malignant neoplasm was the reason for death for all 9 subjects in the tivantinib treatment group.

ARQ 197-215

ARQ 197-215 was a randomized, placebo-controlled study of tivantinib in subjects with HCC who had radiographic disease progression after systemic first-line therapy or were unable to tolerate the therapy. Subjects randomized to placebo were given the opportunity to receive tivantinib under open-label crossover after they had documented radiographic disease progression during the double-blind portion.

Based on healthy volunteer studies and on previous clinical trials in subjects with cancer, a dosing regimen of crystalline tivantinib at 360 mg BID (capsule formulation) was recommended for all clinical trials. Following notification of a Grade 5 pancytopenia event, a detailed review of all cases of Grade ≥ 3 neutropenia was conducted. A review of the data identified 10 subjects who developed Grade ≥ 3 neutropenia. Eight severe neutropenia events occurred within the first month of treatment with study drug; one case occurred in the first week of Cycle 2, and one transient Grade 3 neutropenia occurred in Cycle 3. Three subjects who developed Grade 4 (febrile) neutropenia in Cycle 1 died within 30 days from the onset of the event, though the study drug was not held as recommended by the revised protocol. The review showed a higher rate of Grade ≥ 3 neutropenia, occurring in approximately 20% of HCC subjects, compared to approximately 5% in the total population of subjects who received tivantinib. Based on this observation, coupled with the higher exposure found in the HCC subject population, the decision was made to reduce the dose of tivantinib to 240 mg BID (capsule formulation) for all subjects in this study.

A total of 107 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment during the double-blind period were disease progression (68.2%) and death (13.1%). Twenty-three of the 36 subjects who had been randomized to the placebo group entered the crossover period and were treated with tivantinib. The most common (≥ 10%) AEs during the double-blind period of the study were asthenia (24.3%), fatigue (23.4%), decreased appetite (22.4%), diarrhea (19.6%), edema peripheral (19.6%), neutropenia (18.7%), ascites (16.8%), anemia (15.9%), abdominal pain (15.0%), cough (13.1%), pyrexia (12.1%), and nausea (11.2%). Severe AEs that occurred in at least a 2-fold greater frequency in tivantinib-treated subjects compared to placebo-treated subjects included neutropenia (14.1% versus 0) and anemia (12.7% versus 0). The frequency of these severe AEs was lower in the 240 mg BID group compared to the 360 mg BID group (neutropenia [6.1% versus 21.1%], anemia [9.1% versus 15.8%]). Severe AEs of myelosuppression were reported only in the tivantinib treatment group. Twenty-one of 107 (19.6%) subjects had AEs that led to treatment discontinuation during the double-blind period, including 6 of 33 (18.2%) subjects in the tivantinib 240 mg BID group, 7 of 38 (18.4%) subjects in the tivantinib 360 mg BID group, and 8 of 36 (22.2%) subjects in the placebo group. The most common AE leading to discontinuation from study treatment was disease progression (6.5%).Three of 23 (13.0%) subjects had AEs that led to treatment discontinuation during the crossover period, including asthenia (1 subject) and disease progression (2 subjects). SAEs were reported for 38 of 107 (35.5%) subjects, including 24 of 71 (33.8%) subjects treated with tivantinib and 14 of 36 (38.9%) subjects treated with placebo. The most common

(≥ 5%) SAE reported in this study was disease progression (7.5%). In this study, 23 (21.5%) subjects died on treatment or within 30 days of the last dose of study drug during the double-blind period (13 [18.3%] tivantinib-treated subjects and 10 [27.8%] placebo-treated subjects). The 13 deaths that occurred during the double-blind period for tivantinib-treated subjects were attributed to the following causes: disease progression (4 subjects), neutropenic sepsis (3 subjects, including one subject who died both of neutropenic sepsis and multiorgan failure), hepatic failure (3 subjects), cachexia (1 subject), hemorrhage (1 subject), and metabolic acidosis (1 subject). The 10 deaths that occurred during the double-blind period for placebo-treated subjects were attributed to the following causes: disease progression (4 subjects), cachexia (2 subjects), portal hypertension (1 subject), acute coronary syndrome and pulmonary edema (1 subject), upper gastrointestinal hemorrhage (1 subject), and suicide (1 subject). Three of 23 (13.0%) subjects had AEs resulting in death during the crossover period, including disease progression (2 subjects) and hepatic failure (1 subject).

ARQ 197-A-U251

ARQ 197-A-U251 was an open-label study of tivantinib in subjects with relapsed or refractory non-central nervous system (CNS) germ cell tumors. Twenty-seven subjects were enrolled and treated in this study. The primary reason for discontinuation was disease progression in 24 (88.9%) subjects. The most common (≥ 10%) AEs were fatigue (37.0%), nausea (25.9%), cough and dyspnea (22.2% each), vomiting, edema peripheral, and decreased appetite (14.8% each), and constipation, back pain, and neuropathy peripheral (11.1% each). AEs of Grade 3 or higher occurred in 12 subjects (44.4%). These included anemia, vision blurred, peritoneal hemorrhage, fatigue, hypersensitivity, cellulitis, pneumonia, neutrophil count decreased, pain in extremity, aphasia, cerebral hemorrhage, headache, hemiplegia, paraparesis, sciatica, spinal cord compression, syncope, insomnia, cough, dyspnea, and superior vena caval occlusion, which were reported in 1 subject (3.7%) each and back pain, which was reported in 2 subjects (7.4%). The events of pneumonia and syncope were considered drug-related; all other events of Grade 3 or higher were considered not related to treatment. Three subjects (11.1%) discontinued study treatment due to AEs. Three subjects (3.7% each) discontinued study treatment due to Grade 2 ascites, Grade 4 cerebral hemorrhage, or Grade 3 sciatica. Of these AEs, Grade 4 cerebral hemorrhage and Grade 3 sciatica were SAEs. The primary reason of study treatment discontinuation was progressive disease for all 3 subjects. There were no deaths during treatment or within 30 days of the last dose.

ARQ 197-A-U303

ARQ 197-A-U303 is an ongoing Phase 3 randomized, double-blind study of tivantinib in subjects with MET diagnostic-high inoperable HCC treated with one prior systemic therapy. In August 2013, following a higher than expected incidence of neutropenia-related adverse events, the study Data Monitoring Committee (DMC) evaluated all available unblinded data including preliminary pharmacokinetics. The DMC advised that the tivantinib starting dose should be reduced to 120 mg BID (tablet formulation). The protocol was amended accordingly and enrollment continues. This study remains blinded.

COMBINATION THERAPY STUDIES

ARQ 197-111

ARQ 197-111 was an open-label study of tivantinib in combination with erlotinib, in subjects with locally advanced or metastatic solid tumors that had progressed after at least one prior treatment regimen. A total of 32 subjects were enrolled and treated in this study. Progressive disease (23 [71.9%] subjects) was the most common reason for treatment discontinuation. The most common (≥ 10%) AEs were fatigue (37.5%), nausea (31.3%), diarrhea (28.1%), bradycardia/sinus bradycardia (28.1%), abdominal pain (28.1%), and anemia (21.9%). There were 14 events of myelosuppression (7 anemia, 3 neutropenia, 2 thrombocytopenia, 1 lymphopenia, and 1 leukopenia) reported in 9 subjects. Among them, 10 events (5 anemia, 3 neutropenia, 1 thrombocytopenia, and 1 leukopenia) occurred in 6 subjects and were considered drug-related. Thirteen of the 15 events (86.7%) occurred when subjects were receiving tivantinib at a dose of 360 mg BID (capsule formulation). In this study, a total of 14 cardiac events (9 sinus bradycardia, 2 bradycardia, 1 cardio-respiratory arrest, 1 palpitations, and 1 sick sinus syndrome) were reported in 10 subjects. The majority of bradycardia events were asymptomatic and resolved. Five of 9 subjects with sinus bradycardia, bradycardia, or sick sinus syndrome had a history of bradycardia and/or an abnormal ECG finding of sinus arrhythmia at baseline. Three severe cardiac-related events occurred in 3 subjects including one Grade 3 sinus bradycardia, one Grade 3 sick sinus syndrome, and one Grade 5 cardiac arrest. AEs leading to treatment discontinuation occurred in 7 of 32 (21.9%) subjects. Four of the 7 subjects were discontinued from study medication due to 5 possible or probable drug-related AEs (neutropenia, hypoglycemia, fatigue, nausea, and vomiting). Two of the 8 (25%) AEs that resulted in study drug discontinuation were SAEs: one of life-threatening severity (neutropenia Grade 4) and the other that resulted in death (disease progression Grade 5). Other AEs leading to treatment discontinuation were comprised of hypoglycemia, hyperbilirubinemia, and pleural effusion, each occurring in 1 subject. Two of 32 (6.3%) subjects had AEs (both fatigue) that led to treatment reductions. One of the events of fatigue was considered to be related to study drug. Serious adverse events were reported for 13 subjects. There were no predominant SAEs, although disease progression was reported most often (3 of 32 subjects [9.4%]). There were three SAEs involving cardiac events, sinus bradycardia, cardio-respiratory arrest, and sick sinus syndrome and 2 reports of syncope possibly related to bradycardia. Five of 32 subjects (15.6%) had 6 SAEs that were considered related to combination treatment, including sinus bradycardia (Grade 3) in one subject, sick sinus syndrome (Grade 3) in one subject, neutropenia (Grade 4) in one subject, neutropenia and leukopenia (both Grade 4) in one subject, and syncope (Grade 3) in one subject. Six (18.8%) deaths occurred during the study or within 30 days of study treatment. All deaths were considered by Investigators to be not related to combination treatment and were the result of the following: cardiac arrest (1), disease progression (3), hepatic failure (1), and dyspnea (1).

ARQ 197-116

Study ARQ 197-116 was a study of tivantinib in combination with sorafenib in subjects with solid tumors, including RCC, HCC, NSCLC, and melanoma. A total of 87 subjects were enrolled and treated in this study. The most common reason for discontinuing treatment was

progressive disease (71.3% for radiographic progression and 6.9% for clinical progression). The most common (≥ 20% of subjects) AEs were diarrhea (46%), fatigue (43.7%), rash (43.7%), anorexia (39.1%), weight decreased (37.9%), hypophosphatemia (28.7%), alopecia (27.6%), hyperglycemia (26.4%), nausea (25.3%), hypertension (24.1%), vomiting (21.8%), hypernatremia (21.8%), palmar-plantar erythrodysesthesia syndrome (21.8%), and lymphopenia (20.7%). The distribution of AEs was similar among all cancer types. The drug-related AEs reported most frequently (≥ 20% of subjects) were rash (40.2%), diarrhea (37.9%), anorexia (33.3%), fatigue (31.0%), alopecia (25.3%), palmar-plantar erythrodysesthesia syndrome (21.8%), and weight decreased (20.7%). Severe AEs (≥ Grade 3) were experienced by 61 (70.1%) of the 87 subjects. The severe AEs occurring in ≥ 5% of subjects were hypertension (11.5%), palmar-plantar erythrodysesthesia syndrome (8%), fatigue (6.9%), hyponatremia (6.9%), hypophosphatemia (6.9%), disease progression (5.7%), hyperbilirubinemia (5.7%), pneumonia (5.7%), hyperuricemia (5.7%), and rash (5.7%). Serious adverse events including deaths were reported by 33 (37.9%) of the 87 subjects in the study. Infections and infestations, gastrointestinal disorders, and general disorders and administration site conditions were the most frequent system organ classes (SOC) with 9.2%, 8.0%, and 6.9% of subjects, respectively. There were 9 subjects with AEs that led to death: 3 with HCC, 2 with lung cancer, and 1 each with RCC, melanoma, breast cancer, or other cancer (adenocarcinoma of the esophagus). In four of these subjects, the AE leading to death was progressive disease.

ARQ 197-117

ARQ 197-117 was an open-label study of tivantinib in combination with gemcitabine in subjects with locally advanced, inoperable, or metastatic primary solid tumors, including breast cancer, cholangiocarcinoma, ovarian cancer, and pancreatic cancer. A total of 74 subjects were enrolled and treated in this study. The most common reason for discontinuing tivantinib and gemcitabine treatments was radiographically confirmed disease progression (42 [56.8%] and 40 [54.1%], respectively). The most common AEs were thrombocytopenia (56 [75.7%] subjects), anemia (54 [73.0%] subjects), neutropenia (51 [68.9%] subjects), fatigue (43 [58.1%] subjects), and nausea (39 [52.7%] subjects). Severe AEs (≥ Grade 3) were thrombocytopenia (22 [29.7%] subjects), anemia (28 [37.8%] subjects), neutropenia (32 [43.2%] subjects), leukopenia (5 [6.8%] subjects), febrile neutropenia (3 [4.1%] subjects), and pancytopenia (1 [1.4%] subjects). There were 19 cardiac events (4 tachycardia, 3 palpitations, 2 atrial fibrillation, 2 congestive cardiac failure, 1 acute myocardial infarction, 1 atrial flutter, 1 bradycardia, 1 cardiomyopathy, 1 cardiopulmonary failure, 1 cyanosis, 1 left ventricular failure, and 1 mitral valve incompetence) reported in 12 subjects. Overall, 1 of 74 (1.4%) subjects experienced bradycardia, 2 (2.7%) experienced atrial fibrillation, 3 (4.1%) experienced palpitations, and 3 (4.1%) experienced tachycardia. At the time of the last recorded evaluation, 11 of the 19 (57.9%) cardiac-related events were resolved, 7 (36.8%) were ongoing, and 1 (5.3%) subject died. Seventeen of 74 (23.0%) subjects had a total of 21 AEs that led to treatment discontinuation. Seven of the 17 subjects discontinued due to myelosuppressive events, including neutropenia (4 subjects), thrombocytopenia (2 subjects), anemia (2 subjects), and febrile neutropenia (1 subject). Other AEs leading to study drug discontinuation were single events each of breast cancer, wound complication, bacteremia, gastrointestinal hemorrhage, sepsis, fatigue, acute respiratory failure, dyspnea, respiratory failure, disease progression, small bowel obstruction, and

pneumonitis. Four of 74 (5.4%) subjects each had one tivantinib dose reduction during the study period, from 360 mg BID to 240 mg BID (capsule formulation). Adverse events leading to dose reductions in these 4 subjects included neutropenia (3 subjects) and fatigue (1 subject). All four subjects were among the 32 subjects who experienced AEs leading to a reduction in gemcitabine. All dose reductions for gemcitabine were due to myelosuppressive AEs. Serious adverse events were reported for 39 of 74 (52.7%) subjects. The most commonly reported SAEs were anemia (6 [8.1%] subjects) and disease progression (9 [12.2%] subjects. Overall, 15 (20.3%) deaths occurred during study treatment or within 30 days of the last dose, which resulted from the following: disease progression (8 subjects), acute respiratory failure (1 subject), cardiopulmonary failure (1 subject), hepatic failure (1 subject), neutropenia (1 subject), sepsis (1 subject), upper gastrointestinal hemorrhage (1 subject), and death (1 subject).

ARQ 197-209

ARQ 197-209 was a randomized, double-blind study of erlotinib plus tivantinib treatment compared with erlotinib plus placebo, in subjects with inoperable locally advanced or metastatic (Stage IIIB/IV) NSCLC who had received at least one prior chemotherapy regimen (other than erlotinib or other EGFR-inhibiting agents). A total of 167 subjects enrolled in this study; 84 subjects received erlotinib plus tivantinib and 83 subjects received erlotinib plus placebo during the double-blind period. Thirty-five of 83 (42.2%) subjects who had initiated treatment with erlotinib plus placebo crossed over to receive erlotinib plus tivantinib. The most common AEs reported in the tivantinib combination arm group were rash (65.5%), diarrhea (47.6%), fatigue (33.3%), anorexia (28.6%), nausea and vomiting (26.2% each), and pruritus, dry skin, and dyspnea (22.6%, each). Neutropenia was experienced by 8 subjects in this study who were treated with erlotinib plus tivantinib. No neutropenia events were experienced by subjects during erlotinib plus placebo treatment. Sinus bradycardia was reported for 3 of 84 (3.6%) subjects randomized to the tivantinib combination arm (2 drug-related), and 2 of 35 (5.7%) additional subjects treated with erlotinib plus tivantinib during the crossover period (1 drug-related), for a total of 5 of 119 (4.2%) subjects treated with erlotinib plus tivantinib in the study (3 drug-related). Bradycardia was reported for 1 of 84 (1.2%) subjects in the randomized tivantinib combination arm (considered drug-related) and 1 of 35 (2.9%) subjects in the crossover population (not drug-related), for a total of 2 of 119 (1.7%) subjects treated with erlotinib plus tivantinib. Adverse events leading to treatment discontinuation were reported for 18 of 84 (21.4%) subjects randomized to the tivantinib combination arm and 17 of 83 (20.5%) subjects randomized to the placebo combination arm, including 7 of 35 (20.0%) subjects randomized to the placebo combination arm who crossed over to receive the tivantinib combination treatment. Three subjects had dose reductions, 1 subject in the erlotinib plus tivantinib group (due to Grade 3 diarrhea, Grade 3 vomiting, and Grade 2 nausea) and 2 in the erlotinib plus placebo group (due to Grade 2 rash pustular in one subject and due to Grade 4 diarrhea, Grade 3 dehydration, Grade 3 renal failure acute, and Grade 3 palmar-plantar erythrodysesthesia syndrome in another subject). In this study, 74 subjects (44.3%) experienced SAEs. The most common SAE in both treatment arms was disease progression, reported for 6 (7.1%) and 7 (8.4 %) subjects in the tivantinib and placebo combination arms, respectively. Adverse events with an outcome of death were reported in 38 subjects (22.8%) during study treatment or within 30 days of the last dose of the study drug; 17 (20.2%) deaths

occurred in subjects randomized to the tivantinib combination arm and 21 (25.3%) occurred in subjects randomized to the placebo combination arm, including 7 subjects who died after crossing over to the tivantinib combination arm. The most frequent cause of death in the tivantinib combination and crossover subjects was disease progression (9 subjects). Among subjects in the tivantinib combination arm, 2 subjects died due to AEs considered at least possibly related to both tivantinib and erlotinib (leukopenia and pneumonia).

ARQ 197-A-U252

ARQ 197-A-U252 was a Phase 1/2 study of tivantinib in combination with irinotecan and cetuximab in subjects with colorectal cancer with wild-type KRAS. A total of 131 subjects enrolled in this study and 130 were treated. The primary reason for discontinuing treatment was progressive disease (79 [60.3%]). All 130 treated subjects (100%) in both Phase 1 and Phase 2 experienced at least one AE. In Phase 1, the most common AEs were fatigue (77.8%), nausea and rash (66.7% each), and diarrhea and alopecia (55.6% each). In Phase 2, the most common AEs that occurred in either treatment group were rash, diarrhea, and nausea. The most common AEs reported in the tivantinib combination arm were rash (59.2%), diarrhea (53.5%), nausea (46.5%), fatigue (43.7%), vomiting (33.8%), neutropenia (31.0%), and infections and infestations (29.6%). The proportions of placebo-treated subjects versus the proportions of tivantinib-treated subjects with any grade of myelosuppression events were as follows: febrile neutropenia (1.7 % vs. 1.6%), leukopenia (5.1% vs. 8.1%), and thrombocytopenia (1.7% vs. 8.1%). Among cardiac disorder AEs of special interest, bradycardia and sinus bradycardia were reported by 0% of placebo-treated subjects vs. 3.2% (bradycardia) and 4.8% (sinus bradycardia) of tivantinib-treated subjects and atrial fibrillation was reported by 0% of placebo-treated subjects vs. 3.2% of tivantinib-treated subjects. Acute renal failure was reported by 0% of placebo-treated subjects and 3.6% of tivantinib-treated subjects during Phase 2. In Phase 1, two subjects discontinued study drug because of an AE. In Phase 2, a higher proportion of tivantinib-treated subjects than placebo-treated subjects discontinued study drug due to an AE (19.4% vs. 11.9%). The most common AEs leading to discontinuation of study treatment were neutropenia and rash. One subject each had serious Grade 4 unrelated AEs of renal failure (acute), respiratory failure, or urosepsis that led to discontinuation from study medication. No deaths were reported for any of the 9 subjects in the Phase 1 portion of the study. In Phase 2, two subjects in each treatment group died within 30 days of the end of study drug administration due to a SAE. An additional 3 subjects in each treatment group died due to disease progression after that time period. No AEs leading to death were considered related to study drug.

ARQ 197-A-U302

ARQ 197-A-U302 was a randomized, double-blinded, placebo-controlled study of tivantinib in combination with erlotinib in subjects with locally advanced or metastatic, non-squamous NSCLC. The study enrolled 1048 subjects, and 1037 subjects were included in the safety analysis. Nine hundred seventy-eight (93.3%) subjects discontinued treatment. The most common reason for discontinuation was progressive disease; 645 (61.5%) subjects discontinued for radiographically confirmed progressive disease and another 90 (8.6%) subjects discontinued for clinical disease progression. Adverse events were the reason for discontinuation for 113 (10.8%) subjects. The most common AEs within the erlotinib plus

tivantinib (ET) and the erlotinib plus placebo (EP) groups were diarrhea (ET: 34.6%, EP: 41.0%), rash (ET: 33.1%, EP: 37.3%), decreased appetite (ET: 29.0%, EP: 28.8%), dyspnea (ET: 26.2%, EP: 22.6%), and fatigue (ET: 26.2%, EP: 21.9%). The AEs indicative of myelosuppression were more frequent in the ET group compared with the EP group: neutropenia by any preferred term (ET: 13.8%, EP: 2.3%), febrile neutropenia (ET: 3.3%, EP: 0.4%), leukopenia (ET: 5.8%, EP: 1.0%), and anemia by any preferred term (ET: 16.7%, EP: 10.3%). The occurrence of these AEs at a severity of ≥ Grade 3 was also more common in the ET group. Bradycardia was reported in 2.7% of subjects in the ET group and in no subjects in the EP group; however, only 2 of the 14 cases in the ET group were of Grade 3 or higher severity. Overall, 138 subjects (79 subjects [15.2%] in the tivantinib combination arm, 59 subjects [11.4%] in the placebo combination arm) were discontinued from treatment because of AEs. Overall, there were 410 (39.5%) subjects with SAEs reported during the study; the most commonly reported SAEs were respiratory events including dyspnea and pulmonary embolism, reported in 5.2% and 3.4% of subjects overall. Overall, 614 subjects died during the study or within 30 days of the last dose of study drug, most frequently as the result of disease progression as attributed by the Investigator. A total of 142 subjects had deaths associated with AEs: ET: 77 subjects, EP: 65 subjects. However, the Investigator ultimately determined that many of these AEs were part of the underlying disease and attributed the deaths to disease progression. Using this revised Investigator attribution, 66 subjects died as a result of AEs (other than disease progression): ET: 32 subjects; EP: 34 subjects. Of these deaths associated with AEs (other than disease progression), the most common AEs were respiratory failure (ET: 5 subjects, EP: 6 subjects), sepsis or septic shock (ET: 5 subjects, EP: 1 subject), and pneumonia or bronchopneumonia (ET: 3 subjects, EP: 5 subjects). Five deaths in the ET group and 3 deaths in the EP group were considered by the Investigator to be related to tivantinib/placebo.

