NCT01752920

TITLE:	**A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with FGFR Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with FGFR2 Gene Fusion**
PROTOCOL NUMBER:	**ARQ 087-101**
STUDY DRUG:	**ARQ 087**
SPONSOR:	**ArQule, Inc.** **19 Presidential Way** **Woburn, MA 01801** **Telephone: (781) 994-0300** **Fax: (781) 287-8134**
MEDICAL MONITOR:	[redacted]
HEALTHCARE CONNEXIONS SAFETY FAX:	**888-314-7557**
DATE OF PROTOCOL:	**Original: 07 September 2012** **Amendment 1: 29 October 2012** **Amendment 2: 21 June 2013** **Amendment 3: 12 June 2014** **Amendment 4: 04 November 2014** **Amendment 5: 10 April 2015**

Confidentiality Statement

SYNOPSIS

Study Title:	A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with FGFR Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with FGFR2 Gene Fusion
Study Number:	ARQ 087-101
Study Phase:	1/2
Primary Objective:	To assess the safety and tolerability of ARQ 087 in subjects with advanced solid tumors (Part 1; Dose Escalation/Food-effect Cohorts) or with advanced solid tumors with FGFR genetic alterations, including intrahepatic cholangiocarcinoma (iCCA) with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding).
Secondary Objectives:	• To assess the pharmacokinetic profile of ARQ 087 in subjects enrolled in Part 1 (Dose Escalation/Food-effect Cohorts) of the study • To assess the pharmacodynamic activity of ARQ 087 in blood and tumor biopsy specimens obtained from subjects with advanced solid tumors • To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ARQ 087 (Part 1) • To further evaluate the RP2D of ARQ 087 in subjects with FGFR genetic alterations, including subjects with iCCA with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding) • To generate preliminary evidence of anti-tumor activity • To generate preliminary biomarker evidence of target inhibition • To identify specific target subject (patient) population, e.g., subjects with iCCA with FGFR2 gene fusion or with other solid tumors with FGFR genetic alterations
Exploratory Objectives:	• To validate and assess FGFR family members (specifically, FGFR2 and potentially those harboring activating mutations) as predictive biomarkers • To evaluate the association between known markers of the FGF signaling pathway, toxicity, and clinical activity
Study Design:	This is an open-label, Phase 1/2, dose escalation and signal finding study of ARQ 087 administered to subjects with advanced solid tumors. The study is designed to explore the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of ARQ 087 and to define a RP2D of ARQ 087. To assess the safety of ARQ 087, a minimum of three subjects will be enrolled in each cohort. To assess pharmacodynamic changes, archival and/or fresh tumor tissue biopsy samples and blood samples will be collected. Pharmacokinetic assessments will be performed for a single dose (Cohorts 1-4) and continuous dosing (all Cohorts) with ARQ 087. Radiographic evaluation of potential anti-tumor activity of ARQ 087 (CT scan, MRI, or PET scan) will be performed at Baseline, and every eight weeks (e.g., every two cycles or Week 8, Week 16, etc.) thereafter or as otherwise clinically indicated. Initially, treatment will consist of two treatment periods (Cohorts 1-4): Treatment Period 1 (single dose administration for 72-hour PK assessment) and Treatment Period 2 (continuous dosing), and starting with Cohort 5, a single treatment period of continuous dosing, including a Food-effect Cohort will be implemented. Dose

	escalation will continue until MTD or RP2D is determined (see Sections 4.1, 4.3, and 5.3). Treatment will be initiated at a dose level of 25 mg/qod (every other day). All cycles/cohorts of therapy will consist of the oral administration of ARQ 087 at dose levels and administration schedules specified for their respective dose cohorts; the drug should be taken one hour prior to or two hours after the meal. Dose escalation will be performed after three or six subjects are evaluated in each cohort. In the first four cohorts, the dose may be doubled, and in the next cohorts, the dose escalation will follow a modified Fibonacci scheme (increase by 50%, 30%, and 25%) until RP2D or MTD is determined. The Food-effect Cohort will enroll at least six subjects with luminal breast A or B, endometrial, urothelial, gastric, or lung cancer with known and/or confirmed *FGFR1-3* amplification, mutation or gene rearrangement (fusion, translocation), or with adrenocortical carcinoma, cholangiocarcinoma, or sarcomas, independent from FGFR1-3 status. All subjects enrolled in the Food-effect Cohort should agree to and be eligible for paired biopsy. Once the MTD/RP2D level is determined, the Expanded Cohort (Part 2) will enroll approximately 50-60 subjects with advanced solid tumors with documented (known/confirmed) FGFR genetic alterations, including iCCA with FGFR2 gene fusion. The tumor type eligibility should be confirmed by the Sponsor's Medical Monitor or designee prior to enrollment. The RP2D has been defined as 300 mg qd under fasting conditions.
Study Population:	Adult subjects with advanced solid tumors whose cancer has progressed following standard therapy, or who have been unable to tolerate standard therapy, and/or for whom no standard treatment is available will be enrolled. Subject accrual will occur over a period of time dependent upon the number of cohorts enrolled. The exact number of subjects estimated for this study is dependent on the number of subject cohorts investigated based on the toxicity encountered (Part 1). It is expected that approximately 60-120 subjects at five to fifteen sites in the United States and Italy will be enrolled in this study. Once the MTD/RP2D level is determined, an Expanded Cohort (Part 2) will be enrolled. The Expanded Cohort (Part 2) of approximately 50-60 subjects with advanced solid tumors with FGFR genetic alterations, including iCCA with FGFR2 gene fusion will be enrolled. Inclusion Criteria 1. Signed written informed consent granted prior to initiation of any study-specific procedures 2. Male or female subjects of ≥ 18 years of age 3. Histologically or cytologically confirmed locally advanced, inoperable, or metastatic solid tumors. All subjects eligible for enrollment in the Expanded Cohort must have documented and/or confirmed FGFR genetic alterations, including iCCA with FGFR2 gene fusion. 4. Failure to respond to standard therapy, or for whom standard therapy does not exist. • Subjects enrolled in the Expanded Cohort should have no more than two prior systemic regimens with confirmed disease progression. • If the subject is refractory or has disease progression within 6 months of adjuvant treatment, then the previous treatment should be considered as a line of treatment rather than adjuvant therapy. • Subjects who did not receive prior systemic therapy for locally advanced and/or metastatic iCCA with confirmed FGFR2 gene fusion and for