Detailed data describing the clinical administration of tivantinib and complete safety information can be found in the Tivantinib Investigator's Brochure.[12]

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this extension protocol is to provide subjects who participated in previous tivantinib studies that have reached their designated end-dates with access to tivantinib if, in the opinion of the Investigator and the Sponsor, they may benefit from the treatment.

2.2 Secondary Objectives

The secondary objective of this study is to collect additional safety, tolerability, and efficacy information for tivantinib treatment.

3 SELECTION OF STUDY POPULATION

Enrollment to this study is open to any subject who has previously been enrolled in any tivantinib studies that have reached its designated end-dates and who may, in the opinion of the Investigator and the Sponsor, benefit from treatment. This protocol will allow eligible subjects to continue to receive treatment at the dose(s) and schedule(s) of their original protocols. Subjects who were previously treated with tivantinib only and who, in the opinion of the Investigator and with the Sponsor's approval, may benefit from combination therapy will be allowed to receive combination therapy. Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator and with Sponsor's approval, may benefit from the treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.

The combination therapy(ies) considered must have been evaluated in prior tivantinib combination studies. The combination therapy dose(s) and schedule(s) will be determined to each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.

3.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Signed written informed consent to Study ARQ 197-299
2. Male or female subjects of the age defined in the original protocol they were enrolled
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3 (or ≤ 2 for tivantinib-naïve subjects) (see Appendix 2)
4. Adequate bone marrow, liver, and renal function tests:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Hemoglobin ≥ 8.0 g/dL (or ≥ 9.0 g/dL for tivantinib-naïve subjects)
   - Platelet count ≥ 75 x 10^9/L (or ≥ 60 x 10^9/L for HCC subjects)
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 x upper limit of normal (ULN) (or ≤ 5 x ULN for subjects with liver metastases)
   - Total bilirubin ≤ 2mg/dL
   - Serum creatinine ≤ 1.5 x ULN
5. Enrollment within 14 days of the completion of the End of Treatment Visit of the original study
6. Measurable disease as defined by RECIST. Eligibility assessment must be performed within 28 days (4 weeks) of the first dose of study drug (Day 1)
7. Subjects, who participated in previous tivantinib studies that have reached their designated end-dates, who did not meet discontinuation criteria in their original study, and who may, in the opinion of the Investigator and the Sponsor, benefit from treatment
8. Women of childbearing potential must have a negative pregnancy test performed within 14 days of the start of study drug. "Women of childbearing potential" is defined as sexually mature women who have not undergone a hysterectomy and who have not been naturally postmenopausal for the last 12 consecutive months prior to the first dose of

tivantinib (Day 1). Both men and women enrolled in this study must agree to use adequate birth control measures while on study

3.2 Exclusion Criteria

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

1. Known or suspected allergy to tivantinib
2. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the study or evaluation of the study results
3. Any condition that is unstable or which could jeopardize the safety of the subject and his/her compliance in the study
   - For tivantinib-naïve subjects: active coronary disease, clinically significant bradycardia, or other uncontrolled cardiac arrhythmia defined as ≥ Grade 3 according to NCI CTCAE v. 4.03, or uncontrolled hypertension
4. A serious, uncontrolled medical disorder/condition that in the opinion of the Investigator would impair the ability of the subject to receive protocol therapy
5. Requirement to receive other concurrent chemotherapy (excluding combination therapy defined in original protocol), immunotherapy, radiotherapy, or any other investigational drug while on study. Palliative radiotherapy is allowed provided that:
   - In the opinion of the Investigator, the subject does not have progressive disease
   - The radiation field does not encompass a target lesion
   - No more than 10% of the subject's bone marrow is irradiated

3.3 Number of Subjects

The exact number of subjects for this study is dependent on the number of subjects who will be eligible to continue treatment with tivantinib once their original protocols have reached their designated end-dates.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open label extension protocol for subjects who have been treated in previous tivantinib studies that have reached their designated end-dates. Subjects enrolled in this extension protocol will receive either tivantinib as monotherapy or in combination with other drug(s) at the same dose(s), and same schedule(s) in which they were originally enrolled.

Subjects who were previously treated with tivantinib only and who in the opinion of the Investigator and with the Sponsor's approval may benefit from combination therapy will be allowed to receive combination therapy. The combination therapies considered must have been evaluated in prior tivantinib combination studies. The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.

Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib (tivantinib-naïve) as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to receive treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.

This extension study is designed to further evaluate the safety and tolerability of tivantinib monotherapy or in combination with other drug(s) when given to subjects who tolerated previous treatment well and may benefit from the continuing treatment. Tivantinib will be administered twice daily, orally, **with meals** (regardless of the original protocol requirements).

4.2 Rationale for Study Design

This is an extension study that will allow subjects to continue to receive study treatment when the original studies into which they were enrolled have reached their designated end-dates.

4.3 Administration Schedule

Subjects will be treated according to the original treatment protocols into which they were enrolled or per administration schedules tested in other tivantinib clinical trials. Subjects will be treated until any discontinuation criterion is met. Dose may be delayed or reduced for clinically significant toxicities, but dose escalation is not allowed (see Section 7.3 and Appendix 4).

4.4 Study Duration

For an individual subject, treatment will continue until unacceptable toxicity, disease progression (clinical or radiologic), or another discontinuation criterion is met.

5 STUDY VISITS

Prior to administration of any study-related procedures including evaluation of the subject's eligibility to continue/receive treatment with tivantinib, a signed written informed consent has to be obtained from each potential subject or his/her legal representative. Study visits will consist of a brief Pre-study Visit, during which the subject's eligibility to continue treatment will be evaluated; Weekly or Monthly Visits during which the subject's treatment eligibility will be re-assessed and the study drug(s) will be administered; End of Treatment Visit; 30day Safety Follow-up Visit. (see Appendix 1: Schedule of Assessment)

5.1 Pre-study Visit

After written informed consent is obtained, the subject's study eligibility to receive treatment will be assessed. The following assessments and procedures should be completed prior to the subject's enrollment into this study:

- Inclusion/Exclusion criteria
- Physical examination, including vital signs, weight, and height (see Section 6.2)
- ECOG PS (see Appendix 2)
- Hematology (see Section 6.3)
- Coagulation tests (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Serum pregnancy test (if applicable, see Section 6.3)
- Urinalysis (see Section 6.3)
- 12-lead ECG (see Section 6.4)
- Tumor assessment (see Section 6.5)
- Tumor markers assessment (if applicable)
- Adverse event (AE) assessment: any sign or symptom continuing from the original tivantinib study or beginning after the last visit of the original study, but prior to the first dose of study drug (Day 1) of the Extension study must be documented on a Medical History eCRF page. Resolved AEs from the original tivantinib study are captured in the original study records and will not be re-recorded for this study.

Note: The data collected during the End-of-Treatment Visit of the original study may be used as a pre-study/safety assessment for enrollment into this Extension Study if the visit was done within the following time period:

1. Laboratory tests (hematology, blood chemistry, liver function tests, electrolytes, and serum pregnancy test) and ECG within 14 days of the first dose of study drug (Day 1)
2. Tumor assessment within 28 days (4 weeks) of the first dose of study drug (Day 1)

5.2 Monthly Visits (± 3 days)

Subjects should be seen every four weeks throughout the treatment period. The following assessments and procedures will be performed at each visit:

- Physical examination, including vital signs and weight (see Section 6.2)
- ECOG PS (see Appendix 2)
- Hematology (see s Section 6.3)
- Coagulation tests (see s Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- AE assessment
- Concomitant medications assessment
- Tivantinib dispensation as per schedule
- Combination drug(s) administration/dispensation as per schedule (if applicable)
- Tumor markers assessment (if applicable)
- Tumor assessment (every 12 weeks unless current disease specific standard of care requires performing imaging more often)
- 12-lead ECG (ONLY for subjects with a heart rate of <50 bpm) (see Section 6.4)

Note: Subjects who do not experience Grade 3/4 toxicity and continue to benefit from the treatment after 12 cycles of treatment can be evaluated every two or three months upon agreement between the Investigator and the Sponsor.

5.3 Weekly Visits (if applicable; ± 3 days)

Tivantinib-naïve subjects or subjects who require weekly administration of combination drug(s) should be seen according to the schedule as per the original protocol.

5.3.1 Weekly Visits (applied for combination drug(s) administration; ± 3 days)

At a minimum, the following assessments and procedures will be performed at each visit:

- Vital signs (see Section 6.2)
- Hematology (see Section 6.3)
- AE assessment
- Concomitant medications assessment
- Combination drug(s) administration per schedule

5.3.2 Weekly Visits (applied ONLY for tivantinib-naïve subjects; ± 3 days)

Subjects who did not receive tivantinib when enrolled in the original tivantinib study and who, in the opinion of the Investigator and with the Sponsor's approval, may benefit from

treatment with tivantinib should have weekly visits during the first four weeks of treatment with tivantinib. After the first four weeks, these subjects will follow the original protocol visit schedule to which they were assigned.

At a minimum, the following assessments and procedures will be performed at each visit:

- Physical examination, including vital signs (see Section 6.2)
- ECOG PS (see Appendix 2)
- Hematology (see Section 6.3)
- Coagulation tests (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- AE assessment
- Concomitant medications assessment
- Tivantinib dispensation as per schedule
- Combination drug(s) administration/dispensation as per schedule (if applicable)
- 12-lead ECG (ONLY for subjects with a heart rate of <50 bpm)

Tivantinib-naïve subjects who do not experience Grade 3 /4 toxicity during the first four weeks of treatment and to whom the weekly combination treatment visit schedule does not apply can be evaluated monthly (Cycle 2+) upon agreement between the Investigator and the Sponsor .

5.4 End of Treatment Visit

Subjects, who have been discontinued from the study, should have the End of Treatment Visit within 7 (+3) days of the discontinuation decision. The following assessments and procedures should be done at the End of Treatment Visit:

- Physical examination, including vital signs and weight (see Section 6.2)
- ECOG PS (see Appendix 2)
- Hematology (see Section 6.3)
- Coagulation tests (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Serum pregnancy test (if applicable, see Section 6.3)
- Urinalysis (see Section 6.3)
- AE assessment
- Concomitant medications assessment
- Tumor markers assessment (if applicable)

- Tumor assessment (if not done within 14 days)
- 12-lead ECG (see Section 6.4)

5.5 30-day Safety Follow-up Visit

In this study, the post-treatment safety follow-up period ends 30 days after administration of the last dose of tivantinib. All subjects must have a follow-up visit or phone call.

Subjects with unresolved protocol-therapy related AEs at the time of treatment discontinuation will be followed for 30 days after the last dose of tivantinib or until all study related toxicities have, in the opinion of the Investigator, resolved to baseline, stabilized, or been deemed to be irreversible whichever is later. Treatment-related AEs that occur during the 30-day follow-up period will be followed for a minimum of 30 days from the onset or until all study-related toxicities have, in the opinion of the Investigator, resolved to baseline, stabilized, or been deemed to be irreversible, whichever is later.

If a subject receives other anticancer 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.

5.6 Discontinuation from Study

Subjects will stop study treatment(s) at any time if they meet any of the following criteria:

- Documented radiographic progression of disease. (However, if, in the Investigator's opinion, treatment with tivantinib, as a monotherapy or in combination therapy, is providing clinical benefit to a subject with radiological progression of disease, the subject may continue to receive the treatment after consultation with the ArQule, Inc. [ArQule] Medical Monitor or designee.)
- Noncompliance with any part of the study protocol, as evaluated by the Investigator and the ArQule Medical Monitor or designee
- Clinically unacceptable toxicities
- Withdrawal of consent to treatment
- Lost to follow-up
- Death

6 STUDY PROCEDURES

6.1 Informed Consent

A sample Informed Consent Form (ICF) with core information will be provided to each study site. Prior to study initiation at a given study site, each site/Investigator must obtain a written approval/favorable opinion from its respective Investigational Review Board/Independent Ethics Committee (IRB/IEC) for the ICF and any other written information to be provided to subjects. All ICFs must be compliant with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and local regulations and must be approved by the Sponsor prior to submission to IRB/IEC. The written approval of the IRB/IEC, together with the approved subject information/ICF, must be maintained in the study master files.

Written informed consent must be obtained from a prospective subject before any study-specific procedures are performed on that individual. Subjects who agree to participate in the study will sign the most recently approved ICF and will be provided with a copy of the fully executed document. The original, executed ICF will be maintained in the respective subject's clinical study file.

6.2 Physical Examination

Complete physical examination of the major body systems, vital signs (height [on screening visit only], weight, blood pressure, heart rate, respiratory rate, temperature [oral, axillary or tympanic]), and ECOG PS (see Appendix 2).

6.3 Clinical Laboratory Tests

Safety laboratory assessments will be done at a local laboratory and will include hematology, blood chemistry, liver function tests, coagulation, electrolytes and urinalyses as described below:

- Hematology: Complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell and platelet count
- Coagulation: (at Baseline and End of Treatment; and if clinically indicated): prothrombin time, international normalized ratio (INR) and partial thromboplastin time.
- Blood chemistry: calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, uric acid, total protein and blood urea nitrogen (BUN)
- Liver function tests: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin
- Electrolytes: sodium, potassium, and chloride
- Serum pregnancy test (at Baseline and End of Treatment only) for female subjects of childbearing potential
- Routine urinalysis (at Baseline and End of Treatment only; and if clinically indicated): dipstick and microscopy (only if clinically indicated or dipstick is not done) including protein, specific gravity, glucose and blood

6.4 Twelve-lead Electrocardiogram

Twelve-lead electrocardiograms (ECG) should be conducted at the Pre-study and End of Treatment visits. Additional ECG(s) may be conducted if clinically indicated. Subjects with bradycardia, a heart rate of <50 bpm, should have an ECG done on Day 1 of every cycle. A local ECG laboratory will be employed for ECG testing.

6.5 Tumor Assessment

In this study, tumor measurement will follow the RECIST guidelines version 1.0 or 1.1 (in accordance with the original protocol into which each subject was originally enrolled) and be conducted every 12 weeks unless current disease specific standard of care requires performing imaging more often or as clinically indicated until progression of disease, withdrawal of consent, death, or loss to follow-up. Tumor assessment will also be performed during the End of Treatment Visit if it was not done within 14 days.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s).

All target and non-target lesions are evaluated at each time point of tumor assessment.

6.6 Other Evaluations

All other study tests and evaluations should be conducted according to the original study protocol under which subjects were enrolled.

7 TREATMENT

7.1 Tivantinib

Tivantinib capsules or tablets, provided by the Sponsor, are labeled as investigational agent according to relevant guidelines. Compositions of tivantinib capsules or tablets are described in the study pharmacy manual.

7.1.1 Storage and Handling

At a study site, tivantinib should be stored at controlled room temperature (15-30°C; 59-86°F). Tivantinib is stable at controlled room temperature (15-30°C; 59-86°F) for up to 24 months. The storage instruction must appear on the label of the container in which capsules or tablets are delivered to the subject. Until dispensed to the subject, the study drug will be stored in a secure locked area, accessible to authorized personnel only.

7.1.2 Tivantinib Accountability

The authorized site recipient will acknowledge to ArQule or designee the receipt of the drug, indicating the shipment contents and condition. Damaged supplies will be replaced.

Drug accountability records will be maintained by the research site and must accurately document quantities of study drug received and quantities dispensed to subjects. The records will include the lot number, date dispensed, amount dispensed, subject identifier number, subject initials, protocol number, dose administered, unused quantity returned, balance remaining, and initials of the person dispensing the drug.

The study site must supply a copy of their drug destruction policy to ArQule before authorization for destruction will be granted. Product accountability will be monitored throughout the study. Upon completion or termination of the study, and after inventory by an ArQule clinical trial monitor or designated representative, all unopened drug is to be returned to ArQule or designee in the original container.

7.1.3 Tivantinib Administration

All subjects will receive tivantinib capsules or tablets at the dose and schedule depending on the original study protocol they were enrolled into. Tivantinib will be administered orally, twice daily, once in the morning and once in the evening with meals (regardless of original protocol requirements).

Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.

If a subject stops receiving tivantinib due to tivantinib-related toxicity, he/she should be discontinued from the study.

For individual subjects, treatment will continue until unacceptable toxicity, disease progression (clinical or radiological) or other discontinuation criterion is met.

7.1.4 Tivantinib Missed or Vomited Doses

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

7.2 Combination Drug Administration

Combination therapy (if applicable) will be administered at the same dose(s) and same schedule(s) as in the original study protocol into which subjects were enrolled. If a subject discontinues receiving a combination drug(s) due to the combination drug-related toxicity he/she may continue to receive tivantinib.

Subjects who were previously treated with tivantinib only and who, in the opinion of the Investigator and with the Sponsor's approval, may benefit from combination therapy will be allowed to receive combination therapy. The combination therapies considered must have been evaluated in prior tivantinib combination studies. The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.

7.3 Dose Modification

In principle, when clinically significant tivantinib-related toxicity occurs, the tivantinib dose may be reduced, but a combination therapy drug (if applicable) can be administered at the scheduled dose level. When a clinically significant combination therapy drug related-toxicity occurs, combination therapy drug dose may be reduced (following dose modification guidelines for this drug), but tivantinib can be administered at the scheduled dose level. When a clinically significant toxicity that could be related to either drug occurs, doses of both drugs may be reduced.

Dose administration may be delayed to allow for recovery from toxicity. Combination therapy drug dose modification should follow the original protocol guidelines (see Appendix 4).

In general, once the tivantinib dose has been modified for a subject, all subsequent cycles should be administered to that subject at the modified dose unless additional dose modifications may be required. The modified dose will be considered the maximum dose for that subject for all subsequent cycles.

Dose modification schema:

- 240 mg BID (capsules or tablets)
- 120 mg BID (capsules or tablets)
- 120 mg once a day (capsules or tablets)

Further instructions for tivantinib dose modification due to non-hematologic or hematologic toxicities are listed in the following tables and provided in the original study protocols.

For HCC subjects enrolled in the extension protocol, dose reduction and management of non-hematologic and hematologic toxicities should **strictly** follow the original protocol guidelines.

Table 7.1 Dose Delays/Reductions for Non-hematological Toxicity Related to Tivantinib (non-HCC subjects)

Event Severity	Action
Grade 1 or 2	Continue current dose level
Grade 3	Withhold tivantinib administration for up to 21 days until recovery to Grade 1 or Baseline. Administer tivantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer tivantinib at the next lower dose for all subsequent cycles.
Grade 4	Withhold tivantinib administration for up to 21 days until recovery to Grade 1 or Baseline. Consult with ArQule's Medical Monitor or designee prior to restarting tivantinib. If the Investigator and Medical Monitor concur, administer tivantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer tivantinib at the next lower dose for all subsequent cycles.

* If an event fails to recover to Grade 1 or Baseline and the dose must be delayed >21 days, the subject will be withdrawn from all study treatment, but should continue to undergo all follow-up evaluations.

Table 7.2 Dose Delays/Reductions for Hematological Toxicity Related to Tivantinib (non-HCC subjects)

Event/Severity	Action
Grade 1	Continue current dose level
Grade 2 **Neutropenia** **Thrombocytopenia**	Withhold tivantinib administration for up to 21 days and monitor hematology weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 7 days to: $\geq 1.5\times10^9$/L for ANC, or $\geq 75\times10^9$/L for platelets, resume tivantinib treatment at the same dose level • If the relevant lab value takes more than 7 days to recover to the level described above, restart tivantinib administration at the next lower dose level If a second hold is required for the same event, whichever the grade, administer tivantinib at the next lower dose once lab values allow doing so

Event/Severity	Action
Grade 3 **Neutropenia** **Thrombocytopenia** **Anaemia**	Withhold tivantinib administration for up to 21 days and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 14 days to: $\geq 1.5\times10^9$/L for ANC, 8 g/dL for hemoglobin, or $\geq 60\times10^9$/L for platelet, resume tivantinib treatment at the same dose level. • If the relevant lab value takes more than 14 days to recover to the level described above, treatment with growth factors for neutropenia is recommended. Restart tivantinib administration at the next lower dose once lab values allow doing so. • If a second hold is required for the same event, administer tivantinib at the next lower dose once lab values allow doing so.
Grade 4 **Neutropenia** **Thrombocytopenia** **Anaemia** **Febrile Neutropenia**	Withhold tivantinib administration for up to 21 days, and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 14 days to: $\geq 1.5\times10^9$/L for ANC, ≥ 8 g/dL for hemoglobin, or $\geq 60\times10^9$/L for platelet, resume treatment at the next lower dose once lab values allow doing so, unless further dose reduction is required. Treatment with growth factors and antibiotics is **strongly recommended** for Grade 4 neutropenia and febrile neutropenia (as per 2006 ASCO guidelines)

* If an event fails to recover to Grade 1 or baseline and the dose must be delayed >21 days, the subject will be withdrawn from all study treatment, but should continue to undergo all follow-up evaluations.

The following precautions will be taken to manage neutropenia risk during the study:

- For tivantinib-naïve subjects, ANC levels should be checked weekly during the first four weeks of therapy with tivantinib, and monthly thereafter. Subjects who experience Grade ≥3 neutropenia should be monitored weekly for four consecutive cycles (months).
- Prophylactic treatment with growth factors and antibiotic is suggested for subjects who experience Grade ≥3 neutropenia and febrile neutropenia

If questions or considerations regarding dose modification arise or a specific dose modification is needed, ArQule's Medical Monitor or designee should be consulted.

7.4 Blinding

This is an open label study. Neither the subject nor the Investigator and site research staff will be blinded to the administered treatment.

7.5 Concomitant Medication

All information regarding concomitant treatments (medications or procedures) must be recorded on the subject's CRF (including the name of the medication or procedure and duration of treatment). Palliative and supportive care for disease-related symptoms will be

offered to all subjects in this study. Complete information of analgesic consumption should be obtained and recorded.

7.5.1 Permitted Treatment

- Standard therapies for concurrent medical conditions
- Erythropoietin Stimulating Agents (ESA): Please follow ASCO or MEDICARE guidelines for the use of ESA in subjects diagnosed with cancer, drug labels and the Food and Drug Administration (FDA) alerts dated 9 March 2007, 8 November 2007, 12 March 2008, 31 July 2008, 2 December 2008 (Q&As), 16 February 2010, and any future alerts.
- Hematopoietic growth factors including filgrastim (Neupogen®) or other colony-stimulating factors (G-CSF). ASCO or institutional guidelines should be followed for the use of WBC growth factors: http://jco.ascopubs.org/content/24/19/3187.full.
- Prophylactic and supportive antiemetics may be administered according to standard practice
- Megestrol acetate (Megace®)
- Supportive therapy for toxicities associated with combination therapy drug(s), according to the FDA approved label or institutional practice
- Use of topical corticosteroids, topical antibiotics, and systemic antibiotics according to standard of care or 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 study treatment, in the opinion of the Investigator
- Bisphonates for bone metastases
- Palliative radiotherapy for local pain control provided that the subject does not meet criteria of progressive disease and treated lesion(s) will not be included in the target/non-target lesion assessment

7.5.2 Prohibited Treatment

- Any concurrent anticancer therapy including but not limited to chemotherapy, radiotherapy, hormonal therapy (except megestrol acetate as supportive care), immunotherapy, or other investigational agents
- Immunosuppressive therapies including 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)

7.5.3 Treatment to Avoid During Tivantinib Administration

- CYP3A4 inhibitors such as atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), or voriconazole

- CYP3A4 inducers such as rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort
- CYP 2C19 substrates or inhibitors such as omeprazole, esoprazole, lansoprazole, pantoprazole, fluvoxamine, moclobemide
- Grapefruits and grapefruit juice should be avoided within four hours before and after dosing

As tivantinib is metabolized by hepatic cytochrome P450 enzymes, primarily CYP 2C19 and CYP 3A4, interactions with drugs metabolized via the same enzyme system are possible. Caution should be applied when any CYP 2C19 inhibitors and/or strong CYP 3A4 inhibitors are used as concomitant therapy.