	whom, in the opinion of the Investigator, treatment with ARQ 087 is appropriate may be enrolled 5. Evaluable or measurable disease 6. Archival and/or fresh biopsy tissue samples must be available prior to the first dose of the study drug. • All subjects eligible for enrollment in the Expanded Cohort (Part 2) must have known (documented and/or confirmed) FGFR genetic alterations. • Archival tumor samples should be collected for all subjects enrolled in the Expanded Cohort. Paired fresh tumor biopsy is optional for subjects enrolled in the Expanded Cohort. Both archival and pre-treatment fresh tumor samples (optional) should be collected prior to the first dose of the study drug. • All subjects eligible for enrollment in the Food-effect Cohort must have the following tumor types: luminal breast A or B, endometrial, urothelial, gastric, or lung cancer with known and/or confirmed *FGFR1-3* high level amplification, mutation or gene rearrangement (fusion, translocation), or adrenocortical carcinoma, cholangiocarcinoma, or sarcomas, independent from *FGFR1-3* mutation status • All subjects eligible for enrollment in the Food-effect Cohort should agree to and be eligible for paired biopsy 7. Life expectancy ≥ 12 weeks 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 (Appendix 2) 9. Hemoglobin (Hgb) ≥ 9.0 g/dL 10. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L 11. Platelet count ≥ 100 x 10^9/L 12. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (≤ 2 ULN for subjects with cholangiocarcinoma) 13. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 ULN (≤ 5 x ULN for subjects with liver metastases) 14. Serum creatinine ≤ 1.5 x ULN or creatinine clearance > 60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal 15. Albumin ≥ 2.8 g/dL 16. INR 0.8 to ULN or ≤ 3 for subjects receiving anticoagulant therapy such as Coumadin or heparin 17. Male or female subjects of child-producing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of ARQ 087 18. Women of childbearing potential must have a negative serum pregnancy test during Screening Period and within 48 hours of the first dose of ARQ 087. "Women of childbearing potential" is defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months prior to the first dose of ARQ 087. Exclusion Criteria 1. Anti-cancer therapy, such as chemotherapy, immunotherapy, hormonal, targeted therapy, or investigational agents within four weeks or five times of the drug half-life, whichever is **LONGER**, of the first dose of ARQ 087

	2. Major surgery or radiation therapy within four weeks of the first dose of ARQ 087 3. Previous treatment with FGFR inhibitors (e.g., ponatinib, dovitinib, nintedanib, AZD4547, NVP-BGJ398, LY2784455, BAY1163877) 4. History of allergic reactions attributed to compounds of similar chemical or biologic composition as ARQ 087 5. Unable or unwilling to swallow the complete daily dose of ARQ 087 6. Clinically unstable central nervous system metastasis (to be eligible, subjects must have stable disease ≥ 3 months, confirmed by MRI or CT scan, and/or have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications) 7. History of myocardial infarction (MI) or congestive heart failure defined as Class II to IV per the New York Heart Association (NYHA) classification within 6 months of the first dose of ARQ 087 (MI that occurred > 6 months prior to the first dose of ARQ 087 will be permitted) 8. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of ARQ 087 (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection) 9. History and/or current evidence of clinically relevant ectopic mineralization/calcification including but not limited to the soft tissue, kidneys, intestine, myocardium, and lung with the exception of calcified lymph nodes, asymptomatic nephrolithiasis, and asymptomatic coronary calcification (If indicated, standard CT or MRI may be used to assess ectopic mineralization/ calcification.) 10. Previous malignancy within 2 years of the first dose of ARQ 087, except curatively treated non-melanoma skin cancer, carcinoma in-situ of the breast or cervix, superficial bladder tumors 11. Known human immunodeficiency virus (HIV) infection 12. Concurrent uncontrolled illness not related to cancer, including but not limited to: • Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements • Uncontrolled diabetes mellitus 13. Blood transfusion within 5 days of the blood draw being used to confirm eligibility 14. Pregnant or breastfeeding