8 SAFETY ASSESSMENTS

8.1 Definitions

8.1.1 Adverse Event

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 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).

All AEs/SAEs occurring during the study period from the first day of study drug administration (Day 1 of this study) to the last day of the follow-up period will be captured.

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.

8.1.2 Serious Adverse Event (SAE)

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.

Notes:

- 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

8.1.3 Adverse Event Severity

All AEs will be graded (1 to 5; see below) according to the NCI CTCAE, version 3.0 (publish date: 09 Aug 2006), version 4.0 (publish date: 29 May 2009), or version 4.03 (publish date: 14 Jun 2010) depending on the original protocol.

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Severity vs. 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.

8.1.4 Causality Assessment

The relationship between an adverse event and the study drug or combination therapy drug(s) will be determined by the Investigator on the basis of his/her clinical judgment and the following definitions:

- 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 (e.g., 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
- 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 (e.g., disease under study, concurrent diseases, and concomitant medications)

8.1.5 Action Taken Regarding the Study Product

- None
  - No change in study drug dosage was made
- Discontinued Permanently
  - The study product was permanently stopped

- Reduced
  - The dosage of study product was reduced
- Interrupted
  - The study product was temporarily stopped
- Increased
  - The dosage of study product was increased

8.1.6 Adverse Event Outcome

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

8.1.7 Other Action Taken for Event

- None
  - No treatment was required
- Medication required
  - Prescription and/or OTC medication was required to treat the adverse event
- Hospitalization or prolongation of hospitalization required
  - Hospitalization was required or prolonged due to the adverse event, whether or not medication was required
- Other

8.2 Responsibilities and Procedures

The responsibility for the safety of an individual subject lies in all cases with the Investigator. This includes the timely review of all safety data obtained during the course of the study.

An Investigator must instruct his/her subjects to report any AEs and SAEs they experience.

Investigators must capture, evaluate and document all AEs and SAEs that are continuing from the original tivantinib protocol or begins after the last visit in the previous study or worsens from baseline of the previous study including the protocol-defined 30-day post-treatment follow-up period (21 Code of Federal Regulations [CFR] §312.64[b]) as source documents.

Investigators should assess AEs at each scheduled and non-scheduled visit, by the use of open-ended questioning, physical examination, and review of laboratory results.

Note: It is important to record all AEs and SAEs that result in temporary and permanent discontinuation of study drug, regardless of severity.

Investigators must report all SAEs, whether or not they are considered study-drug related, to the Sponsor or designee within 24 hours from knowledge of the event.

In cases of SUSAR, Investigators or their designees are responsible for reporting to their local IRBs/IECs; and the Sponsor or designee(s) is responsible for notifying regulatory authorities and all relevant investigators of SUSARs.

8.3 Adverse Events or Serious Adverse Events Assessment Criteria

Adverse events and SAEs should be evaluated and graded using NCI CTCAE guidelines, version 3.0, 4.0, or 4.03. The criteria can be found at:
http://ctep.cancer.gov/reporting/ctc.htm.

8.4 Reporting Serious Adverse Events

The Investigators are obligated to immediately report to the Sponsor or designee each SAE that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related. SAE follow-up information including supplementary documents (e.g., discharge letter, autopsy report, etc.), relevant data (e.g., electrocardiograms, lab tests, discharge summaries, post mortem results, etc.) must be reported within 24 hours as well after available. If any questions or considerations regarding a SAE arise, ArQule's Medical Monitor or designee should be consulted.

Safety Hotline and Fax	ArQule Medical Monitor
North America: PPD All others: PPD	PPD Telephone: PPD email: PPD
Fax for North America: PPD Fax for all others: PPD	Fax: PPD

The information provided in a SAE report should be as complete as possible but contain a minimum of:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as serious
- Subject identification and treatment (if applicable)
- Investigator's name and phone number (if applicable)
- Name of the suspect medicinal product and dates of administration
- Assessment of causality (the Investigator must provide a causality assessment for all SAEs and all study drugs, including comparators; however, the SAE must be reported even if the Investigator's causality assessment was unavailable with the initial report)

If full information about the SAE is not yet known, the Investigator will be required to report any additional information within 24 hours as it becomes available.

All SAEs will be evaluated by the Sponsor's Medical Monitor or designee. In the case of a SUSAR, the Sponsor or designee will report the event to all pertinent regulatory authorities having jurisdiction over ongoing tivantinib trials in an expedited manner (within 7 days or 15 days of knowledge) and to all Investigators involved in tivantinib clinical trials.

The Investigators or designee(s) must in turn notify their governing IRB/IEC.

8.5 Post-treatment Safety Follow-up

In this study, the post-treatment safety follow-up period is defined as 30 days after the last dose of assigned treatment. All AEs/SAEs occurring during the study period from the first day of study drug treatment (Day 1 of this study) to the last day of the 30-day post-treatment follow-up period will be captured.

All subjects will be followed for a minimum of 30 days after discontinuation of the study drug(s). All subjects should be instructed to report AEs or SAEs occurring during the 30-day post treatment safety follow-up period. Subjects with unresolved protocol therapy-related AEs at the time of treatment discontinuation will be followed for 30 days after the last dose of tivantinib or until all study-related toxicities have, in the opinion of the Investigator, resolved to baseline, stabilized, or been deemed to be irreversible whichever is later. Treatment-related AEs that occur during the 30-day follow-up period will be followed for a minimum of 30 days from the onset or until all study-related toxicities have, in the opinion of the Investigator, resolved to baseline, stabilized, or been deemed to be irreversible whichever is later.

All SAEs that occur during the 30-day follow-up period should be reported to the Sponsor or its designee within 24 hours following the SAE report procedures described in Section 8.4.

If a subject receives other anticancer therapy within the 30-day follow-up period, the follow-up for AEs will cease, beginning the first day of the new therapy.

9 ASSESSMENT OF ANTI-TUMOR ACTIVITY

Tumor response measurements will be made at the time of the enrollment into the Extension protocol and every 12 weeks after unless current disease specific standard of care requires performing imaging more often. It will be performed following RECIST guidelines, version 1.0 or 1.1 depending on the version used in the original protocol (the guidelines can be found at http://imaging.cancer.gov/clinicaltrials/imaging. Throughout the study, the identical lesions to those identified and measured at baseline must be evaluated using the same technique and preferably by the same Investigator.

MRI/CT scans must meet the standard of care for imaging of lesions of the respective tumor type(s).

10 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the sponsorship of ArQule. Study drug, clinical supplies, and CRFs will be supplied by ArQule or its representative. Representatives of ArQule will monitor the study to verify study data, medical records, and CRFs in accordance with current ICH GCPs and other applicable regulations and guidelines.

11 PLANNED STATISTICAL METHODS

Because of the nature of this study, no formal statistical analysis is planned. Analyses on all baseline, efficacy and safety will consist primarily of listings and descriptive summaries (i.e., descriptive statistics and graphs). Details of all analyses will be included in a separate statistical analysis plan.

12 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS AND INFORMED CONSENT

12.1 Institutional Review Board or Independent Ethics Committee Approval

The protocol, any protocol modifications, the ICF, and, if applicable, permission to use private health information must be approved by the Investigator's IRB/IEC in compliance with Federal regulations 21 CFR 56 prior to study initiation. Documentation of this approval must be provided to ArQule or its designee, and made available during an inspection by the FDA or other regulatory agency inspectors. The Investigator will also provide ArQule with the General Assurance Number documenting that the IRB/IEC is duly constituted, as well as a list of the names, occupations, and affiliations of the members of the IRB/IEC when available.

Before initiating a study, the Investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC and where applicable, competent authorities/regulatory bodies for the trial protocol/amendment(s), written ICF subject recruitment procedures (e.g., advertisements) and written information to be provided to subjects.

12.2 Compliance with GCP and Ethical Considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those affording greater protection to the safety of the trial participants.

This study will also be conducted according to the current revision of the Declaration of Helsinki Revised Edinburgh, Scotland, 2000, with all subsequent revisions and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Changes to the protocol will require written IRB/IEC and, where applicable, competent authorities/regulatory bodies approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

12.3 Subject Information and Consent

The Investigator, or designee, is responsible for the content of the ICF, but the original and any updated versions must be approved by ArQule prior to submission to the IRB/IEC. The ICF should also include any additional information required by local laws relating to institutional review.

Before the start of any study-related procedures are undertaken, the Investigator or authorized designee must obtain written, informed consent from each study participant (or his/her legal representative) in accordance with Federal regulations (21 CFR Part 50) and the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. Informed consent will be obtained by discussing with the subject the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the subject.

The Investigator or designee must explain to the subject that for purposes of evaluating the study results, that subject's private health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRBs/IECs, before enrolling that subject into the study. It is the Investigator's (or designee's) responsibility to obtain permission to use private health information per the Health Information Portability and Accountability Act (HIPAA) from each subject, or if appropriate, the subject's legal representative.

The subject or his/her legal representative will document his/her informed consent by signing the current version of the written, IRB-approved ICF in the presence of a witness. The person who conducted the informed consent discussion with the subject and/or subject's legal representative must also sign the ICF. The subject is given a fully executed copy of the ICF bearing all appropriate signatures, and the original must be maintained in the clinical master files at the site.

All active subjects participating on the protocol must be re-consented each time the ICF is updated and re-approved by the IRB/IEC.

13 STUDY MANAGEMENT AND MATERIALS

13.1 Monitoring, Verification of Data, Audit, and Inspection

An ArQule monitor or designee will periodically visit each clinical study site to discuss the progress of the clinical trial and to review CRFs and original source documents for accuracy of data recording, study drug accountability, and correspondence. When requested, the Investigator must be available to the study monitor for personal, one-to-one consultation.

Periodically, some or all of the facilities used in the trial may be reviewed or inspected by the IRB/IEC and/or regulatory authorities. An audit or inspection may include, for example, a review of all source documents, drug records, and original clinical medical notes.

The Investigator is to ensure that the trial participants are aware of and consent to the review of personal information during the data verification process, as part of the monitoring/auditing process conducted by properly authorized agents of ArQule, or be subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent of applicable law and is not publicly available.

13.2 Data Recording and Retention of Study Data

In compliance with GCP, the medical records/medical notes, and other study-related materials should be clearly marked and permit easy identification of participation by an individual in a specified clinical trial.

The Investigator is to record all data with respect to protocol procedures, drug administration, laboratory data, safety data, and efficacy ratings on the eCRFs.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of the master clinical study records, ArQule must be notified in writing so that adequate provision can be made with regard to the trial documents.

Trial documents should be retained for at least two years after the approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of tivantinib by ArQule. The documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with ArQule that it will inform the Investigator, in writing, as to when the retention of these documents are no longer necessary.

13.3 Electronic Case Report Forms

An Electronic Data Capture (EDC) system will be used to collect the data in this study. The EDC system provides functionality for the clinical sites to enter the data directly into the eCRFs and respond to data discrepancies. Once the data are entered, the information is encrypted and transmitted over the Internet to a clinical trial server where it is electronically reviewed. Any resulting data queries are immediately sent back to the site for resolution. The system automatically keeps a full audit trail of all data changes that occur. The clinical team will undertake additional manual review of the data, but all resulting data queries or

clarifications will be entered into the EDC system for resolution. All eCRFs will be completed according to instructions provided in the eCRF Completion Guidelines and ICH/GCP guidelines.

13.4 Confidentiality, Publication, and Disclosure Policy

The Investigator understands that ArQule will use the information developed in the clinical study in connection with the development of tivantinib. This information may be disclosed to other clinical Investigators, the FDA, and other government agencies.

All information disclosed to the Investigator by ArQule for the purpose of having the Investigator conduct the clinical trial described in this protocol, or information generated by the Investigator as results in the clinical trial shall be treated by the Investigator as strictly confidential. The Investigator shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is made to colleagues and/or employees who reasonably require the information in order to assist in carrying out the clinical trial and who are bound by like-obligations of confidentiality. Notwithstanding, the Investigator may use or disclose to others any information which: (i) was known to the Investigator prior to the date of its disclosure; (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigator on a non-confidential basis by a third party who is not obligated to ArQule or any other party to retain such information in confidence.

ArQule acknowledges that the Investigator has certain professional responsibilities to report to the scientific community on findings made in the clinical investigations they conduct. The Investigator shall have the right to publish the results of research performed under this protocol, provided that such publication does not disclose any Confidential Information or trade secrets of ArQule (other than the Data). If the study is conducted as part of a multi-center protocol, the Investigator agrees not to independently publish the findings except as part of an overall multi-center publication, unless specifically approved in writing by ArQule or unless more than 12 months have elapsed since the last subject in the study has completed his/her study designed treatment.

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APPENDIX 1: SCHEDULE OF ASSESSMENTS

	Pre-Study Visit	Monthly	Weekly [1] (combination tx)	Weekly (tivantinib -naïve tx)	End of Treatment Visit	30-Day Safety FU
Tests and Procedures/ Window (days)	**-14 to Day 1**	**±3 days**	**± 3 days**	**± 3 days**	**within 7 (+3) days**	
Written informed consent[2]	X					
Medical history	X					
Physical examination	X	X		X[3]	X	
ECOG PS	X	X		X[3]	X	
Vital signs and weight[3]	X	X	X[3]	X[3]	X	
Hematology	X	X	X[3]	X[3]	X	
Chemistry panel	X	X		X[3]	X	
Electrolyte panel	X			X[3]	X	
Liver Function test	X			X[3]		
Coagulation panel	X				X	
Serum pregnancy test (if applicable)	X				X	
12-Lead ECG	X				X	
Tumor assessment[4]	X	X			X	
Tumor markers assessment (if applicable)	X	X			X	
Concomitant medications	X	X	X		X	X
AE assessment	X[5]	X	X		X	X
Tivantinib dispensation	X	X				
Combination therapy drug(s) dispensation/ administration (if applicable)	X	X	X			
Telephone call						X

1. Weekly visits may be required for administration of combination therapy drug(s) or for tivantinib-naïve subjects during the first four weeks of treatment with tivantinib
2. Must be obtained before any study related procedures
3. Weight is NOT required for weekly visits
4. Should be done every 12 weeks unless current disease specific standard of care requires performing imaging more often
5. All AEs/SAEs occurring during the study period from the first day of study-drug treatment (Day 1 of this study) to the last day of the 30-day post-treatment follow-up period will be captured. AEs that continue from the original tivantinib study or begin after the last visit of the original study but prior to Day 1 of the Extension study must be documented on a Medical History eCRF page. Resolved AEs from the original tivantinib study are captured in the original study records and will not be re-recorded for this study.

APPENDIX 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

APPENDIX 3: EXAMPLES OF *IN VIVO* SUBSTRATES, INHIBITORS, AND INDUCERS FOR SPECIFIC CYP ENZYMES

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

Note: 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 having 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.

APPENDIX 4: DOSE MODIFICATION GUIDELINES FOR COMBINATION THERAPY

When during combination therapy co-drug related toxicity is observed, dose delays and/or reduction s in co-drug administration are allowed as described below or may follow institutional guidelines/standard of care.

Sorafenib (Nexavar®) Dose Modification

Temporary dose interruption and/or dose reduction may be necessary due to adverse events. For recommendations for skin adverse events, see Table A4-1. If dose reduction is necessary, the sorafenib dose may be reduced to once a day. If further dose reduction is necessary, sorafenib may be given once every other day.

Table A4-1 Sorafenib Dose Modifications for Dermatologic Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet that does NOT disrupt the subject's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the subject's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptom relief.
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1. When resuming treatment, decrease sorafenib dose by 1 dose level (dosing once a day or once every other day).
	4th occurrence	Discontinue sorafenib treatment.
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that causes the subject to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1. When resuming therapy, decrease sorafenib by 1 dose level (dosing once a day or once every other day).
	3rd occurrence	Discontinue sorafenib treatment.

Please refer to the approved sorafenib (Nexavar) package insert for details.

Gemcitabine (Gemzar®) Dose Modification

Dosage adjustment of gemcitabine is based upon the degree of hematologic toxicity experienced by the subjects. Subjects receiving gemcitabine should be monitored prior to each dose with a complete blood count, including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table A4-2.

Table A4-2 Gemcitabine Dosage Reduction Guidelines

Absolute Granulocyte Count ($\times 10^6$/L)	Platelet Count ($\times 10^6$/L)	Percent of Full Dose (%)
≥ 1000 and	≥ 100,000	100
500 – 999 or	50,000 – 99,999	75
< 500 or	< 50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine should be administered with caution in subjects who have evidence of significant renal or hepatic impairment, as there is insufficient information from clinical studies to allow clear dose recommendation for these subject populations.

Refer to the approved gemcitabine (Gemzar) package insert for details.

Erlotinib (Tarceva®) Dose Reduction

When dose reduction is necessary, the erlotinib dose should be reduced by a 50 mg decrement. For this study, no more than 1 dose reduction will be allowed.

Pulmonary Symptoms: In subjects who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough, or fever, treatment with erlotinib should be interrupted pending diagnostic evaluation. If interstitial lung disease is diagnosed, erlotinib should be discontinued and appropriate treatment instituted, as necessary.

Diarrhea: Diarrhea can usually be managed with loperamide. Subjects with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy.

Skin Reactions: Skin reactions experienced by subjects receiving erlotinib tend to be managed easily with topical therapies and do not require treatment interruption or dose modification (please refer to package insert for details). However, rare subjects with severe skin reactions may also require dose reduction or temporary interruption of therapy.

Concomitant CYP3A4 Inhibitors: In subjects concomitantly treated with a strong CYP3A4 inhibitor, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, or voriconazole, a dose reduction should be considered if severe adverse reactions occur.

Hepatic Impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore, caution should be used when administering erlotinib to subjects with hepatic impairment. Dose reduction or interruption of erlotinib should be considered if severe

adverse reactions occur. For additional dose modification information, please refer to the package insert for erlotinib (Tarceva).

Irinotecan (Camptosar) and Cetuximab (Erbitux®) Dose Reductions

Refer to the locally applicable irinotecan and cetuximab package inserts for dose reductions, modifications, or delays due to irinotecan- or cetuximab-related toxicities. The recommended dose levels for reductions in irinotecan and cetuximab are shown in Table A4-3. General recommendations for dose modifications are provided in Table A4-4.

Supportive therapy for toxicities associated with irinotecan and/or cetuximab therapy may be given, according to institutional practice.

A new cycle of treatment may begin when the ANC is $\geq 1.5 \times 10^9$/L, the platelet count is $\geq 100 \times 10^9$/L, and any treatment-related gastrointestinal toxicity is resolved to ≤ Grade 1.

The ANC level at baseline must be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. If the initiation of a new cycle or treatment during a cycle is delayed for 4 weeks or longer, the subject should be removed from study treatment. Doses that are withheld are not to be made up.

Table A4-3 Recommended Irinotecan and Cetuximab Dose Reductions

Agent	Initial Dose	Level -1	Level -2[a]
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
Cetuximab	400 mg/m^2	250 mg/m^2	200 mg/m^2
a: If a reduction below Level -2 is indicated, discontinue treatment with that agent			

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity

Event	Action
Hematologic	
Grade 2 Hematologic	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, resume at the previous dose levels, provided ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L.
Grade 3 to 4 Hematologic	Hold irinotecan. If counts recover to ANC $\geq 1.5 \times 10^9$/L and platelets to $\geq 100 \times 10^9$/L, may be resumed at 1 lower dose level for the remainder of the cycle. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.
Febrile neutropenia	Hold irinotecan. If fever resolves and counts recover to ANC $\geq 1.5 \times 10^9$/L and platelets to $\geq 100 \times 10^9$/L, both agents may be resumed at 1 lower dose level for the remainder of the cycle. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.
Diarrhea	
Grade 2 Diarrhea	Reduce irinotecan for 1 dose level for the remainder of the cycle. If diarrhea persists, hold cetuximab until fully resolved. For subsequent cycles, resume all agents at the previous dose levels, provided diarrhea has fully resolved.
Grade 3 to 4 Diarrhea	Hold irinotecan and cetuximab. If diarrhea resolves to ≤ Grade 2, both agents may be resumed at 1 lower dose level for the remainder of the cycle. If diarrhea persists, hold cetuximab until fully resolved. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.
Nausea/Vomiting[a]	
Grade 3 Nausea and/or Vomiting	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, continue irinotecan at the reduced dose level from the previous cycle.
Grade 4 Nausea and/or Vomiting	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, continue irinotecan at the reduced dose levels from the previous cycle.

a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.
b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.
AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity (Continued)

Event	Action
Mucositis	
Grade 2 Mucositis	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, continue at the reduced dose levels from the previous cycle. No modifications (or delays) will be made for cetuximab.
Grade 3 Mucositis	Hold irinotecan. If mucositis resolves to ≤ Grade 2, treatment may be resumed at 1 lower dose level for the remainder of the cycle. For subsequent cycles, continue at the reduced dose level from the previous cycle. No modifications (or delays) will be made for cetuximab.
Grade 4 Mucositis	Hold ALL study treatment, including irinotecan, cetuximab, and tivantinib. If mucositis resolves to ≤ Grade 2, irinotecan may be resumed at 1 lower dose level for the remainder of the cycle. Cetuximab will be resumed at the prior dose. For subsequent cycles, continue all agents at the dose level from the previous cycle.
Pulmonary	
Grade 2 or worsening pulmonary symptoms unrelated to underlying cancer	Cetuximab treatment should be stopped and symptoms investigated. Cetuximab treatment may resume at 1 lower dose level when symptoms resolve to ≤ Grade 1 and cetuximab-related pneumonitis is ruled out.
≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates	Hold cetuximab until interstitial lung disease is ruled out. Continue irinotecan. Discontinue all study treatment if interstitial lung disease is confirmed.
Hypomagnesemia	
Grade 3 or 4 hypomagnesemia	Hold cetuximab until hypomagnesemia resolves to ≤ Grade 2, then restart cetuximab at the same dose. For any Grade of hypomagnesemia, magnesium supplementation should be provided.

a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.
b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.
AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity (Continued)

Event	Action
Venous thrombotic events	
Grade 3 venous thrombosis or asymptomatic pulmonary embolism	Hold treatment with cetuximab. If the planned duration of full-dose anticoagulation is ≤ 2 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is ≥ 2 weeks, treatment may be resumed during the period of full-dose anticoagulation, if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on a stable dose of low molecular weight heparin prior to restarting treatment. • The subject must not have pathological conditions that carry a high risk of bleeding (eg, tumor involving major vessels). • The subject must not have had hemorrhagic events while on study.
Grade 4 or recurrent/worsening venous thromboembolic events	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Symptomatic pulmonary embolism	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Arterial thrombotic events	
Grade 3 cardiac ischemia/infarction	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Any Grade 4 arterial thrombotic event[b]	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
LV dysfunction	
Grade 3 LV dysfunction	Discontinue cetuximab. Subjects may continue other study treatment.
Grade 4 LV dysfunction	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.