Test Product, Dose, and Mode of Administration:	Part 1: Subjects in Cohorts 1-4 of this study will receive ARQ 087 orally, as a single dose (Treatment Period 1) or on a continuous schedule (Treatment Period 2) at dose levels and administration schedules specified for their respective dose cohorts. Starting with Cohort 5, treatment will consist of a single treatment period of continuous dosing that will cease at the subject's discontinuation from the study. ARQ 087 should be taken one hour prior to or two hours after the meal, except by subjects enrolled in the Food-effect cohort, who will be required to take ARQ 087 with their morning meals. Dosing will begin at 25 mg/qod (first cohort) and escalate until the RP2D or MTD is determined. Based on the drug safety profile and Food-effect Cohort PK data, 300 mg qd has been defined as a RP2D and is recommended for further evaluation in the Expanded Cohort (Part 2). During Treatment Period 2 (Cohorts 1-4) and in all cohorts starting with Cohort 5, including the Expanded Cohort, cycles will be repeated in four-week (28-day) intervals until progression of disease, unacceptable toxicity, or another discontinuation criterion is met. In the case of toxicity, dose adjustment will be permitted.
Criteria for Dose Escalation (Part 1):	Enrollment at the next dose level and/or additional subjects into the ongoing cohort will occur according to the following criteria: • If zero of three initially treated subjects experience a dose-limiting toxicity (DLT) by Day 29 of continuous dosing, then dose escalation will occur • If one of three initially treated subjects experiences a DLT by Day 29 of continuous dosing, then an additional three subjects will be enrolled for a total of six subjects treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort. • If two or more treated subjects at a dose level experience a DLT by Day 29 of continuous dosing, dose escalation will stop and the prior dose level will be considered the MTD. If the first dose results in MTD, subsequent subjects will be enrolled at a lower dose or at a less frequent drug administration schedule (e.g., 25 mg twice a week). The MTD is defined as the dose level at which no more than one out of six subjects has an observable DLT. If a subject withdraws from study treatment for any reason other than a DLT during the first cycle (28 days), that subject will be replaced. During the dose escalation phase, if a subject experiences a DLT, such subject should be permanently discontinued from the treatment.
Duration of Treatment:	For an individual subject, treatment with ARQ 087 will continue until disease progression (clinical or radiological), unacceptable toxicity, or another discontinuation criterion is met. It is expected that most subjects will receive between one and six cycles of ARQ 087 for a treatment period of four to 24 weeks.
Pharmacokinetic and Pharmacodynamic Variables:	**Part 1 only:** Pharmacokinetic variables will include C_{max}, AUC, and half-life. In Cohorts 1-4, for each dose level, blood samples for PK determination will be drawn during Treatment Period 1 (single dose, Days 1-4) and Treatment Period 2 (continuous dosing) on Day 8, Day 15, Day 22, and Day 23 of Cycle 1 of ARQ 087 administration. (Except for subjects enrolled in Cohort 1 [25 mg every other day], for these subjects Cycle 1 Week 4 visits should be scheduled on the day of ARQ 087 administration and the next consecutive day, when drug is not taken, e.g., Cycle 1 Day 21 and Day 22 or Cycle 1 Day 23 and Day 24.) Starting with Cohort 5, PK samples will be collected on Day 1, Day 2, Day 8, Day 15, Day 22, Day 23 of

	Cycle 1, on Day 1 and Day 15 of each subsequent cycle, and at the End of Treatment visit. In **Part 2**, the Expanded Cohort, collection of PK samples will be optional; the recommended timepoints should be as follows: Day 1, Day 8, Day 15, Day 22, Day 23 of Cycle 1, on Day 1 and Day 15 of each subsequent cycle, and at the End of Treatment visit. **Part 1.** In Cohorts 1-4, blood samples will be collected during Treatment Period 1 (single dose, Days 1-4) and Treatment Period 2 (continuous dosing) on Day 8, Day 15, and Day 22 of Cycle 1, and on Day 1 of every subsequent cycle for evaluations of pharmacodynamic changes of factors including phosphate, glucose, FGF 7, 19, 21, and/or 23 utilizing standard blood chemistry methodologies and ELISA-based assays. Starting with Cohort 5 and in all subsequent Cohorts, blood samples for evaluation of pharmacodynamic changes of factors including phosphate, glucose, FGF 19, 21 and 23 will be collected on Day 1, Day 8, Day 15, Day 22 of Cycle 1, and on Day 1 of Cycles 2-5. Information on the tumor‘s genomic characteristics, such as FGFR protein expression, gene copy number and mRNA amplification, and/or mutational/gene re-arrangement (fusion, translocation) status, is required for this study. All baseline samples (archival or newly acquired) will be evaluated by immunohistochemistry (IHC), FISH (gene copy number), ISH or qNPA (mRNA amplification), and/or DNA sequencing (mutational/gene re-arrangement [fusion, translocation] status assessment). Pathology specimens (pre- and post-treatment tumor biopsies) will be evaluated for changes in total FGFR1, total FGFR2, pFGFR, pFRS2α, and/or pERK status by IHC, mesoscale, or immunoprecipitation/Western blot analysis. **Part 2 (Expanded Cohort):** Blood samples for evaluation of pharmacodynamic changes in FGF 19, 21, and 23 will be collected on Day 1 of Cycles 1-6.

Criteria for Determination of Dose-Limiting Toxicity (Part 1):	Dose-limiting toxicities will be determined during the first cycle (four weeks/ 28 days) of treatment. A DLT is defined by the occurrence of any of the following toxicities related to ARQ 087 within the first cycle of treatment and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:
	
	• Grade 4 anemia
	• Grade 4 neutropenia
	• Grade 4 thrombocytopenia
	• Grade 3 neutropenia with fever (≥ 38°C/100.4°F)
	• Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
	• Grade 3 thrombocytopenia in the presence of bleeding
	• ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with metformin)
	• ≥ Grade 3 non-hematological toxicity of any duration, except for the following:
	  o Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours
	  o Alopecia
	• Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject

Statistical Methods:	All subjects receiving at least one daily dose of ARQ 087 will be considered evaluable for safety analyses. In addition to the evaluation and categorization of adverse events, listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented. Subjects who have received at least one cycle of ARQ 087 and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics. For the Expanded Cohort (Part 2), for the iCCA sub-cohort, statistical analysis will include interim monitoring for futility. After response data from 10 subjects with iCCA are available, the response rate will be assessed. If the objective response is observed in ≤ 30% of enrolled subjects, the enrollment will be stopped for lack of efficacy.

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ABBREVIATION	DEFINITION
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
AR	accumulation ratio
ASCO	American Society of Clinical Oncologists
AST	aspartate transaminase
AUC	area under the concentration–time curve
AUC_{0-10}	area under the concentration–time curve from time 0 to 10 hours
AUC_{0-24}	area under the concentration–time curve from time 0 to 24 hours after dose administration
AUC_{0-inf}	area under the concentration–time curve from hour 0 to infinity
AUC_{0-t}	area under the concentration–time curve from time 0 up to the last measurable sampling time
BID	twice a day
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CL/F	apparent clearance, calculated as $Dose/AUC_{(0-inf)}$
C_{max}	maximum plasma concentration
CR	complete regression
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P_{450}
DAG	data analysis group
DCR	disease control rate
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGFR (*EGFR*)	epidermal growth factor receptor (gene)
ELISA	enzyme-linked immunosorbent assay

ABBREVIATION	DEFINITION
ERK1, 2	Extracellular extracellular signal-regulated kinase 1, 2
ESA	erythropoiesis stimulating agent
FAK	focal adhesion kinase
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR *(FGFR)*	fibroblast growth factor receptor
FIH	first-in-human
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
µg	microgram
Gab-1	growth factor receptor-bound protein 2-associated-binding protein 1
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transpeptidase
GI_{50}	concentration required for 50% inhibition of cell growth
GLP	Good Laboratory Practice
Grb-2	growth factor receptor-bound protein 2
h	hour
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
Hct	hematocrit
HERG	human ether-à-go-go–related gene
Hgb	hemoglobin
HGF/SF	hepatocyte growth factor/scatter factor
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IC_{50}	inhibitor concentration required for 50% inhibition
iCCA	intrahepatic cholangiocarcinoma
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
INR	international normalized ratio
IP	intraperitoneal
IRB	institutional review board
ITT	intent to treat
IV	intravenous(ly)
kg	kilogram

ABBREVIATION	DEFINITION
L	liter
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
min	minutes
mL	milliliter
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MTS	colorimetric cell proliferation assay
MUGA	multi gated acquisition scan
NCI	National Cancer Institute
ng	nanogram
nm	nanometer
nM	nanomolar
μM	micromolar
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
pERK	phosphorylated extracellular signal-regulated kinase
PET	positron emission tomography
pFAK	phosphorylated focal adhesion kinase
pFGFR	phosphorylated fibroblast growth factor receptor
pFRS2α	phosphorylated fibroblast growth factor receptor substrate
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
PKC	protein kinase C
PLCγ	phospholipase C gamma
PO	*per os* (by mouth)
PopPK	population pharmacokinetics

ABBREVIATION	DEFINITION
PR	partial response
PROs	patient reported outcomes
PS	performance status
PSI	pulmonary symptoms index
PT	prothrombin time
PTK2B, PYK2PYK2	proline tyrosine kinase 2 beta (gene), proline tyrosine kinase (protein)proline-rich tyrosine kinase 2
PTT	partial thromboplastin time
QD	once daily
qNPA	quantitative nuclease protection assay
QOD Q2D	every other day
QTc	heart rate-corrected QT interval
RBC	red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
s	second(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease standard deviation
SF	scatter factor
Shc	Src homology 2 domain-containing transforming protein
SOC	system organ class
STAT	signal transducer and activator of transcription
STD	severely toxic dose
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
$t_{1/2Z}$	apparent plasma terminal phase half-life; = (ln2)/ λZ
TEAE	treatment-emergent AE
TGI	tumor growth inhibition
TKIs	tyrosine kinase inhibitors
T_{max}	time to maximum observed concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
Vz/F	apparent volume of distribution, calculated as Dose/$AUC_{(0\text{-}inf)}/\lambda Z$