a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.
b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.
AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity (Continued)

Event	Action
Hemorrhage/bleeding	
Grade 3 hemorrhage/bleeding	Hold tivantinib treatment; once hemorrhage or bleeding resolves, tivantinib treatment may be continued at the Investigator's discretion.
Grade 4 hemorrhage/bleeding	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Rash	
Grade 3 rash (1st occurrence)	Hold cetuximab infusion 1 to 2 weeks: • If improvement, continue at 500 mg/m^2. • If no improvement, discontinue cetuximab.
Grade 3 rash (2nd occurrence)	Hold cetuximab infusion 1 to 2 weeks: • If improvement, reduce to 400 mg/m^2. • If no improvement, discontinue cetuximab.
Grade 3 rash (3rd occurrence)	Hold cetuximab infusion 1 to 2 weeks: • If improvement, reduce to 300 mg/m^2. • If no improvement, discontinue cetuximab.
Grade 3 rash (4th occurrence)	Discontinue cetuximab.
Grade 4 rash (1st occurrence)	Discontinue cetuximab.
Hypersensitivity[c]	
Grade 1 hypersensitivity reactions (all agents)	Decrease the infusion rate for all agents by 50% until symptoms resolve; then resume at the initial planned rate (except for cetuximab, see below).
Grade 2 hypersensitivity reactions (all agents)	Stop infusion. Administer histamine 1 and/or histamine 2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pre-treat before all subsequent doses. Treat according to institutional policy.
Grade 3 or Grade 4 hypersensitivity reactions (all agents)	Stop the infusion. Permanently discontinue all study treatment and notify the Study Coordinator.
Grade 1 or 2 cetuximab infusion reactions	Stop the infusion until symptoms resolve, then restart cetuximab at a 50% lower rate of infusion. All subsequent doses should be administered at the lower infusion rate.
≥ Grade 3 cetuximab infusion reactions	Discontinue cetuximab. Other study treatment may be continued.
Other nonhematologic	
Grade 3 or higher nonhematologic toxicities not described above	Hold ALL study treatment, including irinotecan, cetuximab, and tivantinib, and monitor toxicity at least weekly. If toxicity resolves to Grade 1 or lower within 4 weeks, treatment may be resumed, with cetuximab and irinotecan at 1 lower dose level.
a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.	

b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.
AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

SPONSOR SIGNATURE

Study Title:	An Extension Protocol for Subjects Who Were Previously Enrolled in Other Tivantinib (ARQ 197) Protocols
Study Number:	ARQ 197-299

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Sign[PPD] te: 18 FEB 2014

ArQule, Inc

Signed[PPD] Date: 18 Feb 2014

ArQule, Inc

INVESTIGATOR'S SIGNATURE

Study Title:	An Extension Protocol for Subjects Who Were Previously Enrolled in Other ARQ 197 Protocols
Study Number:	ARQ 197-299

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Printed Name:_____

Signature:_____ Date: _____

Summary of Changes

Amendment 1	Amendment 2
Title page	
An Extension Protocol for Subjects Who Were Previously Enrolled in Other ARQ 197 Protocols	An Extension Protocol for Subjects Who Were Previously Enrolled in Other Tivantinib (ARQ 197) Protocols
	Added NCT Number: 01178411
Medical Monitor: PPD [redacted]	Medical Monitor: PPD [redacted]
Synopsis: Study Design (p.2)	
The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator based on the combination drug(s) label(s).	The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.
[redacted]	*Added* Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.
Synopsis: Test Product, Dose, and Mode of Administration (p.3)	
	Added Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.

The combination therapies considered must have been evaluated in prior ARQ 197 combination studies. The combination therapy dose(s) and schedule(s) will be determined to each subject by the Investigator based on the combination drug(s) label(s). ARQ 197 will be administered orally, twice a day, with meals (regardless of original protocol requirements).	The combination therapy(ies) considered must have been evaluated in prior tivantinib combination studies. The tivantinib monotherapy and combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials. Tivantinib will be administered orally, twice a day, with meals (regardless of original protocol requirements).
1 Introduction (pp.9-10)	
ARQ 197 is the most advanced representative of a newly discovered class of trans 3,4 disubstituted pyrrolidine-2,5-diones having the potential to treat cancer. ARQ 197 selectively inhibits tyrosine kinase, c-Met, which has been implicated in tumor invasiveness and metastasis.	Tivantinib is the most advanced representative of a newly discovered class of trans 3,4 disubstituted pyrrolidine-2,5-diones having the potential to treat cancer. Tivantinib is a novel, small molecule inhibitor of c-MET receptor tyrosine kinase. The expression of c-MET is dysregulated in many types of human malignancies with overexpression of c-MET kinase, c-*MET*-activating genetic mutations, c-*MET* amplifications, and increased expression of the c-MET ligand hepatocyte growth factor (HGF). This dysregulation is implicated with a poor prognosis with greater tumor proliferation and increased angiogenesis with migration and invasion.
Deleted Activation of c-Met results in the binding and phosphorylation of adaptor proteins such as Gab-1, Grb-2, Shc, and c-Cbl, and subsequent activation of signal transducers such as PI3K, PLC-g, STATs, ERK1 and 2 and FAK. c-Met and HGF are expressed in numerous tissues and their expression is normally confined predominantly to cells of epithelial and mesenchymal origin, respectively. c-Met and HGF are dysregulated in human cancers and may contribute to dysregulation of cell growth, tumor cell dissemination, and tumor invasion during disease progression and metastasis. c-Met and HGF are highly expressed relative to surrounding tissue in numerous cancers and this expression correlates with poor subject prognosis. c-Met and HGF may protect tumors against cell death induced by DNA-damaging	

agents and, as such, may contribute to chemoresistance and radioresistance of tumors. Therefore, inhibitors of c-Met may be useful as therapeutic agents in the treatment of malignant proliferative disorders.	
	Added Activation of c-MET results in the binding and phosphorylation of adaptor proteins such as growth factor receptor-bound-associated binder-1 (Gab-1), growth factor receptor-bound protein 2 (Grb-2), Src homology 2 domain-containing and Casitas B-lineage lymphoma progene (c-Cbl), and subsequent activation of signaling pathways, including phosphatidylinositol-3-kinase/activated protein kinase B (PI3K/Akt), focal adhesion kinase-1 (FAK), signal transducers and activators of transcription protein (STAT), and mitogen-activated protein kinase/ERK (Ras/MEK/Erk) pathways. Mesenchymal-epithelial transition factor and HGF are expressed in numerous tissues and their expression is normally confined predominantly to cells of epithelial and mesenchymal origin, respectively. Mesenchymal-epithelial transition factor and HGF are deregulated in human cancers and may contribute to dysregulation of cell growth, tumor cell dissemination, and tumor invasion during disease progression and metastasis. Mesenchymal-epithelial transition factor and HGF are highly expressed relative to surrounding tissue in numerous cancers, and this expression correlates with poor subject prognosis. Mesenchymal-epithelial transition factor and HGF may protect tumors against cell death induced by deoxyribonucleic acid (DNA)-damaging agents and, as such, may contribute to chemoresistance and radioresistance of tumors. Therefore, inhibitors of c-MET may be useful as therapeutic agents in the treatment of proliferative disorders. Tivantinib selectively inhibits the inactive or unphosphorylated form of human c-MET and shows *in vitro* biochemical activity against recombinant c-MET with an inhibition constant (Ki) of approximately 355 nM. The potency of tivantinib inhibition of c-MET activity is

	independent of adenosine triphosphate (ATP) concentration, which suggests that tivantinib's inhibition is of noncompetitive nature. Tivantinib was profiled against 230 protein kinases, and while tivantinib inhibits c-MET kinase activity, it is not a promiscuous kinase inhibitor. In nonclinical studies, tivantinib showed broad-spectrum *in vitro* anti-cancer activity against human tumor cell lines, including breast, colon, lung, pancreas, and gastric cancer cell lines. The potency of tivantinib in cancer cells expressing detectable c-MET in anti-proliferative assays yield IC_{50} values from 0.1 mM to 0.6 mM. The ability of tivantinib to inhibit c-MET phosphorylation correlated with its ability to inhibit growth in c-MET expressing cancer cells, thereby indicating its anti-cancer activity. In single-agent *in vivo* studies, tivantinib was shown to be efficacious against multiple human cancer xenograft models and was well tolerated without drug-related clinical signs or deaths. The tivantinib development program is predicated on the hypothesis that tivantinib-mediated inhibition of the c-MET pathway, either alone or in combination with other anti-cancer compounds, will be beneficial in treating malignancies.
1.1 Overview of Clinical Experience (pp.10-11)	
ARQ 197 has been or is currently being evaluated in ten Phase 1 clinical studies, four in healthy normal volunteers to assess pharmacokinetics (PK) and bioavailability (ARQ 197-110 (to assess different polymorphic forms), ARQ 197-112 (to assess PK in CYP2C19 poor and normal metabolizers), ARQ 197-113 (to assess different polymorphic forms), and ARQ 197-A-U151) and six dose escalation studies involving subjects with advanced solid tumors (ARQ 197-101, ARQ 197-103, ARQ 197-111, ARQ 197-114, ARQ 197-116, and ARQ 197-117). Five Phase 2 studies are being conducted, including one randomized placebo controlled combination study with erlotinib in subjects with previously treated non small-cell	As of 23 Aug 2013, 30 Phase 1 and Phase 2 studies (completed and ongoing) have been conducted; refer to the IB for additional information on these studies. One Phase 3 study in subjects with non-small cell lung cancer (NSCLC) is ongoing (ARQ 197-006) and one is completed (ARQ 197-A-U302). A Phase 3 study in subjects with hepatocellular carcinoma (HCC) is ongoing (ARQ 197-A-U303). Completed and ongoing studies have included subjects with colorectal cancer, gastric cancer, HCC, microphthalmia transcription factor associated tumors, non-central nervous system germ cell tumors, NSCLC, and pancreatic adenocarcinoma. Approximately 127 healthy subjects have received tivantinib in completed Phase 1 studies. Another 2691 subjects with cancer have been randomized in ongoing or completed

lung cancer (ARQ 197-209), one single agent open label study in subjects with microphthalmia transcription factor associated tumors (ARQ 197-204), one randomized, placebo controlled single agent study in subjects with unresectable hepatocellular carcinoma (ARQ 197-215), one single agent open label study in subjects with relapsed or refractory germ cell tumors (ARQ 197-A-U251), and one randomized, placebo controlled combination study irinotecan and cetuximab in subjects with previously treated wild-type KRAS metastatic colorectal cancer (ARQ 197-A-U252). In addition, one Phase 2 randomized, open-label single agent (ARQ 197 vs. gemcitabine) study (now terminated) was conducted in subjects with advanced pancreatic carcinoma (ARQ 197-205).	Phase 1, 2, and 3 studies of tivantinib. Phase 1 and Phase 2 studies demonstrated early clinical activity of tivantinib as monotherapy and in combination with other anticancer agents (including erlotinib, sorafenib, gemcitabine, irinotecan, and cetuximab).
Clinical PK data from multiple ARQ 197 clinical studies demonstrated that the C_{max} increased with increasing doses of ARQ 197; however, the exposure was not dose proportional. Inter-subject variability in PK appears to be due in part to CYP 2C19 genetic polymorphism. In healthy normal volunteers (Study ARQ 197-112) the PK of ARQ 197 was compared in CYP 2C19 poor metabolizers (PMs) vs CYP 2C19 extensive metabolizers (EMs). The study confirmed that CYP 2C19 PMs had much higher exposure as reflected by $AUC_{(0-48)}$ and C_{max} (11-fold and 3-fold higher, respectively and lower clearance (mean of 2.4 L/hr versus mean of 33.9 L/hr) than EMs.	Clinical pharmacokinetic (PK) studies of tivantinib have been conducted in 14 Phase 1 studies that include 127 healthy subjects and 426 subjects with cancer. In general, AUC and C_{max} increased with an increasing dose of tivantinib, although this increase was not dose proportional. Following human oral administration with a meal, tivantinib is rapidly and almost completely absorbed. The drug is extensively metabolized by CYP3A4 and CYP2C19 isozymes with no parent compound being detected in the urine and only traces of parent compound being detected in the feces. Tivantinib exposure is affected by the following factors: CYP2C19 genotype, history of hepatocellular carcinoma, coadministration of a CYP3A4 inhibitor, dosage form (i.e., crystalline vs. amorphous), formulation (capsule vs. tablet), and fed status during tivantinib administration.
1.1.1 Summary of the Most Common Drug Related AEs and SAEs (pp.11-29)	**1.1.1 Safety in Clinical Trials** (pp.11-29)
	Added Tivantinib demonstrated a manageable safety profile with adverse drug reactions of myelosuppression (including anemia, neutropenia, febrile neutropenia, thrombocytopenia, leukopenia, pancytopenia, and neutropenic sepsis) and

bradycardia. The majority of drug-related adverse events (AEs) have been mild to moderate with manageable toxicities.

Myelosuppression

Myelosuppression (including anemia, neutropenia, febrile neutropenia, thrombocytopenia, leukopenia, pancytopenia, and neutropenic sepsis) has been reported in single agent and combination therapy clinical studies of tivantinib. There have been fatal outcomes for some neutropenic events. Complete blood count should be performed as advised in the protocols. Caution is advised when any CYP2C19 inhibitors and/or strong CYP3A4 inhibitors are used as concomitant therapy, and in subjects with known CYP2C19 poor metabolizer status. Dose modifications were made in the HCC studies because of higher incidences of neutropenia and febrile neutropenia, which were associated with higher drug levels in these subjects. Subjects who experience severe myelosuppression including neutropenia should be monitored more closely throughout the study, and dose modifications or interruptions should be made as specified in the original protocols. For subjects with severe neutropenia, febrile neutropenia, or neutropenic sepsis, supportive care, including use of haematopoietic growth factors and antibiotics should be considered.

Bradycardia

Bradycardia has been reported in single agent and combination therapy clinical studies of tivantinib. In general, bradycardia was most commonly reported as a nonserious adverse event. Most of these events were mild to moderate in severity (Grade 1–2.) Most subjects were asymptomatic and recovered without additional therapy, though the bradycardic effect may be prolonged. However, cases of bradycardia requiring hospitalization have been reported, and some subjects received placement of permanent pacemakers.

Subjects who appear to be at a greater risk for severe bradycardia are those with pre-existing bradycardia or sick sinus syndrome or those patients receiving beta-blocker therapy. In these patients, tivantinib should be used with caution.

	Electrocardiogram (ECG) monitoring is recommended prior to initiation of tivantinib therapy and is to be repeated at any visit when a subject has a heart rate ≤50 beats per minute (bpm), or as clinically indicated. In general, heart rate and ECG should be monitored as specified in the original protocol, and dose reduction should be considered for subjects with persistent bradycardia and symptomatic hypotension. **Interstitial Lung Disease** There have been reports of interstitial lung disease (ILD) or similar events in subjects enrolled in tivantinib studies. The reported events included ILD, pneumonitis, acute respiratory distress syndrome, acute lung injury, and diffuse alveolar damage. In the majority of the reports, tivantinib was given in combination with agents with known association with ILD, including erlotinib and gemcitabine. An association of tivantinib and ILD has not been established. However, it is recommended to investigate the cause for a marked increase in respiratory symptoms in subjects participating in tivantinib studies, particularly in Asian patients. **MONOTHERAPY STUDIES** **ARQ 197-101** ARQ 197-101 was an open-label study of tivantinib in subjects with metastatic solid tumors, including renal cell carcinoma (RCC) and other c-MET-expressing tumors, that were refractory to available systemic therapies or for whom no standard effective systemic therapy existed. A total of 79 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment were disease progression (59.5%), symptomatic deterioration without evidence of progression (19.0%), and subject request (10.1%). The most common (≥ 10%) AEs were fatigue (40.5%), nausea and vomiting (27.8% each), anemia/hemoglobin decreased (24.0%), and diarrhea (21.5%). One subject had an AE (neutropenia) that led to a dose reduction, which was considered drug-related. A total of 28 of 79 (35.4%) subjects reported serious adverse events (SAEs). The most common SAEs were disease

	progression and dehydration, each experienced by 5 (6.3%) subjects. There were eight deaths within 30 days of the last dose of study drugs; five of the deaths resulted from disease progression. The other deaths, one each, were due to the following: cardio-pulmonary arrest, pancytopenia, and respiratory failure. **ARQ 197-103** ARQ 197-103 was an open-label study of tivantinib in subjects with advanced solid tumors who were refractory to available therapy or for whom no standard effective systemic therapy existed, including subjects with advanced prostate cancer. A total of 51 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment were progressive disease (74.5%), AE (13.7%), and symptomatic deterioration without evidence of progression (5.9%). The most common AEs were fatigue (49.0%), nausea (29.4%), anemia (27.5%), vomiting (25.5%), anorexia and constipation (23.5% each), and back pain and weight decreased (21.6% each). Seven (13.7%) subjects experienced AEs that led to treatment discontinuation. Two subjects discontinued treatment due to hyperbilirubinaemia and one subject each discontinued treatment due to chest infection, infection, fatigue, palmar-plantar erythrodysesthesia syndrome, febrile neutropenia, and nausea. Serious adverse events were reported in 22 (43.1%) subjects. Serious adverse events reported at a ≥ 5% incidence (more than one subject) were febrile neutropenia (5.9%) and disease progression (9.8%). There were five deaths during treatment or within 30 days of the last dose of study drug. All deaths were due to disease progression and were judged to be not related to study drug. **ARQ 197-114** ARQ 197-114 was an open-label study of tivantinib in cirrhotic subjects with HCC who had received not more than two prior systemic regimens. A total of 21 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment were progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST)

	(61.9%), clinically unacceptable toxicities (19.0%), and clinical disease progression (9.5%). The most common AEs were asthenia and neutropenia (57.1% each), anemia (52.4%), anorexia (47.6%), leukopenia (38.1%), and fatigue, edema peripheral, and diarrhea (33.3% each). In this study, AEs leading to dose reduction occurred in 4 of 21 (19.0%) subjects and all were considered to be drug-related. One subject had a dose reduction due to neutropenia and anemia. A second subject had dose reduction due to bradycardia and dyspnea. A third subject had dose reduction due to anemia. The fourth subject had a dose reduction due to asthenia. Serious adverse events reported for more than one subject were neutropenia (three subjects), and anemia, leukopenia, and disease progression (two subjects each). Five subjects died during treatment or within 30 days of the last dose of study drug. The cause of death in one subject (septic shock) was considered related to study drug. Other deaths were considered unrelated to study drug and were the result of the following causes: disease progression (two subjects), peritoneal hemorrhage (one subject), and pneumonia (one subject). **ARQ 197-A-U157** ARQ 197-A-U157 was an open-label, randomized, two-treatment, two-period, two-way crossover, relative bioavailability study of a capsule and a tablet formulation of tivantinib in subjects with advanced solid tumors. A total of 26 subjects were enrolled in the study and 25 (96.2%) completed the 14-day crossover study phase. One subject withdrew from the 14-day crossover study phase due to disease progression, and 25 (96.2%) subjects continued in the extension phase. Bradycardia was reported for 6 of 26 (23.1%) subjects and 6 of 25 (24.0%) subjects in the cross-over and extension phases, respectively; the majority of the events of bradycardia were considered related to study treatment. Neutropenia was reported for 4 of 25 (16.0%) subjects in the extension phase; 2 subjects had neutropenia that was considered to be study-drug related. Most of the AEs were Grade 1 or Grade 2. Grade ≥3 events in the extension phase of the study included anemia, neutropenia,

	pneumonia, failure to thrive, haemoptysis, respiratory failure (Grade 5), lactic acidosis, and bone pain, which were experienced by 1 subject (4.0%) each, and Grade ≥3 dyspnoea, experienced by 2 subjects (8.0%). There were no SAEs reported during the crossover phase of the study. During the extension phase of the study, four subjects had SAEs considered unrelated to study treatment and three of these subjects died due to the SAEs, which included progressive disease (fatal), respiratory failure (fatal), and metastatic NSCLC (fatal). None of the deaths were considered related to study treatment. **ARQ 197-0701** ARQ 197-0701 was an open-label study of tivantinib in Japanese subjects with advanced or recurrent solid tumors who had been classified as extensive metabolizers (EM) or poor metabolizers (PM) based on CYP2C19 genotype, including 25 subjects with NSCLC, and who were refractory to available therapy or for whom no standard therapy existed. A total of 47 subjects were enrolled and treated in the study. The most common reason for discontinuing treatment was disease progression (43 subjects). Sixteen SAEs were reported in 11 subjects. Two SAEs were reported more than once: neutrophil count decreased (2 subjects) and white blood cell count decreased (2 subjects). No subjects died during the study or within 30 days of the last dose of study drug. **ARQ 197-A-U158** ARQ 197-A-U158 was a Phase 1, open-label, single-sequence, crossover study to determine the effect of multiple doses of tivantinib on the single-dose PK of omeprazole/S-warfarin/caffeine/ midazolam and digoxin when co-administered with tivantinib in cancer subjects. A total of 28 subjects were enrolled into the study. All 28 subjects completed Probe Reference Treatment and initiated tivantinib. Twenty-two (78.6%) subjects completed the Primary Objective Phase. Of the six (21.4%) subjects who discontinued from the Primary Objective Phase, three (10.7%) discontinued due to an AE, two (7.1%) due to other reasons, and one (3.6%) due to progressive disease.

	The most commonly reported AEs were fatigue (7 [25.0%] subjects), constipation (5 [17.9%] subjects), and vomiting (5 [17.9%] subjects). Twenty-four SAEs were reported in 13 subjects. Disease progression was reported in 4 subjects, anemia was reported in 3 subjects, and neutropenia, nausea, vomiting, and white blood cell count decreased were each reported in 2 subjects. No subject died due to an adverse event during the Primary Objective Phase of the study or during the Extension Phase. Three subjects died after completing the Primary Objective Phase and one subject died before completing the Primary Objective Phase, all due to disease progression. **ARQ 197-A-U159** ARQ 197-A-U159 was a single-blind, single-sequence study assessing the effect of tivantinib on the QTc interval in subjects with cancer. A total of 38 subjects were enrolled in the study; 1 subject was discontinued from the study prior to dosing with tivantinib. The remaining 37 (97.4%) subjects all completed the Primary Objective Phase. All of the 37 subjects entered the Extension Phase. Of these, 30 received tivantinib in combination with one or two other drugs while 7 continued on tivantinib monotherapy. Adverse events were reported in 37 (97.4%) subjects during the study. During the Primary Objective Phase, the most commonly (≥ 5%) reported AEs occurring after tivantinib dosing were fatigue (6 [16.2%] subjects), nausea (3 [8.1%] subjects), vomiting (2 [5.4%] subjects), and headache (2 [5.4%] subjects). During the Extension Phase, AEs reported by ≥ 10% of subjects included neutropenia (11 [29.7%] subjects); nausea, fatigue (9 [24.3%] subjects each); diarrhea (8 [21.6%] subjects); constipation, dyspnea (7 [18.9%] subjects each); anemia, dermatitis acneiform (6 [16.2%] subjects each); and decreased appetite, tumor pain, and alopecia (5 [13.5%] subjects each). No subject had an SAE during the Primary Objective Phase, and 4 (10.8%) subjects experienced SAEs during the Extension Phase. No subject was discontinued due to AEs during any phase of the study. No subject died during the study due to an AE. One subject died

	during the Extension Phase due to disease progression. **ARQ 197-004** ARQ 197-004 was an open-label study of tivantinib in gastric cancer subjects following gastrectomy, to determine exposure and progression free survival (PFS) rate in gastric cancer. A total of 31 subjects were enrolled and treated in this study. The most common reason for discontinuing treatment was progressive disease (27 [87.1%] subjects). The most common AEs were anorexia (33.3%), nausea (30.0%), alkaline phosphatase increased, anemia, and fatigue (each 23.3%), and abdominal pain, aspartate aminotransferase (AST) increased, and constipation (each 20.0%). There were no deaths during study treatment or within 30 days after the last dose of study drug. **ARQ 197-204** ARQ 197-204 was an open-label study of tivantinib in subjects 13 years of age or older with histologically or cytologically confirmed MiT tumors (alveolar soft part sarcoma, clear cell sarcoma, or translocation associated RCC). A total of 47 subjects were enrolled and treated in the study. The most common reason for discontinuing treatment was disease progression (31 [66.0%] subjects discontinued due to progressive disease by RECIST and 7 [14.9%] subjects discontinued due to clinical progression). Of the 47 enrolled subjects, 18 received tivantinib 120 mg twice daily (BID) (capsule formulation), 21 received tivantinib 360 mg BID (capsule formulation), and 8 initiated treatment with tivantinib 120 mg BID and had their dose escalated to 360 mg BID. The most common (≥ 10%) AEs were the following: fatigue (66.0%), nausea (51.1%), vomiting (38.3%), anemia (25.5%), cough (25.5%), and bradycardia/sinus bradycardia, diarrhea, and headache (21.3% for each). Seven subjects (14.9%) experienced neutropenia. Six subjects (12.8%) experienced leukopenia. One additional event of febrile neutropenia was reported as an SAE. In this study, 2 of 47 (4.3%) subjects discontinued treatment due to an AE. One subject in the 360 mg BID treatment group experienced thrombocytopenia, and one

	subject in the 120 mg BID treatment group experienced diarrhea, fatigue, headache, and cough. In this study, AEs leading to dose reduction (neutropenia, leukopenia, and febrile neutropenia) occurred in 3 of 47 (6.4%) subjects. Disease progression was reported in two subjects during the treatment phase of the study. Three subjects had SAEs (febrile neutropenia, thrombocytopenia, and deep vein thrombosis) that were considered possibly related to study treatment; all three of these events resolved (the deep vein thrombosis resolved with sequelae). There were two deaths during the study or within 30 days of the last dose of study drug. Both deaths resulted from disease progression and were not attributed to study drug. **ARQ 197-205** ARQ 197-205 was an open-label study comparing tivantinib to gemcitabine in treatment-naïve subjects with unresectable locally advanced or metastatic pancreatic adenocarcinoma. A total of 43 subjects were enrolled and randomized in this study and 40 subjects received study drug. All subjects in the tivantinib group received 120 mg BID (capsule formulation) in the fasted state. The most common reason for discontinuation was progressive disease (12 [63.2%] and 13 [61.9%] subjects in the tivantinib and gemcitabine groups, respectively). Three subjects (15.8%) and 2 subjects (9.5%) in the tivantinib and gemcitabine groups, respectively, discontinued treatment due to AEs. The most common (≥ 10%) AEs were fatigue (42.1%), edema peripheral, anorexia, and ascites (26.3% for each), and nausea, abdominal pain, and blood alkaline phosphatase increased (21.1% for each). Five subjects in the gemcitabine group (23.8%) experienced neutropenia and two subjects in the gemcitabine group (9.5%) experienced leukopenia. There were no events of neutropenia or leukopenia in the tivantinib group. There were no events of bradycardia reported in this study. There were 13 subjects (32.5%), 5 (26.3%) in the tivantinib treatment arm and 8 (38.1%) in the gemcitabine treatment arm, who discontinued treatment due to an AE. Adverse events leading to treatment discontinuation in the tivantinib arm included

	ascites (2 subjects), vomiting (1 subject), malignant neoplasm progression (1 subject), and cholangitis (1 subject). Adverse events leading to treatment discontinuation in the gemcitabine arm included abdominal pain upper (1 subject), fatigue (3 subjects), malignant neoplasm progression (2 subjects), pneumonia (1 subject), and hip fracture (1 subject). Malignant neoplasm progression was the most common SAE, occurring in 13 (32.5%) subjects; anemia and fatigue were the second most common SAEs, occurring in 3 (7.5%) subjects each. Thirteen (32.5%) subjects died during study treatment or within 30 days of the last dose of study drug, including 9 subjects who received tivantinib and 4 subjects who received gemcitabine. None of the AEs leading to death was considered related to treatment. Malignant neoplasm was the reason for death for all 9 subjects in the tivantinib treatment group. **ARQ 197-215** ARQ 197-215 was a randomized, placebo-controlled study of tivantinib in subjects with HCC who had radiographic disease progression after systemic first-line therapy or were unable to tolerate the therapy. Subjects randomized to placebo were given the opportunity to receive tivantinib under open-label crossover after they had documented radiographic disease progression during the double-blind portion. Based on healthy volunteer studies and on previous clinical trials in subjects with cancer, a dosing regimen of crystalline tivantinib at 360 mg BID (capsule formulation) was recommended for all clinical trials. Following notification of a Grade 5 pancytopenia event, a detailed review of all cases of Grade ≥ 3 neutropenia was conducted. A review of the data identified 10 subjects who developed Grade ≥ 3 neutropenia. Eight severe neutropenia events occurred within the first month of treatment with study drug; one case occurred in the first week of Cycle 2, and one transient Grade 3 neutropenia occurred in Cycle 3. Three subjects who developed Grade 4 (febrile) neutropenia in Cycle 1 died within 30 days from the onset of the event, though the study drug was not held as recommended by the

	revised protocol. The review showed a higher rate of Grade ≥ 3 neutropenia, occurring in approximately 20% of HCC subjects, compared to approximately 5% in the total population of subjects who received tivantinib. Based on this observation, coupled with the higher exposure found in the HCC subject population, the decision was made to reduce the dose of tivantinib to 240 mg BID (capsule formulation) for all subjects in this study. A total of 107 subjects were enrolled and treated in this study. The most common reasons for discontinuing treatment during the double-blind period were disease progression (68.2%) and death (13.1%). Twenty-three of the 36 subjects who had been randomized to the placebo group entered the crossover period and were treated with tivantinib. The most common (≥ 10%) AEs during the double-blind period of the study were asthenia (24.3%), fatigue (23.4%), decreased appetite (22.4%), diarrhea (19.6%), edema peripheral (19.6%), neutropenia (18.7%), ascites (16.8%), anemia (15.9%), abdominal pain (15.0%), cough (13.1%), pyrexia (12.1%), and nausea (11.2%). Severe AEs that occurred in at least a 2-fold greater frequency in tivantinib-treated subjects compared to placebo-treated subjects included neutropenia (14.1% versus 0) and anemia (12.7% versus 0). The frequency of these severe AEs was lower in the 240 mg BID group compared to the 360 mg BID group (neutropenia [6.1% versus 21.1%], anemia [9.1% versus 15.8%]). Severe AEs of myelosuppression were reported only in the tivantinib treatment group. Twenty-one of 107 (19.6%) subjects had AEs that led to treatment discontinuation during the double-blind period, including 6 of 33 (18.2%) subjects in the tivantinib 240 mg BID group, 7 of 38 (18.4%) subjects in the tivantinib 360 mg BID group, and 8 of 36 (22.2%) subjects in the placebo group. The most common AE leading to discontinuation from study treatment was disease progression (6.5%).Three of 23 (13.0%) subjects had AEs that led to treatment discontinuation during the crossover period, including asthenia (1 subject) and disease progression (2 subjects). SAEs were reported for 38 of 107 (35.5%) subjects,

	including 24 of 71 (33.8%) subjects treated with tivantinib and 14 of 36 (38.9%) subjects treated with placebo. The most common (≥ 5%) SAE reported in this study was disease progression (7.5%). In this study, 23 (21.5%) subjects died on treatment or within 30 days of the last dose of study drug during the double-blind period (13 [18.3%] tivantinib-treated subjects and 10 [27.8%] placebo-treated subjects). The 13 deaths that occurred during the double-blind period for tivantinib-treated subjects were attributed to the following causes: disease progression (4 subjects), neutropenic sepsis (3 subjects, including one subject who died both of neutropenic sepsis and multiorgan failure), hepatic failure (3 subjects), cachexia (1 subject), hemorrhage (1 subject), and metabolic acidosis (1 subject). The 10 deaths that occurred during the double-blind period for placebo-treated subjects were attributed to the following causes: disease progression (4 subjects), cachexia (2 subjects), portal hypertension (1 subject), acute coronary syndrome and pulmonary edema (1 subject), upper gastrointestinal hemorrhage (1 subject), and suicide (1 subject). Three of 23 (13.0%) subjects had AEs resulting in death during the crossover period, including disease progression (2 subjects) and hepatic failure (1 subject). **ARQ 197-A-U251** ARQ 197-A-U251 was an open-label study of tivantinib in subjects with relapsed or refractory non-central nervous system (CNS) germ cell tumors. Twenty-seven subjects were enrolled and treated in this study. The primary reason for discontinuation was disease progression in 24 (88.9%) subjects. The most common (≥ 10%) AEs were fatigue (37.0%), nausea (25.9%), cough and dyspnea (22.2% each), vomiting, edema peripheral, and decreased appetite (14.8% each), and constipation, back pain, and neuropathy peripheral (11.1% each). AEs of Grade 3 or higher occurred in 12 subjects (44.4%). These included anemia, vision blurred, peritoneal hemorrhage, fatigue, hypersensitivity, cellulitis, pneumonia, neutrophil count decreased, pain in extremity, aphasia,

cerebral hemorrhage, headache, hemiplegia, paraparesis, sciatica, spinal cord compression, syncope, insomnia, cough, dyspnea, and superior vena caval occlusion, which were reported in 1 subject (3.7%) each and back pain, which was reported in 2 subjects (7.4%). The events of pneumonia and syncope were considered drug-related; all other events of Grade 3 or higher were considered not related to treatment. Three subjects (11.1%) discontinued study treatment due to AEs. Three subjects (3.7% each) discontinued study treatment due to Grade 2 ascites, Grade 4 cerebral hemorrhage, or Grade 3 sciatica. Of these AEs, Grade 4 cerebral hemorrhage and Grade 3 sciatica were SAEs. The primary reason of study treatment discontinuation was progressive disease for all 3 subjects. There were no deaths during treatment or within 30 days of the last dose.

ARQ 197-A-U303

ARQ 197-A-U303 is an ongoing Phase 3 randomized, double-blind study of tivantinib in subjects with MET diagnostic-high inoperable HCC treated with one prior systemic therapy. In August 2013, following a higher than expected incidence of neutropenia-related adverse events, the study Data Monitoring Committee (DMC) evaluated all available unblinded data including preliminary pharmacokinetics. The DMC advised that the tivantinib starting dose should be reduced to 120 mg BID (tablet formulation). The protocol was amended accordingly and enrollment continues. This study remains blinded.

COMBINATION THERAPY STUDIES

ARQ 197-111

ARQ 197-111 was an open-label study of tivantinib in combination with erlotinib, in subjects with locally advanced or metastatic solid tumors that had progressed after at least one prior treatment regimen. A total of 32 subjects were enrolled and treated in this study. Progressive disease (23 [71.9%] subjects) was the most common reason for treatment discontinuation. The most common (≥ 10%) AEs were fatigue (37.5%), nausea (31.3%), diarrhea (28.1%), bradycardia/sinus bradycardia (28.1%), abdominal pain (28.1%), and anemia

	(21.9%). There were 14 events of myelosuppression (7 anemia, 3 neutropenia, 2 thrombocytopenia, 1 lymphopenia, and 1 leukopenia) reported in 9 subjects. Among them, 10 events (5 anemia, 3 neutropenia, 1 thrombocytopenia, and 1 leukopenia) occurred in 6 subjects and were considered drug-related. Thirteen of the 15 events (86.7%) occurred when subjects were receiving tivantinib at a dose of 360 mg BID (capsule formulation). In this study, a total of 14 cardiac events (9 sinus bradycardia, 2 bradycardia, 1 cardio-respiratory arrest, 1 palpitations, and 1 sick sinus syndrome) were reported in 10 subjects. The majority of bradycardia events were asymptomatic and resolved. Five of 9 subjects with sinus bradycardia, bradycardia, or sick sinus syndrome had a history of bradycardia and/or an abnormal ECG finding of sinus arrhythmia at baseline. Three severe cardiac-related events occurred in 3 subjects including one Grade 3 sinus bradycardia, one Grade 3 sick sinus syndrome, and one Grade 5 cardiac arrest. AEs leading to treatment discontinuation occurred in 7 of 32 (21.9%) subjects. Four of the 7 subjects were discontinued from study medication due to 5 possible or probable drug-related AEs (neutropenia, hypoglycemia, fatigue, nausea, and vomiting). Two of the 8 (25%) AEs that resulted in study drug discontinuation were SAEs: one of life-threatening severity (neutropenia Grade 4) and the other that resulted in death (disease progression Grade 5). Other AEs leading to treatment discontinuation were comprised of hypoglycemia, hyperbilirubinemia, and pleural effusion, each occurring in 1 subject. Two of 32 (6.3%) subjects had AEs (both fatigue) that led to treatment reductions. One of the events of fatigue was considered to be related to study drug. Serious adverse events were reported for 13 subjects. There were no predominant SAEs, although disease progression was reported most often (3 of 32 subjects [9.4%]). There were three SAEs involving cardiac events, sinus bradycardia, cardio-respiratory arrest, and sick sinus syndrome and 2 reports of syncope possibly related to bradycardia. Five of 32 subjects (15.6%) had 6 SAEs that were

	considered related to combination treatment, including sinus bradycardia (Grade 3) in one subject, sick sinus syndrome (Grade 3) in one subject, neutropenia (Grade 4) in one subject, neutropenia and leukopenia (both Grade 4) in one subject, and syncope (Grade 3) in one subject. Six (18.8%) deaths occurred during the study or within 30 days of study treatment. All deaths were considered by Investigators to be not related to combination treatment and were the result of the following: cardiac arrest (1), disease progression (3), hepatic failure (1), and dyspnea (1). **ARQ 197-116** Study ARQ 197-116 was a study of tivantinib in combination with sorafenib in subjects with solid tumors, including RCC, HCC, NSCLC, and melanoma. A total of 87 subjects were enrolled and treated in this study. The most common reason for discontinuing treatment was progressive disease (71.3% for radiographic progression and 6.9% for clinical progression). The most common (≥ 20% of subjects) AEs were diarrhea (46%), fatigue (43.7%), rash (43.7%), anorexia (39.1%), weight decreased (37.9%), hypophosphatemia (28.7%), alopecia (27.6%), hyperglycemia (26.4%), nausea (25.3%), hypertension (24.1%), vomiting (21.8%), hypernatremia (21.8%), palmar-plantar erythrodysesthesia syndrome (21.8%), and lymphopenia (20.7%). The distribution of AEs was similar among all cancer types. The drug-related AEs reported most frequently (≥ 20% of subjects) were rash (40.2%), diarrhea (37.9%), anorexia (33.3%), fatigue (31.0%), alopecia (25.3%), palmar-plantar erythrodysesthesia syndrome (21.8%), and weight decreased (20.7%). Severe AEs (≥ Grade 3) were experienced by 61 (70.1%) of the 87 subjects. The severe AEs occurring in ≥ 5% of subjects were hypertension (11.5%), palmar-plantar erythrodysesthesia syndrome (8%), fatigue (6.9%), hyponatremia (6.9%), hypophosphatemia (6.9%), disease progression (5.7%), hyperbilirubinemia (5.7%), pneumonia (5.7%), hyperuricemia (5.7%), and rash (5.7%). Serious adverse events including deaths were reported by 33 (37.9%) of the 87 subjects in the study.

	Infections and infestations, gastrointestinal disorders, and general disorders and administration site conditions were the most frequent system organ classes (SOC) with 9.2%, 8.0%, and 6.9% of subjects, respectively. There were 9 subjects with AEs that led to death: 3 with HCC, 2 with lung cancer, and 1 each with RCC, melanoma, breast cancer, or other cancer (adenocarcinoma of the esophagus). In four of these subjects, the AE leading to death was progressive disease. **ARQ 197-117** ARQ 197-117 was an open-label study of tivantinib in combination with gemcitabine in subjects with locally advanced, inoperable, or metastatic primary solid tumors, including breast cancer, cholangiocarcinoma, ovarian cancer, and pancreatic cancer. A total of 74 subjects were enrolled and treated in this study. The most common reason for discontinuing tivantinib and gemcitabine treatments was radiographically confirmed disease progression (42 [56.8%] and 40 [54.1%], respectively). The most common AEs were thrombocytopenia (56 [75.7%] subjects), anemia (54 [73.0%] subjects), neutropenia (51 [68.9%] subjects), fatigue (43 [58.1%] subjects), and nausea (39 [52.7%] subjects). Severe AEs (≥ Grade 3) were thrombocytopenia (22 [29.7%] subjects), anemia (28 [37.8%] subjects), neutropenia (32 [43.2%] subjects), leukopenia (5 [6.8%] subjects), febrile neutropenia (3 [4.1%] subjects), and pancytopenia (1 [1.4%] subjects). There were 19 cardiac events (4 tachycardia, 3 palpitations, 2 atrial fibrillation, 2 congestive cardiac failure, 1 acute myocardial infarction, 1 atrial flutter, 1 bradycardia, 1 cardiomyopathy, 1 cardiopulmonary failure, 1 cyanosis, 1 left ventricular failure, and 1 mitral valve incompetence) reported in 12 subjects. Overall, 1 of 74 (1.4%) subjects experienced bradycardia, 2 (2.7%) experienced atrial fibrillation, 3 (4.1%) experienced palpitations, and 3 (4.1%) experienced tachycardia. At the time of the last recorded evaluation, 11 of the 19 (57.9%) cardiac-related events were resolved, 7 (36.8%) were ongoing, and 1 (5.3%) subject died. Seventeen of 74 (23.0%) subjects had a total of 21

	AEs that led to treatment discontinuation. Seven of the 17 subjects discontinued due to myelosuppressive events, including neutropenia (4 subjects), thrombocytopenia (2 subjects), anemia (2 subjects), and febrile neutropenia (1 subject). Other AEs leading to study drug discontinuation were single events each of breast cancer, wound complication, bacteremia, gastrointestinal hemorrhage, sepsis, fatigue, acute respiratory failure, dyspnea, respiratory failure, disease progression, small bowel obstruction, and pneumonitis. Four of 74 (5.4%) subjects each had one tivantinib dose reduction during the study period, from 360 mg BID to 240 mg BID (capsule formulation). Adverse events leading to dose reductions in these 4 subjects included neutropenia (3 subjects) and fatigue (1 subject). All four subjects were among the 32 subjects who experienced AEs leading to a reduction in gemcitabine. All dose reductions for gemcitabine were due to myelosuppressive AEs. Serious adverse events were reported for 39 of 74 (52.7%) subjects. The most commonly reported SAEs were anemia (6 [8.1%] subjects) and disease progression (9 [12.2%] subjects. Overall, 15 (20.3%) deaths occurred during study treatment or within 30 days of the last dose, which resulted from the following: disease progression (8 subjects), acute respiratory failure (1 subject), cardiopulmonary failure (1 subject), hepatic failure (1 subject), neutropenia (1 subject), sepsis (1 subject), upper gastrointestinal hemorrhage (1 subject), and death (1 subject). **ARQ 197-209** ARQ 197-209 was a randomized, double-blind study of erlotinib plus tivantinib treatment compared with erlotinib plus placebo, in subjects with inoperable locally advanced or metastatic (Stage IIIB/IV) NSCLC who had received at least one prior chemotherapy regimen (other than erlotinib or other EGFR-inhibiting agents). A total of 167 subjects enrolled in this study; 84 subjects received erlotinib plus tivantinib and 83 subjects received erlotinib plus placebo during the double-blind period. Thirty-five of 83 (42.2%) subjects who had initiated treatment with erlotinib plus

	placebo crossed over to receive erlotinib plus tivantinib. The most common AEs reported in the tivantinib combination arm group were rash (65.5%), diarrhea (47.6%), fatigue (33.3%), anorexia (28.6%), nausea and vomiting (26.2% each), and pruritus, dry skin, and dyspnea (22.6%, each). Neutropenia was experienced by 8 subjects in this study who were treated with erlotinib plus tivantinib. No neutropenia events were experienced by subjects during erlotinib plus placebo treatment. Sinus bradycardia was reported for 3 of 84 (3.6%) subjects randomized to the tivantinib combination arm (2 drug-related), and 2 of 35 (5.7%) additional subjects treated with erlotinib plus tivantinib during the crossover period (1 drug-related), for a total of 5 of 119 (4.2%) subjects treated with erlotinib plus tivantinib in the study (3 drug-related). Bradycardia was reported for 1 of 84 (1.2%) subjects in the randomized tivantinib combination arm (considered drug-related) and 1 of 35 (2.9%) subjects in the crossover population (not drug-related), for a total of 2 of 119 (1.7%) subjects treated with erlotinib plus tivantinib. Adverse events leading to treatment discontinuation were reported for 18 of 84 (21.4%) subjects randomized to the tivantinib combination arm and 17 of 83 (20.5%) subjects randomized to the placebo combination arm, including 7 of 35 (20.0%) subjects randomized to the placebo combination arm who crossed over to receive the tivantinib combination treatment. Three subjects had dose reductions, 1 subject in the erlotinib plus tivantinib group (due to Grade 3 diarrhea, Grade 3 vomiting, and Grade 2 nausea) and 2 in the erlotinib plus placebo group (due to Grade 2 rash pustular in one subject and due to Grade 4 diarrhea, Grade 3 dehydration, Grade 3 renal failure acute, and Grade 3 palmar-plantar erythrodysesthesia syndrome in another subject). In this study, 74 subjects (44.3%) experienced SAEs. The most common SAE in both treatment arms was disease progression, reported for 6 (7.1%) and 7 (8.4 %) subjects in the tivantinib and placebo combination arms, respectively. Adverse events with an outcome of death were reported in 38 subjects (22.8%) during study treatment or within 30 days of the last dose of the study drug; 17 (20.2%)

	deaths occurred in subjects randomized to the tivantinib combination arm and 21 (25.3%) occurred in subjects randomized to the placebo combination arm, including 7 subjects who died after crossing over to the tivantinib combination arm. The most frequent cause of death in the tivantinib combination and crossover subjects was disease progression (9 subjects). Among subjects in the tivantinib combination arm, 2 subjects died due to AEs considered at least possibly related to both tivantinib and erlotinib (leukopenia and pneumonia). **ARQ 197-A-U252** ARQ 197-A-U252 was a Phase 1/2 study of tivantinib in combination with irinotecan and cetuximab in subjects with colorectal cancer with wild-type KRAS. A total of 131 subjects enrolled in this study and 130 were treated. The primary reason for discontinuing treatment was progressive disease (79 [60.3%]). All 130 treated subjects (100%) in both Phase 1 and Phase 2 experienced at least one AE. In Phase 1, the most common AEs were fatigue (77.8%), nausea and rash (66.7% each), and diarrhea and alopecia (55.6% each). In Phase 2, the most common AEs that occurred in either treatment group were rash, diarrhea, and nausea. The most common AEs reported in the tivantinib combination arm were rash (59.2%), diarrhea (53.5%), nausea (46.5%), fatigue (43.7%), vomiting (33.8%), neutropenia (31.0%), and infections and infestations (29.6%). The proportions of placebo-treated subjects versus the proportions of tivantinib-treated subjects with any grade of myelosuppression events were as follows: febrile neutropenia (1.7 % vs. 1.6%), leukopenia (5.1% vs. 8.1%), and thrombocytopenia (1.7% vs. 8.1%). Among cardiac disorder AEs of special interest, bradycardia and sinus bradycardia were reported by 0% of placebo-treated subjects vs. 3.2% (bradycardia) and 4.8% (sinus bradycardia) of tivantinib-treated subjects and atrial fibrillation was reported by 0% of placebo-treated subjects vs. 3.2% of tivantinib-treated subjects. Acute renal failure was reported by 0% of placebo-treated subjects and 3.6% of tivantinib-treated subjects

during Phase 2. In Phase 1, two subjects discontinued study drug because of an AE. In Phase 2, a higher proportion of tivantinib-treated subjects than placebo-treated subjects discontinued study drug due to an AE (19.4% vs. 11.9%). The most common AEs leading to discontinuation of study treatment were neutropenia and rash. One subject each had serious Grade 4 unrelated AEs of renal failure (acute), respiratory failure, or urosepsis that led to discontinuation from study medication. No deaths were reported for any of the 9 subjects in the Phase 1 portion of the study. In Phase 2, two subjects in each treatment group died within 30 days of the end of study drug administration due to a SAE. An additional 3 subjects in each treatment group died due to disease progression after that time period. No AEs leading to death were considered related to study drug.