ABBREVIATION	DEFINITION
WBC	white blood cell (count)
WT	wild type

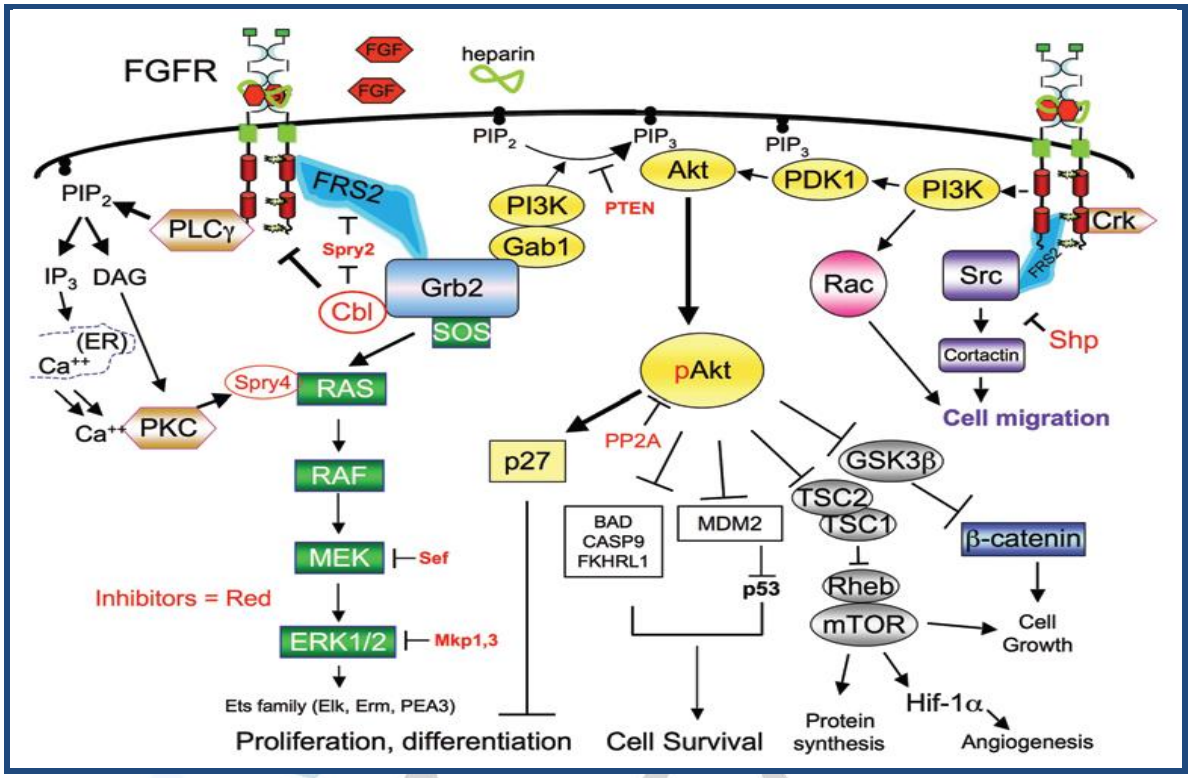
1 INTRODUCTION

1.1 Background and Rationale

Fibroblast growth factors (FGFs) and their receptors (FGFRs) play important roles in cell proliferation, cell differentiation, cell migration, cell survival, protein synthesis, and angiogenesis. The FGFR family consists of four genes encoding tyrosine kinase receptors (FGFR1, FGFR2, FGFR3, and FGFR4). Dysregulation of FGFR signaling has been implicated in a number of developmental syndromes as well as cancers, e.g., squamous non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), gastric, liver, breast, ovarian, endometrial, and bladder carcinomas, fueling significant interest in FGFRs as targets for therapeutic intervention. In human cancers, FGFRs have been found to be dysregulated by multiple mechanisms, including aberrant expression, mutations, chromosomal rearrangements, and amplifications.[1,2,3,4] A growing body of evidence establishes the role of FGFR signaling including *FGFR2* gene fusion in the development of intrahepatic cholangiocarcinoma (iCCA).[5,6,7,8] Intrahepatic cholangiocarcinoma is a rare disease (incidence rate in the US is 0.9 per 100,000) with a very poor prognosis and limited treatment options for advanced, inoperable tumors.[9,10,11]

FGFRs like other receptor tyrosine kinases are activated by tyrosine phosphorylation and signal through multiple signal transduction pathways including mitogen-activated protein kinases (MAPK), phosphatidylinositol 3-kinase (PI3K) phospholipase Cγ (PLCγ), protein kinase C (PKC) and signal transducer and activator of transcription (STAT). Activation leads to a series of cellular signaling events including increased cell proliferation, differentiation and migration (Figure 1.1).

Figure 1.1. Schematic Diagram of Intracellular Signaling Cascade Mediated by FGF/FGFRs[12]



ArQule, Inc. (ArQule) has discovered a novel class of FGFR inhibitors from which ARQ 087 emerged as the lead candidate for advancement into clinical development. Nonclinical studies were conducted in order to characterize the biological activity of ARQ 087. These studies included *in vitro* and *in vivo* assessments of the activity of ARQ 087 against isolated kinases, anti-proliferative effects in cell culture, *in vitro* and *in vivo* pharmacodynamic effects, and growth inhibitory effects in human tumor xenograft models in mice.