ARQ 197-A-U302

ARQ 197-A-U302 was a randomized, double-blinded, placebo-controlled study of tivantinib in combination with erlotinib in subjects with locally advanced or metastatic, non-squamous NSCLC. The study enrolled 1048 subjects, and 1037 subjects were included in the safety analysis. Nine hundred seventy-eight (93.3%) subjects discontinued treatment. The most common reason for discontinuation was progressive disease; 645 (61.5%) subjects discontinued for radiographically confirmed progressive disease and another 90 (8.6%) subjects discontinued for clinical disease progression. Adverse events were the reason for discontinuation for 113 (10.8%) subjects. The most common AEs within the erlotinib plus tivantinib (ET) and the erlotinib plus placebo (EP) groups were diarrhea (ET: 34.6%, EP: 41.0%), rash (ET: 33.1%, EP: 37.3%), decreased appetite (ET: 29.0%, EP: 28.8%), dyspnea (ET: 26.2%, EP: 22.6%), and fatigue (ET: 26.2%, EP: 21.9%). The AEs indicative of myelosuppression were more frequent in the ET group compared with the EP group: neutropenia by any preferred term (ET: 13.8%, EP: 2.3%), febrile neutropenia (ET: 3.3%, EP: 0.4%), leukopenia (ET: 5.8%, EP: 1.0%), and anemia by any preferred term (ET: 16.7%, EP: 10.3%). The

	occurrence of these AEs at a severity of ≥ Grade 3 was also more common in the ET group. Bradycardia was reported in 2.7% of subjects in the ET group and in no subjects in the EP group; however, only 2 of the 14 cases in the ET group were of Grade 3 or higher severity. Overall, 138 subjects (79 subjects [15.2%] in the tivantinib combination arm, 59 subjects [11.4%] in the placebo combination arm) were discontinued from treatment because of AEs. Overall, there were 410 (39.5%) subjects with SAEs reported during the study; the most commonly reported SAEs were respiratory events including dyspnea and pulmonary embolism, reported in 5.2% and 3.4% of subjects overall. Overall, 614 subjects died during the study or within 30 days of the last dose of study drug, most frequently as the result of disease progression as attributed by the Investigator. A total of 142 subjects had deaths associated with AEs: ET: 77 subjects, EP: 65 subjects. However, the Investigator ultimately determined that many of these AEs were part of the underlying disease and attributed the deaths to disease progression. Using this revised Investigator attribution, 66 subjects died as a result of AEs (other than disease progression): ET: 32 subjects; EP: 34 subjects. Of these deaths associated with AEs (other than disease progression), the most common AEs were respiratory failure (ET: 5 subjects, EP: 6 subjects), sepsis or septic shock (ET: 5 subjects, EP: 1 subject), and pneumonia or bronchopneumonia (ET: 3 subjects, EP: 5 subjects). Five deaths in the ET group and 3 deaths in the EP group were considered by the Investigator to be related to tivantinib/placebo. Detailed data describing the clinical administration of tivantinib and complete safety information can be found in the Tivantinib Investigator's Brochure.[0]

Deleted

As of 01 May 2009, 175 subjects with solid tumors had been treated with ARQ 197 monotherapy. The most common adverse events (AEs) (≥10% of subjects) are listed in Table 1.1.

Table 1.1. Number and Percent of ARQ 197 (Single Agent)-Treated Subjects with Solid Tumors with AEs that Occurred in 10% or More of Subjects

MedDRA System Organ Class	Preferred term	ARQ 197 (N=175) n (%)
General disorders and administration site conditions	Fatigue	75 (42.9)
	Pyrexia	21 (12.0)
	Oedema peripheral	20 (11.4)
Gastrointestinal disorders	Nausea	50 (28.6)
	Vomiting	37 (21.1)
	Diarrhoea	27 (15.4)
	Abdominal pain	18 (10.3)
Metabolism and nutrition disorders	Anorexia	28 (16.0)
Musculoskeletal and connective tissue disorders	Back pain	19 (10.9)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	32 (18.3)
Blood and lymphatic system disorders	Anaemia	75 (42.9)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

The most common drug-related AEs (≥5% and ≥2 events) for ARQ 197 monotherapy are listed in Table 1.2.

Table 1.2. Number and Percent of ARQ 197 Treated Subjects with Solid Tumors with Related AEs that Occurred in 5% or More of Subjects (≥2 Events)

MedDRA System Organ Class	Preferred term	ARQ 197 (N=175) n (%)
Gastrointestinal disorders	Nausea	32 (18.3)
	Vomiting	16 (9.1)
	Diarrhoea	11 (6.3)
General disorders and administration site conditions	Fatigue	35 (20.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

A total of 17 drug-related serious adverse events (SAEs) occurred in nine (5.1%) of these 175 subjects (Table 1.3). Among them, seven SAEs in five (2.9%) subjects were myelosuppression events, including febrile neutropenia, neutropenia, leucopenia and thrombocytopenia; five SAEs in two (1.1%) subjects were gastrointestinal disorders, and the other five SAEs in four (2.3%) subjects were disorders belonging to other system organ classes. All myelosuppression events occurred in subjects treated at a dose of 360 mg BID or higher.

Table 1.3. Number and Percent of Subjects with Solid Tumors Treated with ARQ 197 Monotherapy Who Had Drug-Related SAEs

MedDRA System Organ Class	Preferred term	ARQ 197 (N=175) n (%)	Dose Level (mg BID)

Blood and lymphatic system disorders	Febrile neutropenia	3 (1.7)	360, 400, 400
	Neutropenia	1 (0.6)	360
	Leukopenia	1 (0.6)	360
	Thrombocytopenia	2 (1.1)	360, 360
Gastrointestinal disorders	Nausea	2 (1.1)	120, 360
	Vomiting	2 (1.1)	120, 360
	Abdominal pain	1 (0.6)	120
Other system organ classes	Dehydration	1 (0.6)	360
	Fatigue	1 (0.6)	200
	Palmar-plantar erythrodysaesthesia syndrome	1 (0.6)	400
	Hepatic failure	1 (0.6)	120
	Mucosal inflammation	1 (0.6)	400

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

Among the 175 subjects with tumors treated with ARQ 197 monotherapy as of 01 May 2009, a total of three events of drug-related febrile neutropenia (all Grade 3), three events of drug-related neutropenia (Grade 2, Grade 3 and Grade 4), and one event of drug-related leucopenia (Grade 4) occurred in six (3.4%) subjects. One event of Grade 3 neutropenia occurred in one subject treated at 150 mg BID, and the other six events (one Grade 2, three Grade 3 and two Grade 4) occurred in five subjects treated at doses of 300 mg BID or higher. All events were reversible. Three events of drug-related thrombocytopenia occurred in three (1.7%) subjects; one of these events of thrombocytopenia was Grade 3, and the other two were Grade 4. All three subjects were treated at a dose of 360 mg BID or 400 mg BID. All events were reversible.

A total of 16 episodes (all Grade 1) of sinus bradycardia/bradycardia (15 sinus bradycardia, one unspecified bradycardia) were reported in five of 175 (2.9%) subjects. Fourteen of 16 episodes occurred in three subjects treated at 360 mg BID continuously, and the other two episodes occurred in two subjects treated at 120 mg BID continuously. As of 01 May 2009, 14 of 16 were resolved and two were ongoing.

As of 01 May 2009, 111 subjects with solid tumors had been treated with ARQ 197/placebo (ARQ 197-209 study) or in combination with another drug (ARQ 197-111 study). The most common ARQ 197/placebo-related or combination-related AEs (≥ 5% and ≥2 events) are listed in Table 1.4.

Table 1.4: Number and Percent of the Most Common Related Adverse Events in Subjects with Solid Tumors in Combination Studies

		No. Subjects (%) (N=111)		
MedDRA System Organ Class (SOC)	**MedDRA preferred term**	**ARQ 197-111 (N=32)**	**ARQ 197-209 (N=79)**	**Total (N=111)**
Skin and subcutaneous tissue disorders	Rash	6(18.8)	26(32.9)	32 (28.8)

Table 1.4: Number and Percent of the Most Common Related Adverse Events in Subjects with Solid Tumors in Combination Studies

MedDRA System Organ Class (SOC)	MedDRA preferred term	No. Subjects (%) (N=111) ARQ 197-111 (N=32)	ARQ 197-209 (N=79)	Total (N=111)
	Dermatitis acneiform	4(12.5)	6(7.6)	10 (9.0)
	Pruritus	5(15.6)	2 (2.5)	7 (6.3)
Gastrointestinal disorders	Diarrhoea	6(18.8)	9(11.4)	15 (13.5)
	Nausea	4(12.5)	3 (3.8)	7 (6.3)
General disorders and administration site conditions	Fatigue	8(25.0)	5(6.3)	13 (11.7)
Cardiac disorders	Sinus bradycardia /bradycardia	8 (25.0)	1 (1.3)	9 (8.1)
Blood and lymphatic system disorders	Anaemia	4(12.5)	2 (2.5)	6 (5.4)
Metabolism and nutrition disorders	Anorexia	2(6.3)	4(5.1)	6 (5.4)
	Decrease appetite	0 (0.0)	8(10.1)	8 (7.2)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	0 (0.0)	6(7.6)	6 (5.4)

A total of 20 ARQ 197/placebo related (in ARQ 197-209 study) or combination-related (in ARQ 197-111 study) SAEs occurred in 11 (9.9%) subjects in these two combination studies. Among them, seven events in five (4.5%) subjects were myelosuppression events including one anaemia, two neutropenia, one neutrophils/ANC (G4), one leukopenia, and one thrombocytopenia; two events of dehydration in two subjects, two events of diarrhoea in two subjects, two events of pulmonary embolism in two subjects, two events of sinus bradycardia in two subjects, and one event each of pneumonia, vomiting, septic knee, recurrent left knee pain and acute renal failure (Table 1.5). All ARQ 197/placebo-related or combination-related SAEs occurred in subjects treated with ARQ 197 at dose of 360 mg BID and erlotinib at dose of 150 mg QD except one sinus bradycardia in a subject treated with ARQ 197 at 240 mg BID and erlotinib at 150 mg QD.

Table 1.5: Drug-Related SAEs in Two Combination Studies of ARQ 197 and Erlotinib

Study ID	Subject ID	ARQ 197 dose at time of event (mg BID)	Erlotinib dose at time of event (mg QD)	Event	Relationship to ARQ 197/ placebo and/or erlotinib	CTCAE Grade	Outcome
209	PPD	360	150	Acute renal failure	Related	3	Resolved with Sequelae
209		360	150	Anaemia	Related	4	Resolved
209		360	150	Dehydration	Related	4	Resolved with Sequelae
209		360	150	Dehydration	Related	3	Resolved
209		360	150	Diarrhoea	Related	4	Resolved with Sequelae
209		360	150	Diarrhoea	Related	3	Ongoing
209		360	150	Leucopenia	Related	5	Death
111		360	150	Leukocytes	Related	4	Resolved
209		360	150	Neutropenia	Related	4	Ongoing
111		360	150	Neutropenia	Related	4	Resolved
111		360	150	Neutrophils/anc	Related	4	Resolved
209		360	150	Pneumonia	Related	5	Death
209		360	150	Pulmonary embolism	Related	5	Death
209		360	150	Pulmonary embolism	Related	4	Resolved
209		360	150	Recurrent left knee pain	Related	3	Unknown
209		360	150	Septic knee	Related	3	Ongoing
209		360	150	Sinus bradycardia	Related	2	Resolved
111		240	150	Sinus bradycardia	Related	3	Resolved with Seq.
111		360	150	Thrombocytopenia	Related	3	Resolved
209		360	150	Vomiting	Related	3	Resolved with Sequelae

As of 01 May 2009, there were 32 subjects enrolled and treated with ARQ 197 in ARQ 197-111 study (Phase 1 study of ARQ 197 in combination with erlotinib). As of 12 May 2009, there were 79 subjects enrolled and treated with ARQ 197 or placebo (there subjects have 50% chance to receive placebo) in ARQ 197-209 study (Phase 2 randomized and blinded study of ARQ 197 in combination with erlotinib). In total, 111 subjects have received combination treatment of ARQ 197/placebo and erlotinib. Among them a total of 18 events of myelosuppression (nine anaemia, three thrombocytopenia, two neutropenia, one neutrophils/ANC, one leucopenia, one leukocytes, one lymphopenia) were reported in 12 (10.8%) subject (Table 1.6) of which 13 events (seven

anaemia, two neutropenia, one neutrophils/ANC, one leukopenia, one leukocytes, and one thrombocytopenia) in nine (8.1%) subjects were reported to be related to ARQ 197/placebo or to combination treatment. Seven drug-related events were resolved, five were ongoing and the outcome was death for the other event (leucopenia). All events occurred when subjects receiving ARQ 197/placebo at 360 mg BID and erlotinib at 150 mg QD.

Anaemia

A total of nine events of anaemia were reported in these two studies of which seven events (six Grade 2 and one Grade 4) in six (5.4%) subjects were related to ARQ 197/placebo or to combination studies. All subjects were treated with ARQ 197 at dose of 360 mg BID and erlotinib at 150 mg QD. Four of seven ARQ 197/placebo or combination treatment-related events were ongoing and three resolved.

Neutropenia/leucopenia

A total of five events (two neutropenia (both Grade 4), one neutrophils (Grade 4), one leucopenia (Grade 5) and one leukocytes (Grade 4)) were reported in three subjects in these two studies. All five events were related to ARQ 197/placebo or combination treatment. All three subjects were receiving ARQ 197/placebo at dose of 360 mg BID and erlotinib at 150 mg QD when these events occurred. Three events (one neutropenia, one neutrophils, one leukocytes) were resolved, one event (neutropenia) was ongoing. The outcome of the event of leucopenia was death.

Thrombocytopenia

A total of three events (one Grade 2, one Grade 3 and one Grade 5) of thrombocytopenia were reported in three subjects in these two studies. Of which one event in one subject (Grade 3) was considered to be related to combination treatment. All subjects were treated with ARQ 197 at dose of 360 mg BID and erlotinib at dose of 150 mg QD. The related event was resolved.

Table 1.6: List of Subjects with Myelosuppression AEs in Two Combination Studies of ARQ 197 and Erlotinib

Study Number	Subject ID	ARQ 197 dose at time of event (mg BID)	Erlotinib dose at time of event (mg QD)	Event	Worst NCI Grade	Relationship to ARQ 197 /placebo	Relationship to erlotinib	Outcome
111	PPD	360	150	Anaemia	2	Related	Related	Ongoing
111		360	150	Anaemia	1	Unrelated	Unrelated	Ongoing
111		360	150	Anaemia	2	Related	Related	Ongoing
111		360	150	Anaemia	2	Unrelated	Unrelated	Ongoing
111		360	150	Anaemia	2	Related	Related	Resolved
111		360	150	Anaemia	2	Related	Related	Resolved
111		360	150	Anaemia	2	Related	Related	Ongoing
209		360	150	Anaemia	2	Related	Related	Ongoing
209		360	150	Anaemia	4	Related	Unrelated	Resolved
209		360	150	Leukopenia	5	Related	Related	Death
111		360	150	Leukocytes	4	Related	Related	Resolved

Table 1.6: List of Subjects with Myelosuppression AEs in Two Combination Studies of ARQ 197 and Erlotinib

Study Number	Subject ID	ARQ 197 dose at time of event (mg BID)	Erlotinib dose at time of event (mg QD)	Event	Worst NCI Grade	Relationship to ARQ 197 /placebo	Relationship to erlotinib	Outcome
111	PPD	360	150	Lymphopenia	2	Unrelated	Unrelated	Resolved
111		360	150	Neutropenia	4	Related	Related	Resolved
209		360	150	Neutropenia	4	Related	Unrelated	Ongoing
111		360	150	Neutrophils/ANC	4	Related	Related	Resolved
111		360	150	Thrombocytopenia	5	Unrelated	Unrelated	Death
111		360	150	Thrombocytopenia	2	Unrelated	Unrelated	Resolved
111		360	150	Thrombocytopenia	3	Related	Related	Resolved

Among the 111 subjects enrolled and treated in the two ARQ 197 combination studies of ARQ 197 and erlotinib (ARQ 197-111 [N=32] and ARQ 197-209 [N=79]), total of 12 episodes (eight Grade 1, three Grade 2 and one Grade 3) of sinus bradycardia/bradycardia (nine sinus bradycardia, three unspecified) were reported in nine (8.1%) subjects. All 12 events were related to ARQ 197 and 11 events were also related to erlotinib (Table 1.7).

Five drug-related episodes occurred in four subjects treated with ARQ 197 at 360 mg BID, three events occurred in two subjects treated at 240 mg BID, and the other four events occurred in four subjects treated at 120 mg BID. All subjects received erlotinib at 150 mg QD. Eight events were resolved and four were ongoing.

Table 1.7: Sinus Bradycardia/Bradycardia in Two Combination Studies of ARQ 197 and Erlotinib

Study Number	Subject ID	Dose of ARQ 197/ placebo at time of event (mg BID)	Dose of erlotinib at time of event (mg QD)	Event	CTCAE Grade	Relationship to ARQ 197	Relationship to erlotinib	Outcome
111	PPD	120	150	Sinus bradycardia	1	Related	Related	Resolved
111		120	150	Bradycardia	1	Related	Related	Resolved
111		240	150	Sinus bradycardia	1	Related	Related	Ongoing
		240	150	Sinus bradycardia	3	Related	Related	Resolved with Sequelae
111		120	150	Sinus bradycardia	1	Related	Related	Resolved
111		120	150	Bradycardia	1	Related	Related	Resolved
		240	150	Bradycardia	1	Related	Related	Ongoing

Table 1.7: Sinus Bradycardia/Bradycardia in Two Combination Studies of ARQ 197 and Erlotinib

Study Number	Subject ID	Dose of ARQ 197/ placebo at time of event (mg BID)	Dose of erlotinib at time of event (mg QD)	Event	CTCAE Grade	Relationship to ARQ 197	Relationship to erlotinib	Outcome
111	PPD	360	150	Sinus bradycardia	2	Related	Related	Resolved with Sequelae
		360	150	Sinus bradycardia	1	Related	Related	Ongoing
111		360	150	Sinus bradycardia	2	Related	Related	Ongoing
111		360	150	Sinus bradycardia	1	Related	Related	Resolved
209		360	150	Sinus bradycardia	2	Related	Unrelated	Resolved

Detailed data describing the clinical administration of ARQ 197 in subjects can be found in the ARQ 197 Investigator's Brochure.

3 Selection of Study Population (p. 31)	
	Added Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator and with Sponsor's approval, may benefit from the treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.
The combination therapy dose(s) and schedule(s) will be determined to each subject by the Investigator based on the combination drug(s) label(s) clinical trials.	The combination therapy dose(s) and schedule(s) will be determined to each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.
3.1 Inclusion Criteria (pp. 31-32)	
Each subject must meet the following criteria to be enrolled in this study: 1. Signed written informed consent to Study ARQ 197-299	Each subject must meet the following criteria to be enrolled in this study: 1. Signed written informed consent to Study ARQ 197-299

2. Male or female subjects of the age defined in the original protocol they were enrolled 3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3 (see Appendix 2) 4. Adequate bone marrowfunction: - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L - Hemoglobin ≥ 8.0 g/dL 5. Enrollment within 14 days of the completion of the End of Study Visit of the original study 6. Subjects, who participated in previous studies that have reached their designated end-dates, who did not meet discontinuation criteria in their original study, and who may, in the opinion of the Investigator and the Sponsor, benefit from treatment 7. Women of childbearing potential must have a negative pregnancy test performed within 14 days of the start of study drug. Both men and women enrolled in this study must agree to use adequate birth control measures while on study	2. Male or female subjects of the age defined in the original protocol they were enrolled 3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3 (or ≤ 2 for tivantinib-naïve subjects) (see Appendix 2) 4. Adequate bone marrow, liver, and renal function tests: - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L - Hemoglobin ≥ 8.0 g/dL (or ≥ 9.0 g/dL for tivantinib-naïve subjects) - Platelet count ≥ 75 x 10^9/L (or ≥ 60 x 10^9/L for HCC subjects) - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 x upper limit of normal (ULN) (or ≤ 5 x ULN for subjects with liver metastases) - Total bilirubin ≤ 2mg/dL - Serum creatinine ≤ 1.5 x ULN 5. Enrollment within 14 days of the completion of the End of Treatment Visit of the original study 6. Measurable disease as defined by RECIST. Eligibility assessment must be performed within 28 days (4 weeks) of the first dose of study drug (Day 1) 7. Subjects, who participated in previous tivantinib studies that have reached their designated end-dates, who did not meet discontinuation criteria in their original study, and who may, in the opinion of the Investigator and the Sponsor, benefit from treatment 8. Women of childbearing potential must have a negative pregnancy test performed within 14 days of the start of study drug. "Women of childbearing potential" is defined as sexually mature women who have not undergone a hysterectomy and who have not been naturally postmenopausal for the last 12 consecutive months prior to the first dose of tivantinib (Day 1). Both men and women enrolled in this study must agree to use adequate birth control measures while on study.
3.2 Exclusion Criteria (p.32)	
3. Any condition that is unstable or which could jeopardize the safety of the subject and his/her compliance in the study	3. Any condition that is unstable or which could jeopardize the safety of the subject and his/her compliance in the study - For tivantinib-naïve subjects: active coronary disease, clinically significant bradycardia, or other uncontrolled cardiac arrhythmia defined as ≥ Grade 3 according to NCI CTCAE v. 4.03, or uncontrolled hypertension

4.1 Overall Study Design (p.32)	
The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator based on the combination drug(s) label(s).	The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.
	Added Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib (tivantinib-naïve) as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to receive treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.
4.3 Administration Schedule (p.33)	
Subjects will be treated according to the original treatment protocols into which they were enrolled until any discontinuation criterion is met. Dose may be delayed or reduced for clinically significant toxicities, but dose escalation is not allowed (see Section 7.3).	Subjects will be treated according to the original treatment protocols into which they were enrolled or per administration schedules tested in other tivantinib clinical trials. Subjects will be treated until any discontinuation criterion is met. Dose may be delayed or reduced for clinically significant toxicities, but dose escalation is not allowed (see Section 7.3 and Appendix 4).
5.1 Pre-study Visit (p.34-35)	
• Physical examination ECOG PS Vital signs (blood pressure, heart rate, respiratory rate, body temperature) and weight • Complete blood count (CBC, hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count including differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts) • Chemistry panel (aspartate	• Physical examination, including vital signs, weight, and height (see Section 6.2) • ECOG PS (see Appendix 2) • Hematology (see Section 6.3) • Coagulation tests (see Section 6.3) • Blood chemistry (see Section 6.3) • Liver function tests (see Section 6.3) • Electrolytes (see Section 6.3) • Serum pregnancy test (if applicable, see Section 6.3) • Urinalysis (see Section 6.3)

aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, uric acid, total protein, albumin, calcium, lipase, amylase, phosphate, lactic dehydrogenase, glucose, creatinine, blood urea nitrogen or urea and bicarbonate (if clinically indicated)) • Electrolyte panel (sodium, potassium, and chloride) • Coagulation panel (International Normalized Ratio (INR) or prothrombin time (PT), and partial thromboplastin time (PTT)) • Serum pregnancy test • 12-lead ECG • Tumor assessment • Tumor markers assessment (if applicable)	• 12-lead ECG (see Section 6.4) • Tumor assessment (see Section 6.5) • Tumor markers assessment (if applicable) • Adverse event (AE) assessment: any sign or symptom continuing from the original tivantinib study or beginning after the last visit of the original study, but prior to the first dose of study drug (Day 1) of the Extension study must be documented on a Medical History eCRF page. Resolved AEs from the original tivantinib study are captured in the original study records and will not be re-recorded for this study.
5.2 Monthly Visit (± 3 days) (p. 35)	
Subjects should be seen every four weeks throughout treatment period. The following assessments and procedures will be performed at each visit: Physical examination ECOG PS Vital signs and weight CBC Blood chemistry Electrolytes AE assessment Concomitant medications assessment ARQ 197 dispensation as per schedule Combination drug(s) administration/dispensation as per schedule (if applicable)	Subjects should be seen every four weeks throughout the treatment period. The following assessments and procedures will be performed at each visit: •Physical examination, including vital signs and weight (see Section 6.2) •ECOG PS (see Appendix 2) •Hematology (see s Section 6.3) •Coagulation tests (see s Section 6.3) •Blood chemistry (see Section 6.3) •Liver function tests (see Section 6.3) •Electrolytes (see Section 6.3) •AE assessment •Concomitant medications assessment •Tivantinib dispensation as per schedule •Combination drug(s) administration/dispensation as per schedule (if applicable) •Tumor markers assessment (if applicable)

Tumor markers assessment (if applicable) Tumor assessment (every 12 weeks unless current disease specific standard of care requires performing imaging more often) 12-lead ECG (ONLY for bradycardic subjects with a heart rate <50 beats per minute)	•Tumor assessment (every 12 weeks unless current disease specific standard of care requires performing imaging more often) •12-lead ECG (ONLY for subjects with a heart rate of <50 bpm) (see Section 6.4) Note: Subjects who do not experience Grade 3/4 toxicity and continue to benefit from the treatment after 12 cycles of treatment can be evaluated every two or three months upon agreement between the Investigator and the Sponsor.
5.3 Weekly Visits (if applicable; ± 3 days) (pp.35-37)	
Subjects who require weekly administration of combination drug(s) should be seen according to the schedule as per the original protocol.	Tivantinib-naïve subjects or subjects who require weekly administration of combination drug(s) should be seen according to the schedule as per the original protocol.
The following assessments and procedures will be performed at each visit: • Vital signs • CBC	5.3.1 Weekly Visits (applied for combination drug(s) administration; ± 3 days) At a minimum, the following assessments and procedures will be performed at each visit: • Vital signs (see Section 6.2) • Hematology (see Section 6.3)
	Added 5.3.2 Weekly Visits (applied ONLY for tivantinib-naïve subjects; ± 3 days) Subjects who did not receive tivantinib when enrolled in the original tivantinib study and who, in the opinion of the Investigator and with the Sponsor's approval, may benefit from treatment with tivantinib should have weekly visits during the first four weeks of treatment with tivantinib. After the first four weeks, these subjects will follow the original protocol visit schedule to which they were assigned. At a minimum, the following assessments and procedures will be performed at each visit: • Physical examination, including vital signs (see Section 6.2)

	• ECOG PS (see Appendix 2) • Hematology (see Section 6.3) • Coagulation tests (see Section 6.3) • Blood chemistry (see Section 6.3) • Liver function tests (see Section 6.3) • Electrolytes (see Section 6.3) • AE assessment • Concomitant medications assessment • Tivantinib dispensation as per schedule • Combination drug(s) administration/dispensation as per schedule (if applicable) • 12-lead ECG (ONLY for subjects with a heart rate of <50 bpm) Tivantinib-naïve subjects who do not experience Grade 3 /4 toxicity during the first four weeks of treatment and to whom the weekly combination treatment visit schedule does not apply can be evaluated monthly (Cycle 2+) upon agreement between the Investigator and the Sponsor
5.4 End of Treatment Visit (pp. 37-38)	
Subjects, who have been discontinued from the study, should have the End of Study Visit within 7 days of the discontinuation decision. The following assessments and procedures should be done at the End of Study Visit: • Physical examination • ECOG PS • Vital signsand weight • CBC • Chemistry panel • Electrolyte panel • Coagulation panel • Serum pregnancy test • 12-lead ECG • AE assessment	Subjects, who have been discontinued from the study, should have the End of Treatment Visit within 7 (+3) days of the discontinuation decision. The following assessments and procedures should be done at the End of Treatment Visit: • Physical examination, including vital signs and weight (see Section 6.2) • ECOG PS (see Appendix 2) • Hematology (see Section 6.3) • Coagulation tests (see Section 6.3) • Blood chemistry (see Section 6.3) • Liver function tests (see Section 6.3) • Electrolytes (see Section 6.3) • Serum pregnancy test (if applicable, see Section 6.3) • Urinalysis (see Section 6.3) • AE assessment • Concomitant medications assessment

• Concomitant medications assessment • Tumor markers assessment if applicable • Tumor assessment (if not done within 14 days)	• Tumor markers assessment (if applicable) • Tumor assessment (if not done within 14 days) • 12-lead ECG (see Section 6.4)
5.6 Discontinuation from Study (p.38)	
• Documented radiographic progression of disease.	• Documented radiographic progression of disease. (However, if, in the Investigator's opinion, treatment with tivantinib, as a monotherapy or in combination therapy, is providing clinical benefit to a subject with radiological progression of disease, the subject may continue to receive the treatment after consultation with the ArQule, Inc. [ArQule] Medical Monitor or designee.)
6.3 Clinical Laboratory Tests (p.39)	
• Hematology: complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count (WBC) with 5-part differential, red blood cell (RBC) and platelet count • Coagulation (at baseline and end of study, only): prothrombin time, international normalized ratio, and partial thromboplastin time • Blood chemistry: calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, uric acid, total protein, and blood urea nitrogen (BUN) • Liver function tests: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin • Electrolytes: sodium, potassium, and chloride • Routine urinalysis: dipstick and microscopy (only if clinically indicated) including protein, specific gravity, glucose, and blood • Serum pregnancy test for female	• Hematology: Complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell and platelet count • Coagulation: (at Baseline and End of Treatment; and if clinically indicated): prothrombin time, international normalized ratio (INR) and partial thromboplastin time. • Blood chemistry: calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, uric acid, total protein and blood urea nitrogen (BUN) • Liver function tests: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin • Electrolytes: sodium, potassium, and chloride • Serum pregnancy test (at Baseline and End of Treatment only) for female subjects of childbearing potential • Routine urinalysis (at Baseline and End of Treatment only; and if clinically indicated): dipstick and microscopy (only if clinically indicated or dipstick is not done) including protein, specific gravity, glucose and blood

subjects of childbearing potential	
7.1.3 Tivantinib Administration (p.41)	
All subjects will receive at the dose and schedule depending on the original study protocol they were enrolled into.	All subjects will receive tivantinib capsules or tablets at the dose and schedule depending on the original study protocol they were enrolled into.
	Added Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.
7.2 Combination Drug Administration (p.42)	
The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator based on the combination drug(s) label(s).	The combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on the combination drug(s) label(s) and prior tivantinib clinical trials.
7.3 Dose Modification (p. 42)	
Dose administration may be delayed to allow for recovery from toxicity. Combination therapy drug dose modification should follow the original protocol guidelines. In general, dose reduction should be done according to the following guidelines: • 240 mg BID • 120 mg BID • 120 mg once a day	Dose administration may be delayed to allow for recovery from toxicity. Combination therapy drug dose modification should follow the original protocol guidelines (see Appendix 4). In general, once the tivantinib dose has been modified for a subject, all subsequent cycles should be administered to that subject at the modified dose unless additional dose modifications may be required. The modified dose will be considered the maximum dose for that subject for all subsequent cycles. Dose modification schema: • 240 mg BID (capsules or tablets) • 120 mg BID (capsules or tablets)

	• 120 mg once a day (capsules or tablets) Further instructions for tivantinib dose modification due to non-hematologic or hematologic toxicities are listed in the following tables and provided in the original study protocols. For HCC subjects enrolled in the extension protocol, dose reduction and management of non-hematologic and hematologic toxicities should **strictly** follow the original protocol guidelines.

Dose Delays/ Reduction Tables (pp. 43-44)

Dose Delays/Reductions for Non-hematological Toxicity

Event Severity	Action
Grade 1 or 2	Continue current dose level
Grade 3	Withhold until recovery to Grade 1 or Baseline. Administer at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer at lower dose for subsequent cycles.
Grade 4	Withhold until recovery to Grade 1 or Baseline. Consult with ArQule's Medical Monitor or designee prior to restarting . If the Investigator and Medical Monitor concur, administer at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer at lower dose for subsequent cycles.

Dose Delays/Reductions for Hematological Toxicity

Event/Severity	Action
Grade 1	Continue current dose level
Grade 2 Neutropenia Thrombocytopenia	Withhold and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 7 days to: 1.5×10^9/L for ANC, or 75×10^9/L for platelets, resume treatment at the same dose level • If the relevant lab value takes more than 7 days to recover to the level described above, restart administration at the next lower dose If a second hold is required for the same event, whichever the grade, administer at the next lower dose once lab values allow doing so

Grade 3 **Neutropenia** **Thrombocytopenia** **Anaemia**	Withhold and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 7 days to: 1.5×10^9/L for ANC, 8 g/dL for hemoglobin, or 75×10^9/L for platelet, resume treatment at the same dose level. • If the relevant lab value takes more than 7 days to recover to the level described above, treatment with growth factors for neutropenia is recommended. Restart administration at the next lower dose once lab values allow doing so. • If a second hold is required for the same event, administer at the next lower dose once lab values allow doing so.
Grade 4 **Neutropenia** **Thrombocytopenia** **Anaemia** **Febrile Neutropenia**	Withhold , and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers to: 1.5×10^9/L for ANC, 8 g/dL for hemoglobin, or 75×10^9/L for platelet, resume treatment at the next lower dose once lab values allow doing so, unless further dose reduction is required. Treatment with growth factors is **strongly recommended** for Grade 4 neutropenia and febrile neutropenia (as per 2006 ASCO guidelines)

Revised

Table 7.1 Dose Delays/Reductions for Non-hematological Toxicity Related to Tivantinib (non-HCC subjects)

Event Severity	Action
Grade 1 or 2	Continue current dose level
Grade 3	Withhold tivantinib administration for up to 21 days until recovery to Grade 1 or Baseline. Administer tivantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer tivantinib at the next lower dose for all subsequent cycles.
Grade 4	Withhold tivantinib administration for up to 21 days until recovery to Grade 1 or Baseline. Consult with ArQule's Medical Monitor or designee prior to restarting tivantinib. If the Investigator and Medical Monitor concur, administer tivantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer tivantinib at the next lower dose for all subsequent cycles.

* If an event fails to recover to Grade 1 or Baseline and the dose must be delayed >21 days, the subject will be withdrawn from all study treatment, but should continue to undergo all follow-up evaluations.

Table 7.2 Dose Delays/Reductions for Hematological Toxicity Related to Tivantinib (non-HCC subjects)

Event/Severity	Action
Grade 1	Continue current dose level

Grade 2 **Neutropenia** **Thrombocytopenia**	Withhold tivantinib administration for up to 21 days and monitor hematology weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 7 days to: $\geq 1.5\times10^9$/L for ANC, or $\geq 75\times10^9$/L for platelets, resume tivantinib treatment at the same dose level • If the relevant lab value takes more than 7 days to recover to the level described above, restart tivantinib administration at the next lower dose level If a second hold is required for the same event, whichever the grade, administer tivantinib at the next lower dose once lab values allow doing so
Grade 3 **Neutropenia** **Thrombocytopenia** **Anaemia**	Withhold tivantinib administration for up to 21 days and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 14 days to: $\geq 1.5\times10^9$/L for ANC, 8 g/dL for hemoglobin, or $\geq 50\times10^9$/L for platelet, resume tivantinib treatment at the same dose level. • If the relevant lab value takes more than 14 days to recover to the level described above, treatment with growth factors for neutropenia is recommended. Restart tivantinib administration at the next lower dose once lab values allow doing so. • If a second hold is required for the same event, administer tivantinib at the next lower dose once lab values allow doing so.
Grade 4 **Neutropenia** **Thrombocytopenia** **Anaemia** **Febrile Neutropenia**	Withhold tivantinib administration for up to 21 days, and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 14 days to: $\geq 1.5\times10^9$/L for ANC, ≥8 g/dL for hemoglobin, or $\geq 50\times10^9$/L for platelet, resume treatment at the next lower dose once lab values allow doing so, unless further dose reduction is required. Treatment with growth factors and antibiotics is **strongly recommended** for Grade 4 neutropenia and febrile neutropenia (as per 2006 ASCO guidelines)

* If an event fails to recover to Grade 1 or baseline and the dose must be delayed >21 days, the subject will be withdrawn from all study treatment, but should continue to undergo all follow-up evaluations.

The following precautions will be taken to manage neutropenia risk during the study:

- For tivantinib-naïve subjects, ANC levels should be checked weekly during the first four weeks of therapy with tivantinib, and monthly thereafter. Subjects who experience Grade ≥3 neutropenia should be monitored weekly for four consecutive cycles (months).
- Prophylactic treatment with growth factors and antibiotic is suggested for subjects who experience Grade ≥3 neutropenia and febrile neutropenia

7.5.1 Permitted Treatment (p. 45)	
Hematopoietic growth factors including filgrastim (Neupogen®) or other colony-stimulating factors. ASCO or institutional guidelines should be followed for the use of WBC growth factors.	Hematopoietic growth factors including filgrastim (Neupogen®) or other colony-stimulating factors (G-CSF). ASCO or institutional guidelines should be followed for the use of WBC growth factors: http://jco.ascopubs.org/content/24/19/3187.full
	Added • Megestrol acetate (Megace®) • Supportive therapy for toxicities associated with combination therapy drug(s), according to the FDA approved label or institutional practice • Use of topical corticosteroids, topical antibiotics, and systemic antibiotics according to standard of care or 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 study treatment, in the opinion of the Investigator • Bisphonates for bone metastases • Palliative radiotherapy for local pain control provided that the subject does not meet criteria of progressive disease and treated lesion(s) will not be included in the target/non-target lesion assessment
7.5.2 Prohibited Treatment (p. 45)	
Any concurrent anticancer therapy including but not limited to chemotherapy, radiotherapy, hormonal therapy (except megestrol acetate as supportive care), immunotherapy, or locoregional therapy	Any concurrent anticancer therapy including but not limited to chemotherapy, radiotherapy, hormonal therapy (except megestrol acetate as supportive care), immunotherapy
Immunosuppressive therapies	Immunosuppressive therapies including 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)

7.5.3 Treatment to Avoid (pp. 45-46)	**7.5.3 Treatment to Avoid During Tivantinib Administration (pp. 45-46)**
Deleted •Bisphosphonates, unless initiated before screening	
	Added As tivantinib is metabolized by hepatic cytochrome P450 enzymes, primarily CYP 2C19 and CYP 3A4, interactions with drugs metabolized via the same enzyme system are possible. Caution should be applied when any CYP 2C19 inhibitors and/or strong CYP 3A4 inhibitors are used as concomitant therapy.
8.1.1 Adverse Event (p. 47)	
[redacted]	*Added* All AEs/SAEs occurring during the study period from the first day of study drug administration (Day 1 of this study) to the last day of the follow-up period will be captured.
8.4 Reporting Serious Adverse Events/ArQule Medical Monitor (p. 50)	
PPD [redacted]	
14 REFERENCES	
(Added) Munshi N, Jeay S, Li Y, et al. ARQ 197, a novel and selective inhibitor of the human c-Met receptor tyrosine kinase with antitumor activity. *Mol Cancer Ther*. 2010;9:1544-53. Tivantinib (ARQ 197) Investigator's Brochure, Version 9.0, Dated: 06 November, 2013. Laux I, Goldman J, Just R, et al. Phase I dose escalation study (ARQ 197-111) evaluating combination of selective c-Met inhibitor ARQ 197 and erlotinib. *J Clin Oncol*. 2009;27:Suppl;abstr 3549. Mekhail T, Rich T, Rosen L, et al. Final results: A dose escalation phase I study of ARQ 197, a selective c-MET inhibitor, in patients with metastatic solid tumors. 2009 ASCO Annual Meeting. *J Clin Oncol*. 2009; 27:15s(suppl;abstr 3548). Rosen LS, Senzer N, Mekhail T et al. A phase I dose-escalation study of Tivantinib in adult patients with metastatic solid tumors. *Clin Cancer Res*. 2011;17:7754-64. Sequist LV, von Pawel J, Garmey EG, et al. Randomized phase II study of erlotinib plus	

tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. *J Clin Oncol*. 2011;29:3307-15.

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ADDED

APPENDIX 4: DOSE MODIFICATION GUIDELINES FOR COMBINATION THERAPY

When during combination therapy co-drug related toxicity is observed, dose delays and/or reduction s in co-drug administration are allowed as described below or may follow institutional guidelines/standard of care.

Sorafenib (Nexavar®) Dose Modification

Temporary dose interruption and/or dose reduction may be necessary due to adverse events. For recommendations for skin adverse events, see Table A4-1. If dose reduction is necessary, the sorafenib dose may be reduced to once a day. If further dose reduction is necessary, sorafenib may be given once every other day.

Table A4-1 Sorafenib Dose Modifications for Dermatologic Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling,	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief.

erythema, or discomfort of the hands or feet that does NOT disrupt the subject's normal activities		
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the subject's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptom relief.
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1. When resuming treatment, decrease sorafenib dose by 1 dose level (dosing once a day or once every other day).
	4th occurrence	Discontinue sorafenib treatment.
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that causes the subject to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0 or 1. When resuming therapy, decrease sorafenib by 1 dose level (dosing once a day or once every other day).
	3rd occurrence	Discontinue sorafenib treatment.

Please refer to the approved sorafenib (Nexavar) package insert for details.

Gemcitabine (Gemzar®) Dose Modification

Dosage adjustment of gemcitabine is based upon the degree of hematologic toxicity experienced by the subjects. Subjects receiving gemcitabine should be monitored prior to each dose with a complete blood count, including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table A4-2.

Table A4-2 Gemcitabine Dosage Reduction Guidelines

Absolute Granulocyte Count (× 10^6/L)	Platelet Count (× 10^6/L)	Percent of Full Dose (%)
≥ 1000 and	≥ 100,000	100
500 – 999 or	50,000 – 99,999	75
< 500 or	< 50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine should be administered with caution in subjects who have evidence of significant

renal or hepatic impairment, as there is insufficient information from clinical studies to allow clear dose recommendation for these subject populations.

Refer to the approved gemcitabine (Gemzar) package insert for details.

Erlotinib (Tarceva®) Dose Reduction

When dose reduction is necessary, the erlotinib dose should be reduced by a 50 mg decrement. For this study, no more than 1 dose reduction will be allowed.

Pulmonary Symptoms: In subjects who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough, or fever, treatment with erlotinib should be interrupted pending diagnostic evaluation. If interstitial lung disease is diagnosed, erlotinib should be discontinued and appropriate treatment instituted, as necessary.

Diarrhea: Diarrhea can usually be managed with loperamide. Subjects with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy.

Skin Reactions: Skin reactions experienced by subjects receiving erlotinib tend to be managed easily with topical therapies and do not require treatment interruption or dose modification (please refer to package insert for details). However, rare subjects with severe skin reactions may also require dose reduction or temporary interruption of therapy.

Concomitant CYP3A4 Inhibitors: In subjects concomitantly treated with a strong CYP3A4 inhibitor, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, or voriconazole, a dose reduction should be considered if severe adverse reactions occur.

Hepatic Impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore, caution should be used when administering erlotinib to subjects with hepatic impairment. Dose reduction or interruption of erlotinib should be considered if severe adverse reactions occur. For additional dose modification information, please refer to the package insert for erlotinib (Tarceva).

Irinotecan (Camptosar) and Cetuximab (Erbitux®) Dose Reductions

Refer to the locally applicable irinotecan and cetuximab package inserts for dose reductions, modifications, or delays due to irinotecan- or cetuximab-related toxicities. The recommended dose levels for reductions in irinotecan and cetuximab are shown in Table A4-3. General recommendations for dose modifications are provided in Table A4-4.

Supportive therapy for toxicities associated with irinotecan and/or cetuximab therapy may be given, according to institutional practice.

A new cycle of treatment may begin when the ANC is $\geq 1.5 \times 10^9$/L, the platelet count is $\geq 100 \times 10^9$/L, and any treatment-related gastrointestinal toxicity is resolved to ≤ Grade 1.

The ANC level at baseline must be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. If the initiation of a new cycle or treatment during a cycle is delayed for 4 weeks or longer, the subject should be removed from study treatment. Doses that are withheld are not to be made up.