ARQ 087 is a potent multi-kinase inhibitor with pan-FGFR activity against FGFR1, FGFR2, mutant FGFR2 (N549H), FGFR3, and FGFR4 kinases, all exhibiting IC_{50} values in the low nanomolar range in biochemical assays. In cell-based systems, ARQ 087 inhibited endogenously expressed FGFR2 and ectopically expressed FGFR1, 2, and 3 in COS-1 cells (a fibroblast-like cell line derived from monkey kidney tissue). ARQ 087 displayed potent inhibition of FGFR2 phosphorylation in Kato III and SNU-16 human gastric carcinoma cells with comparable antiproliferative potencies in the MTS assay. Concentration-dependent inhibition of phosphorylation of downstream FGFR pathway signals (FRS2α, MEK, ERK, and AKT) was evident in response to ARQ 087 treatment in both *in vitro* and *in vivo* pharmacodynamic assays. Cell proliferation studies suggested a correlation of FGFR2 mRNA amplification in gastric and other cancers with associated sensitivity to treatment with ARQ 087. Correspondingly, ARQ 087 induced regressions in FGFR2-driven xenograft models (SNU-16 and BaF3/FGFR2) and inhibited tumor progression in a model harboring a FGFR2-activating mutation (AN3CA).

ARQ 087 has been formulated as a capsule filled with a powder blend of ARQ 087 and suitable excipients for use in a Phase 1 study to be conducted in adult subjects with locally advanced or metastatic malignant tumors.

1.2 Preclinical Data

1.3 In Vitro Pharmacology

Dysregulation in the FGFR tyrosine kinase family has been implicated in a number of human cancers, including gastric, breast, lung, endometrial, and bladder carcinomas fueling significant interest in FGFRs as targets for therapeutic intervention.[1,2,3,4] A novel class of pan-FGFR inhibitors has been discovered and developed at ArQule. From this class, ARQ 087 emerged as the candidate for advancement into full pre-clinical development for potential clinical evaluation.

1.3.1 Biochemistry: Inhibition of FGFR Kinase Activity by ARQ 087

FGFR kinase biochemical assays were developed by ArQule. FGFR2 (N549H) mutant protein was used throughout the lead optimization process due to higher enzymatic activity when compared to wild-type protein. Lead compound selectivity against all four FGFR isoforms were assayed using a PYK2-derived biotinylated peptide substrate (biotin-AGAGSIESDIYAEIPDETC-NH_2) and the AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) technology.

ARQ 087, the lead candidate for clinical development, inhibits FGFR1, FGFR2, and FGFR3 with biochemical IC_{50} values in the 1.8-14 nM range and FGFR4 with somewhat lower potency (IC_{50} value = 34.3-37 nM) (Table 1.1.)[13]. The biochemical potency of ARQ 087 against FGFR1, FGFR2, FGFR3 and FGFR4 was determined in-house using an AlphaScreen™ assay and also using a mobility shift assay (MSA) at Carna Biosciences (Table 1.1). ARQ 087 was most potent against FGFR2 in the MSA assay with an IC_{50} value of 1.8 nM. Together the data suggest that the potencies against FGFR kinases determined using the in-house FGFR AlphaScreen™ assay were comparable (within 10-fold) to the Carna Biosciences FGFR MSA.[13]

Table 1.1. Biochemical Activity of ARQ 087 Against FGFR1, FGFR2, FGFR2 (N549H), FGFR3, and FGFR4

ARQ 087	FGFR1 (nM)	FGFR2 (nM)	FGFR2 (N549H) (nM)	FGFR3 (nM)	FGFR4 (nM)
AlphaScreen™	6 ± 1	14 ± 4	22 ± 8	8 ± 2	37 ± 23
MSA (Carna Biosciences)	4.5	1.8	NT	4.5	34.3

Table 1.1: Diluted ARQ 087 and enzyme were added to each well of a reaction plate and were pre-incubated together for 20 minutes. The final concentration for FGFR1, FGFR2, FGFR2 (N549H), FGFR3, and FGFR4 were 6 nM, 6 nM, 1 nM, 13 nM, and 13 nM, respectively. After pre-incubation, the kinase reaction was initiated by the addition of a PYK2/ATP mixture. The final concentrations of PYK2 were 69 nM for FGFR1, FGFR2, FGFR2 (N549H), and FGFR3, and 227 nM for FGFR4. The final concentrations for ATP were 30 µM for FGFR1, FGFR2, FGFR2 (N549H), and FGFR3, and 150 µM for FGFR4. The plates were incubated for 1 hour and the reaction was stopped by the addition of stop/detection reagent (10 mM EDTA and 500 ng/well of

both AlphaScreen™ streptavidin and phospho-tyrosine beads [PerkinElmer]). The assay plates were then incubated for an additional 1 hour. Fluorescence (excitation λ: 680 nm, emission λ: 570 nm) to determine PYK2 substrate phosphorylation was measured on the Envision® Multilabel Reader (PerkinElmer) and IC_{50} values were calculated using XLFit™ (IDBS Limited). The MSA data was generated by Carna Biosciences using the Caliper microfluidics platform.

NT = not tested.

Note AlphaScreen™ data are reported as the mean ± SD (standard deviation). The MSA data are reported as the average of two values.

To determine the kinase selectivity of ARQ 087, the compound was tested against a panel of 298 kinases at a concentration of 0.1 μM. Among 298 kinases assayed, ~50 kinases (including FGFR1, FGFR2, FGFR3, and FGFR4) were inhibited greater than 50% by ARQ 087 at 0.1 μM.[13] In this subset of kinases, examination of IC_{50} values revealed that ARQ 087 inhibited (within a 3-fold range of the IC_{50} value for FGFR2) five other kinases (RET, DDR2, PDGFRβ, FMS, and mutant KIT [V560G]) which are outside of the FGFR family. Overall, of ~50 kinases assayed, 25, with the exception of FGFR4, exhibited sensitivities to ARQ 087 within a 3- to 10-fold range of the IC_{50} value for FGFR2 (Table 1.2). Together the data confirmed that ARQ 087 is highly potent against the FGFR family kinases, and also showed that it is a moderately selective kinase inhibitor.

Table 1.2 Biochemical Activity of ARQ 087 Against a Panel of Kinases Using the MSA Assay

Kinase	Average IC_{50} (nM)
FGFR2	1.8
RET	3.0
DDR2	3.6
FMS	3.8
PDGFRβ	4.1
FGFR3	4.5
FGFR1	4.5
KIT (V560G)	5.2
LCK	6.2
RET (M918T)	7.4
YES	7.6
ARG	7.9
KIT	8.2
FGFR3 (K650E)	9.2
PDGFRα	9.5
QIK	9.7
PDGFRα (V561D)	10.5
FLT1	10.7
SRC	11.1
FGFR3 (K650M)	11.3
ABL	13.7

Kinase	Average IC_{50} (nM)
EPHA1	14.7
FGR	17.0
CSK	17.4
FGFR4	34.3

Table 1.2: Biochemical Activity of ARQ 087 against a Panel of Kinases Using the MSA Assay. FGFR family members are highlighted. Kinase assays were conducted as described (www.carnabio.com) and ARQ 087 was tested in duplicate at concentrations of 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, and 0.0003 µM. Data reported is the average of two determinations.

1.3.2 Cell Biology: Anti-Proliferative Effect and FGFR Pathway Inhibition by ARQ 087 in Human Cancer Cell Lines

To determine whether ARQ 087 inhibits FGFR1, FGFR2, FGFR3, and FGFR4 in cells, we ectopically expressed full-length FGFR1, FGFR2, FGFR3, and FGFR4 in COS-1 cells and found that ARQ 087 inhibited the phosphorylation of FGFR1, FGFR2, and FGFR3 but not FGFR4 in this system (Figure 1.2). The IC_{50} values for inhibition of FGFR phosphorylation for FGFR1-, FGFR2-, FGFR3-, and FGFR4-overexpressing cells were < 0.123 µM, 0.185 µM, 0.463 µM, and > 10 µM, respectively. These data indicate that ARQ 087 is able to inhibit FGFR1, FGFR2 and FGFR3 in cells.[14]