Table A4-3 Recommended Irinotecan and Cetuximab Dose Reductions

Agent	Initial Dose	Level -1	Level -2[a]
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
Cetuximab	400 mg/m^2	250 mg/m^2	200 mg/m^2
a: If a reduction below Level -2 is indicated, discontinue treatment with that agent			

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity

Event	Action
Hematologic	
Grade 2 Hematologic	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, resume at the previous dose levels, provided ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L.
Grade 3 to 4 Hematologic	Hold irinotecan. If counts recover to ANC $\geq 1.5 \times 10^9$/L and platelets to $\geq 100 \times 10^9$/L, may be resumed at 1 lower dose level for the remainder of the cycle. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.
Febrile neutropenia	Hold irinotecan. If fever resolves and counts recover to ANC $\geq$ 1.5 x 10^9/L and platelets to $\geq$ 100 x 10^9/L, both agents may be resumed at 1 lower dose level for the remainder of the cycle. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.
Diarrhea	
Grade 2 Diarrhea	Reduce irinotecan for 1 dose level for the remainder of the cycle. If diarrhea persists, hold cetuximab until fully resolved. For subsequent cycles, resume all agents at the previous dose levels, provided diarrhea has fully resolved.
Grade 3 to 4 Diarrhea	Hold irinotecan and cetuximab. If diarrhea resolves to $\leq$ Grade 2, both agents may be resumed at 1 lower dose level for the remainder of the cycle. If diarrhea persists, hold cetuximab until fully resolved. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.
Nausea/Vomiting[a]	
Grade 3 Nausea and/or Vomiting	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, continue irinotecan at the reduced dose level from the previous cycle.
Grade 4 Nausea and/or Vomiting	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, continue irinotecan at the reduced dose levels from the previous cycle.
a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy. b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia. c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions,	

although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.

AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity (Continued)

Event	Action
Mucositis	
Grade 2 Mucositis	Reduce irinotecan 1 dose level for the remainder of the cycle. For subsequent cycles, continue at the reduced dose levels from the previous cycle. No modifications (or delays) will be made for cetuximab.
Grade 3 Mucositis	Hold irinotecan. If mucositis resolves to ≤ Grade 2, treatment may be resumed at 1 lower dose level for the remainder of the cycle. For subsequent cycles, continue at the reduced dose level from the previous cycle. No modifications (or delays) will be made for cetuximab.
Grade 4 Mucositis	Hold ALL study treatment, including irinotecan, cetuximab, and tivantinib. If mucositis resolves to ≤ Grade 2, irinotecan may be resumed at 1 lower dose level for the remainder of the cycle. Cetuximab will be resumed at the prior dose. For subsequent cycles, continue all agents at the dose level from the previous cycle.
Pulmonary	
Grade 2 or worsening pulmonary symptoms unrelated to underlying cancer	Cetuximab treatment should be stopped and symptoms investigated. Cetuximab treatment may resume at 1 lower dose level when symptoms resolve to ≤ Grade 1 and cetuximab-related pneumonitis is ruled out.
≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates	Hold cetuximab until interstitial lung disease is ruled out. Continue irinotecan. Discontinue all study treatment if interstitial lung disease is confirmed.
Hypomagnesemia	
Grade 3 or 4 hypomagnesemia	Hold cetuximab until hypomagnesemia resolves to ≤ Grade 2, then restart cetuximab at the same dose. For any Grade of hypomagnesemia, magnesium supplementation should be provided.

a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.
b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions,

although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.

AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity (Continued)

Event	Action
Venous thrombotic events	
Grade 3 venous thrombosis or asymptomatic pulmonary embolism	Hold treatment with cetuximab. If the planned duration of full-dose anticoagulation is ≤ 2 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is ≥ 2 weeks, treatment may be resumed during the period of full-dose anticoagulation, if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on a stable dose of low molecular weight heparin prior to restarting treatment. • The subject must not have pathological conditions that carry a high risk of bleeding (eg, tumor involving major vessels). • The subject must not have had hemorrhagic events while on study.
Grade 4 or recurrent/worsening venous thromboembolic events	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Symptomatic pulmonary embolism	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Arterial thrombotic events	
Grade 3 cardiac ischemia/infarction	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Any Grade 4 arterial thrombotic event[b]	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
LV dysfunction	
Grade 3 LV dysfunction	Discontinue cetuximab. Subjects may continue other study treatment.
Grade 4 LV dysfunction	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.

a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.
b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine

release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.

AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Table A4-4 Dose Modifications to Irinotecan and Cetuximab Dose Due to Irinotecan- or Cetuximab-Toxicity (Continued)

Event	Action
Hemorrhage/bleeding	
Grade 3 hemorrhage/bleeding	Hold tivantinib treatment; once hemorrhage or bleeding resolves, tivantinib treatment may be continued at the Investigator's discretion.
Grade 4 hemorrhage/bleeding	Discontinue all study treatment, including tivantinib, irinotecan, and cetuximab.
Rash	
Grade 3 rash (1st occurrence)	Hold cetuximab infusion 1 to 2 weeks: • If improvement, continue at 500 mg/m^2. • If no improvement, discontinue cetuximab.
Grade 3 rash (2nd occurrence)	Hold cetuximab infusion 1 to 2 weeks: • If improvement, reduce to 400 mg/m^2. • If no improvement, discontinue cetuximab.
Grade 3 rash (3rd occurrence)	Hold cetuximab infusion 1 to 2 weeks: • If improvement, reduce to 300 mg/m^2. • If no improvement, discontinue cetuximab.
Grade 3 rash (4th occurrence)	Discontinue cetuximab.
Grade 4 rash (1st occurrence)	Discontinue cetuximab.
Hypersensitivity[c]	
Grade 1 hypersensitivity reactions (all agents)	Decrease the infusion rate for all agents by 50% until symptoms resolve; then resume at the initial planned rate (except for cetuximab, see below).
Grade 2 hypersensitivity reactions (all agents)	Stop infusion. Administer histamine 1 and/or histamine 2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pre-treat before all subsequent doses. Treat according to institutional policy.
Grade 3 or Grade 4 hypersensitivity reactions (all agents)	Stop the infusion. Permanently discontinue all study treatment and notify the Study Coordinator.
Grade 1 or 2 cetuximab infusion reactions	Stop the infusion until symptoms resolve, then restart cetuximab at a 50% lower rate of infusion. All subsequent doses should be administered at the lower infusion rate.

≥ Grade 3 cetuximab infusion reactions	Discontinue cetuximab. Other study treatment may be continued.
Other nonhematologic	
Grade 3 or higher nonhematologic toxicities not described above	Hold ALL study treatment, including irinotecan, cetuximab, and tivantinib, and monitor toxicity at least weekly. If toxicity resolves to Grade 1 or lower within 4 weeks, treatment may be resumed, with cetuximab and irinotecan at 1 lower dose level.

a: Dose modifications for nausea and/or vomiting should be made only if nausea and/or vomiting persist or occur despite 2 treatments with adequate (combination) antiemetics therapy.
b: Including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.
c: Note that the NCI CTCAE defines hypersensitivity and infusion reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the NCI CTCAE Version 4 for a complete list of signs and symptoms of "cytokine release syndrome/acute infusion reaction" and see the "Allergy/Immunology" section for a description of hypersensitivity.
AE = adverse event; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LV = left ventricular; NCI = National Cancer Institute.

Statistical Analysis Plan

Title: An Extension Protocol for Subjects Who Were Previously Enrolled in Other Tivantinib (ARQ 197) Protocols.

Protocol Number: ARQ 197-299

Study Drug: ARQ 197

EudraCT Number: 2010-020151-31

NCT NUMBER: 01178411

Sponsor: ArQule, Inc.
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Version: Final

Date: Aug 18, 2017

APPROVALS (SIGNATURE AND DATE)

The undersigned have approved this Statistical Analysis Plan for use in this study.

PPD

08/18/2017
Date

08/18/2017
Date

29-Aug-2017
Date

29 Aug 2017
Date

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1 LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
CTCAE	Common Terminology Criteria for Adverse Events
CRF/eCRF	Case Report Form/electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
HCC	Hepatocellular Carcinoma
NCI	National Cancer Institute
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

2 INTRODUCTION

This document describes the detailed statistical methodology applied in analyzing data of the study ARQ 197-299. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to data base lock.

The material presented in this section is based on the trial protocol dated 18 Feb, 2014. This plan may be revised during the study to accommodate protocol amendments.

2.1 Study Objectives

2.1.1 Primary Objective

To provide subjects who participated in previous tivantinib studies that have reached their designated end-dates and who may have benefited from the treatment with access to the study drug(s).

2.1.2 Secondary Objective

- To collect additional safety, tolerability, and efficacy information for tivantinib.

2.2 Overview of Study Design

2.2.1 Dose Schemes

Subjects will be treated according to the original treatment protocols into which they were enrolled until any discontinuation criterion is met. Dose may be delayed or reduced for clinically significant toxicities, but dose escalation is not allowed.
Subjects who were previously treated with tivantinib only and who in the opinion of the investigator and the sponsor approval may benefit from combination therapy will be allowed to receive combination therapy. The combination therapies dose(s) and schedule(s) will be determined to each subject by the investigator based on the combination drug(s) label(s).
Subjects who were previously enrolled in tivantinib studies but did not receive tivantinib as part of their treatment, and who, in the opinion of the Investigator, may benefit from treatment with tivantinib as a single agent or in combination therapy, will be allowed to initiate treatment with tivantinib. The tivantinib monotherapy or combination therapy dose(s) and schedule(s) will be determined for each subject by the Investigator and with the Sponsor's approval based on administration schedules tested in and defined by prior tivantinib clinical trials.

Dose modification for combination therapy drugs should follow the original protocol guidelines. In general, tivantinib dose reduction should be done according to the following guidelines:

- 240 mg BID (capsules or tablets)
- 120 mg BID (capsules or tablets)

- 120 mg once a day (capsules or tablets)

Further instructions for tivantinib dose modification due to non-hematologic or hematologic toxicities are listed in table 1 and 2, except for HCC subjects enrolled in the extension protocol, dose reduction and management should strictly follow the original protocol guidelines.

Table 1: Dose Delays/Reductions for Non-hematological Toxicity (non-HCC subjects)

Event severity	Action
Grade 1 or 2	Continue current dose level
Grade 3	Withhold tivantinib administration for up to 21 days until recovery to Grade 1 or Baseline. Administer tivantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer tivantinib at the next lower dose for all subsequent cycles.
Grade 4	Withhold tivantinib administration for up to 21 days until recovery to Grade 1 or Baseline. Consult with ArQule's Medical Monitor or designee prior to restarting tivantinib. If the Investigator and Medical Monitor concur, administer tivantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer tivantinib at the next lower dose for all subsequent cycles.

Table 2: Dose Delays/Reductions for Hematological Toxicity (non-HCC subjects)

Event severity	Action
Grade 1	Continue current dose level
Grade 2 **Neutropenia** **Thrombocytopenia**	Withhold tivantinib administration for up to 21 days and monitor hematology weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 7 days to: $\geq 1.5 \times 10^9$/L for ANC, or $\geq 75 \times 10^9$/L for platelet, resume tivantinib treatment at same dose level. • If the relevant lab value takes more than 7 days to recover to the level described above, restart tivantinib administration at the next lower dose. • If a second hold is required for the same event, whichever the grade, administer tivantinib at the next lower dose once lab values allow doing so

Grade 3 **Neutropenia** **Thrombocytopenia** **Anemia**	Withhold tivantinib administration for up to 21 days and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 14 days to: $\geq 1.5 \times 10^9$/L for ANC, 8 g/dL for hemoglobin, or $\geq 60 \times 10^9$/L for platelet, resume tivantinib treatment at same dose level. • If the relevant lab value takes more than 14 days to recover to the level described above, treatment with growth factors for neutropenia is recommended. Restart tivantinib administration at the next lower dose once lab values allow doing so. • If a second hold is required for the same event, administer tivantinib at the next lower dose once lab values allow doing so
Grade 4 **Neutropenia** **Thrombocytopenia** **Anemia** **Febrile Neutropenia**	Withhold tivantinib administration for up to 21 days, and monitor hematology and/or chemistry weekly until relevant lab value(s) recover to Grade 1 or: • If the relevant lab value recovers in less than 14 days to: $\geq 1.5 \times 10^9$/L for ANC, ≥ 8 g/dL for hemoglobin, or $\geq 60 \times 10^9$/L for platelet, resume treatment at next lower dose once lab values allow doing so, unless further dose reduction is required. Treatment with growth factors is strongly recommended for Grade 4 neutropenia and febrile neutropenia (as per 2006 ASCO guidelines)

If questions or considerations regarding dose modification arise or a specific dose modification is needed, ArQule's Medical Monitor or designee should be consulted.

2.2.2 Schedule of Assessments

Study visits will consist of a brief Pre-study Visit, during which subject's eligibility to continue treatment with tivantinib will be evaluated; Weekly or Monthly Visits during which subjects' treatment eligibility will be re-assessed and the study drug(s) will be administered; End of Study Visit and 30-day Safety Follow-up Visit. Detailed assessment plans are listed in table 3.

Table 3: Schedule of Assessments

	Pre-Study Visit	Monthly (combination tx)	Weekly [1]	Weekly (tivantinib -naïve tx)	End of Study Visit	30-Day Safety FU
Tests and Procedures/Window(days)	-14 to Day 1	± 3 days	± 3 days	± 3 days	Within 7 (+3) days	
Written informed consent[2]	X					
Medical history	X					
Physical examination	X	X		X[3]	X	
ECOG PS	X	X		X[3]	X	
Vital signs and weight[3]	X	X	X[3]	X[3]	X	
Hematology	X	X	X[3]	X[3]	X	
Chemistry panel	X	X		X[3]	X	
Electrolyte panel	X			X[3]	X	
Liver Function test	X			X[3]	X	
Coagulation panel	X				X	
Serum pregnancy test (if applicable)	X				X	
12-Lead ECG	X				X	
Tumor assessment[4]	X	X			X	
Tumor markers assessment (if applicable)	X	X			X	
Concomitant medications	X	X	X		X	X
AE assessment	X[5]	X	X		X	X
Tivantinib dispensation	X	X				
Combination therapy drug(s) Dispensation/administration (if applicable)	X	X	X			
Telephone call						X

1. Weekly visit may be required for administration of combination therapy drug(s) or for tivantinib-naïve

subjects during the first four weeks of treatment with tivantinib
2. Must be obtained before any study related procedures
3. Weight is NOT required for weekly visits
4. Should be done every 12 weeks unless current disease specific standard of care requires performing imaging more often
5. All AEs/SAEs occurring during the study period from the first day of study-drug treatment (Day 1 of this study) to the last day of the 30-day post-treatment follow-up period will be captured. AEs that continue from the original tivantinib study or begin after the last visit of the original study but prior to Day 1 of the Extension study must be documented on a Medical History eCRF page. Resolved AEs from the original tivantinib study are captured in the original study records and will not be re-recorded for this study

3 DEFINITIONS AND DATA PROCESSING RULES

3.1 Definitions

3.1.1 Study Drug

Study drug refers to Tivantinib (ARQ 197) and all combination therapy drug(s), including but not limit to Erlotinib (Tarceva®), Gemcitabine (Gemzar®) and Sorafenib (Nexavar®).

3.1.2 Study Day

The study day for all safety and non-safety (e.g. tumor assessment, death, disease progression, performance status) assessments will be calculated as:

For days on or after the date of the first dose of the study drug:
Study day = the date of the event (visit date, onset date of an event, assessment date etc.) – date of the first dose of the study drug + 1.

The first dose date of study drug is therefore study Day 1. Example: If the start of study drug is on 01JAN2014 and start date of an adverse event is on 05JAN2014, then the study day of the adverse event onset is 5.

For days prior to start date of study drug the study day will be negative:
Study Day = the date of the event - the date of the first dose of the study drug.

The study day will be derived in the SDTM data sets.

3.2 Analysis Variables

3.2.1 Demographic and Baseline Variables

Demographics and baseline characteristics will include but not limit to:

- Subject demographics (age, gender, race)
- Baseline disease characteristics (cancer type, stage and all other prognostic factors)

- Clinically significant medical history
- Prior and concomitant medications

3.2.2 Safety Variables

Safety variables include adverse events, laboratory test, vital signs, ECOG PS, ECG and physical examination.

3.2.3 Efficacy Variables

N/A.

4 STATISTICAL ANALYSIS POPULATIONS

Two populations are considered in the statistical analysis of the study.

4.1 Enrolled Population

Subjects who enrolled in ARQ 197-299 study will be included in the enrolled population.

4.2 Safety Population

Subjects who have received any amount of study drug will be included in the safety population.

5 STATISTICAL METHODS AND DATA ANALYSIS

5.1 Determination of Sample Size

No formal statistical tests of hypotheses will be performed in this study. The exact number of subjects estimated for this study depends on the number of subjects who will be eligible to continue treatment per the ARQ 197-299 protocol once their original protocols have reached their designated end-dates.

5.2 General

Categorical variables will be summarized as the number and percentage of subjects in each category. Continuous variables will be summarized as mean, standard deviation, median, minimum and maximum.

Because of the nature of this study, analyses on all baseline efficacy and safety will consist primarily of listings and descriptive summaries and all summaries will be presented in one treatment group for all subjects in the corresponding population.

As appropriate, data collected on the electronic case report form (eCRF) will be presented in data listings upon request. All statistical analyses will be performed using SAS® version 9.2 or higher.

5.3 Statistical Method

5.3.1 Subject Disposition

The number and percentage of subjects will be presented for enrolled population and safety population if it differs from enrolled population.

Subject disposition information will be summarized for all enrolled subjects. Reasons for discontinuation (as reported on eCRF) will be summarized in the corresponding table. A listing will be presented for data relevant to subject disposition.

5.3.2 Demographic and Baseline Characteristics

5.3.2.1 Demographic Characteristics

Demographic characteristics will be summarized in the safety populations. This include but not limit to age, age groups (<65, >=65), gender, race, ethnicity, ECOG performance status, height, weight.

5.3.2.2 Baseline Disease Characteristics

For cancer history, listing and summary statistics will be presented for safety population. Cancer types will be categorized into lung cancer, colon cancer, and hepatocellular cancer and other. The 95% confidence interval for percent of subjects in each cancer type will be estimated.

5.3.2.3 Prior and Concomitant Medications

Prior and concomitant medication is defined as any medication besides the study drug(s) that was administered to a subject preceding or coinciding with the study assessment period.

Descriptive summary statistics on the prior and concomitant medications will be presented for safety populations in ATC class 2 and preferred term.

The related listings will be presented.

5.3.2.4 Medical History

Medical history and ongoing conditions, including cancer-related conditions, symptoms and current grade will be presented in the by subject listing for enrolled population.

5.3.3 Efficacy Analyses

No efficacy summarized table would be presented for tumor response is NOT evaluated in this study. Only percent change from the minimum sum of longest diameters (including baseline, if that is the minimum value, up to the preceding tumor assessment) and from baseline sum of longest diameters will be computed in the listing for target lesions.

5.3.4 Exposure Analyses

Duration of exposure (in days), cumulative dosage and average daily dose will be summarized descriptively for tivantinib only in safety population.

Duration of exposure (in days) = (date of the last dose of the study drug – date of first dose of study drug) + 1. Temporary drug discontinuation will be ignored.

Cumulative dosage is defined as the total dose given during study treatment period.

Average daily dose is defined as cumulative dose /duration of treatment exposure in days.

Details of all study drug(s) administration will be presented in the by subject listings.

5.3.5 Analyses of Safety Variables

All analyses for the safety evaluation variables will be performed for safety population. Safety parameters include adverse events, laboratory parameters, vital signs, ECOG performance status, 12-lead ECG and physical exams.

Descriptive statistics will be calculated for quantitative safety data, and frequency counts and percentages will be compiled for classification of qualitative safety data. All percentages will be calculated based on the number of subjects in the safety population, unless otherwise indicated. Unless otherwise noted, baseline is defined as the last non-missing value prior to the first dose date on day 1.

5.3.5.1 Adverse Events

Adverse events will be evaluated for severity using NCI-CTCAE, version 3.0 (publish date 09 Aug, 2006), version 4.0 (publish date 29 May, 2009) or version 4.03 (published June 14, 2010) depending on the original protocol. AE summaries will include the incidence of TEAEs. All TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) Version 13.1 and summaries will be presented with data in system organ class and preferred term. Separate TEAE summaries will be generated for the following:

- All TEAEs
- Severe TEAEs (Grade 3 or higher)
- SAEs
- TEAEs related to treatment (ARQ 197, combination therapy)
- TEAEs leading to treatment discontinuation
- TEAEs resulting in death
- TEAEs listed according to maximum severity

A TEAE is defined as follows:

- an AE which developed or worsened during the treatment period or within 30 days after the last dose of study drug(s);

- an AE which is considered study drug-related regardless of the start date of the event.

TEAEs will be summarized by presenting the number and percentage of subjects having at least one TEAE in each system organ class and preferred term. A subject with multiple occurrences of the same TEAE will be counted only once in the AE category.

Separate TEAE summaries will be presented by system organ class, preferred term. A subject with multiple CTCAE grades for the same TEAE will be summarized under the maximum CTCAE grade recorded for the event.

5.3.5.2 Laboratory Test

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for all quantitative parameters in safety population.

Baseline is defined as the last non-missing value assessment made prior to the first dose of study medication, which is, for most subjects, the clinical laboratory assessment taken on Day 1 prior to the first dose. If it's missing, the laboratory assessment at screening (including pre-study visit and unscheduled visit) will be used as baseline value.

If there are multiple measurements/samples, within the same post-baseline visit, the last measurement/sample within the visit (sorted by date and as available by time) will be used in the analysis by visit. Except for the baseline, no unscheduled visit would be included in summary tables.

All laboratory assessments will be presented in the corresponding data listings.

5.3.5.3 Vital Signs

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for each vital sign parameter.

Individual absolute vital sign values and the change from baseline will be summarized descriptively by assessment visit for safety population.

The corresponding related listings will be produced.

5.3.5.4 ECOG Performance Status

Number and percentage of subjects having each ECOG performance status level will be summarized for baseline and each post-baseline measurement. And related data listing will be presented per assessment visit and subject for enrolled population.

In addition, the shift table comparing worst post baseline to baseline will be also presented.

5.3.5.5 12-lead ECG

Shift tables from baseline to end of treatment results will be provided for the ECG overall interpretation. The following categories will be used: normal, abnormal and not clinically significant, abnormal and clinically significant.

All ECG data will be listed by subject.

5.3.5.6 Physical Exams

Data from physical exams will be presented in the data listing as per subject per visit per body system for enrolled population.

6 CONVENTION FOR HANDLING PARTIAL AND MISSING DATES

No imputation will be performed for any partial or missing date.

7 CHANGES TO THE PLANNED ANALYSES

N/A.

8 REFERENCES

1. ARQ 197-299 Protocol Amendment 1 dated June 16, 2010
2. ARQ 197-299 Protocol Amendment 2 dated February 18, 2014
3. SAS/Stat User's Guide Version 9.2.

9 MOCK-UP TABLES AND LISTING OF APPENDICES

Raw measurements will be reported to the number of significant digits as captured electronically or on the CRF. The mean and median will be displayed to one decimal place beyond the number of decimal places the original parameter is presented, and the measure of variability (e.g., standard deviation) will be displayed to two decimal places beyond the number of decimal places the original parameter is presented. Minimums and maximums will be reported to the same number of significant digits as the parameter. Calculated percentages will be reported with 1 decimal place. When count data are presented as category frequencies and corresponding percentages, the percent will be suppressed when the count is zero. If there are missing observations for the variable, percentages will not be displayed for this row. Listings of subjects will be sorted by the original treatments and subsequent by subject ID. When available, listings will also be sorted by study day.

LIST OF TABLES

LIST OF LISTINGS

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Listing 16.2.13.1	Tumor Marker	Enrolled Population