Figure 1.2 ARQ 087 Inhibits Ectopically Expressed FGFR1, 2, and 3 in COS-1 Cells

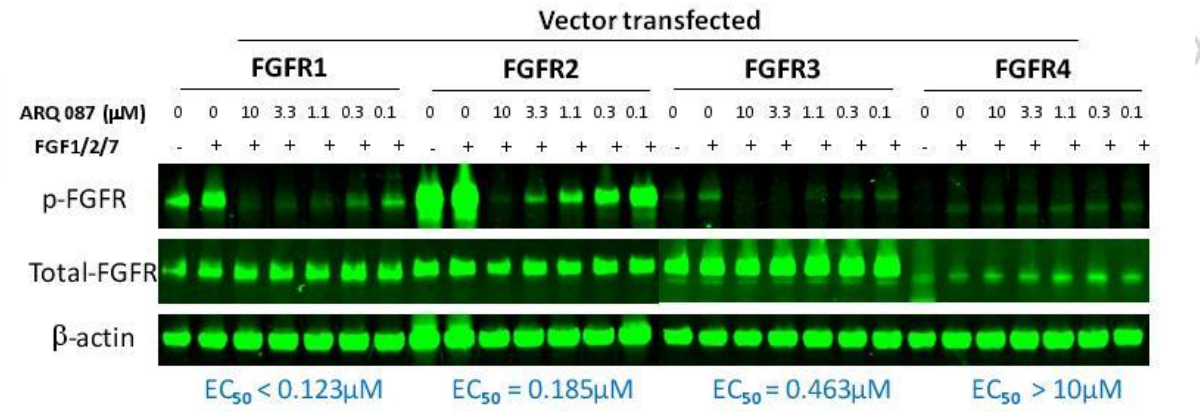


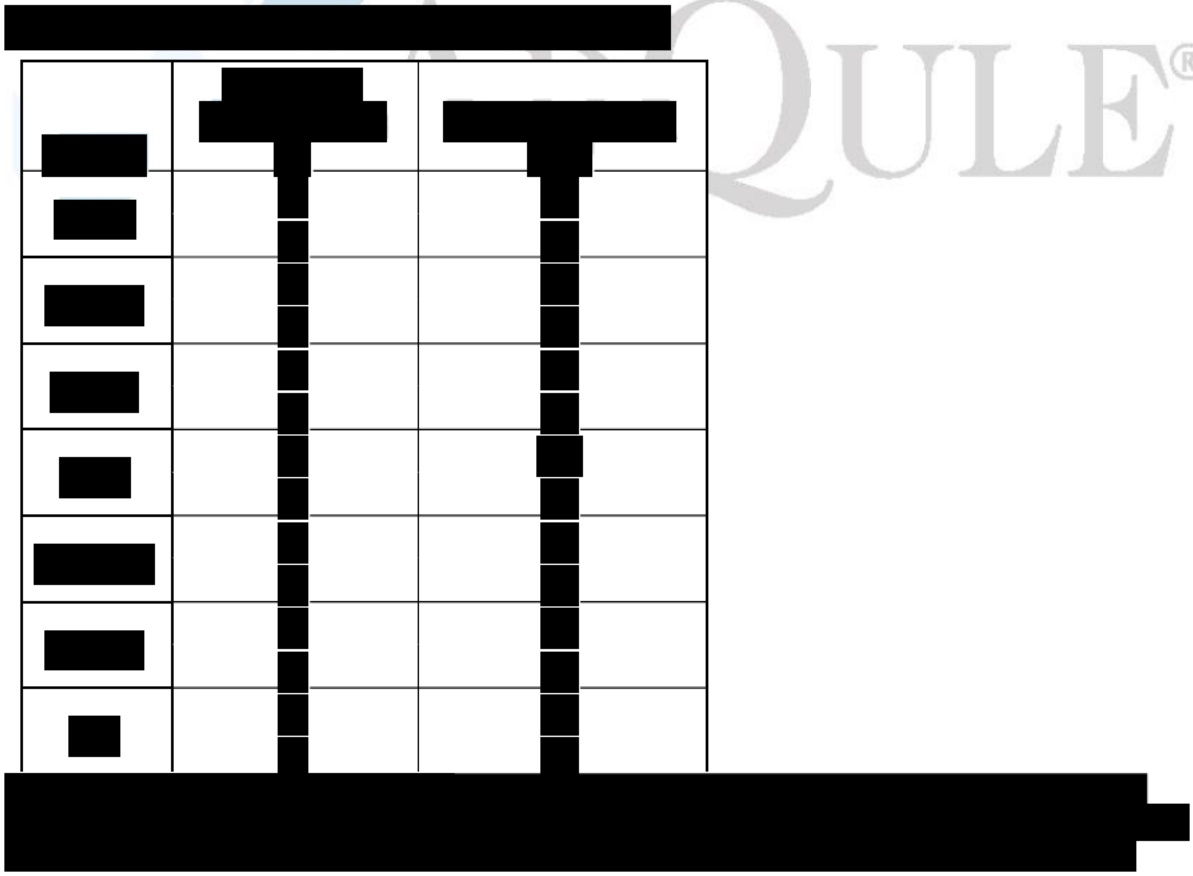
Figure 1.2: COS-1 cells were transfected with mammalian expression vectors encoding full-length *FGFR1*, *FGFR2*, *FGFR3,* or *FGFR4*. Forty-eight hours post-transfection cells were treated with indicated concentrations of ARQ 087 for 2 hours followed by stimulation with a mixture of FGF1, FGF2, and FGF7 for 15 minutes. Cell lysates were subjected to Western blot analysis to determine the expression of FGFR2, phospho-FGFR2, and ß-actin.[14]

ARQ 087 was active in several tumor cell lines over-expressing wild type or mutant FGFRs. From a panel of ~50 cell lines, in general, those that overexpressed FGFR2 were the most sensitive to ARQ 087 in the MTS cell proliferation assays.[14] These included the gastric carcinoma cell lines SNU-16 and Kato III, the breast carcinoma cell line MFM-223, the colorectal adenocarcinoma cell line NCI-H716, and the endometrial carcinoma cell line MFE-280 (possesses an activating mutant form of FGFR2). In addition, the FGFR2-

transfected mouse Ba/F3 cell line was more sensitive to ARQ 087 when compared to Ba/F3 cells over expressing the insulin receptor (GI_{50} values of 0.223 vs. 1.105 μM, respectively[14]). In addition to these anti-proliferative effects in FGFR2 over-expressing cell lines, ARQ 087 also inhibited growth in the lung cancer cell line NCI-H1581 (which is reported to be dependent upon FGFR1)[17,18], the acute myeloid leukemia cell line KG-1 (harbors a fusion gene, FGFR1OP2 to FGFR1, and is dependent upon this fusion gene for survival[19]), the multiple myeloma cell line KMS-11 (expresses FGFR3 [Y373C], a constitutively active mutant form of FGFR3[20]), the bladder cancer cell line J82 (harbors a mutated FGFR3 [K560E]), and the endometrial cancer cell line MFE-280 (expresses an activated mutant form of FGFR2 [S252W]). Taken together, these *in vitro* data suggest that ARQ 087 has potential to inhibit tumor progression in FGFR over-expressing tumors as well as those harboring activating mutations of this receptor family across a variety of tumor types.

FGFR2 and FGFR3 fusions have been identified in many solid tumors, including cholangiocarcinomas.[15] The expression of FGFR1 and FGFR2 was evaluated by IHC analysis in 19 patient tumor samples, 6 patient samples for FGFR1 staining and 13 patient samples for FGFR2 staining. The results demonstrate that multiple cholangiocarcinoma samples have increased FGFR1 and FGFR2 protein expression.[16]

Subsequent to the IHC studies which demonstrated high levels of FGFR1 and FGFR2 protein expression in cholangiocarcinoma patient samples, the sensitivity of seven cholangiocarcinoma cell lines to ARQ 087 in 24 and 72 hour proliferation assays was assessed. [redacted]

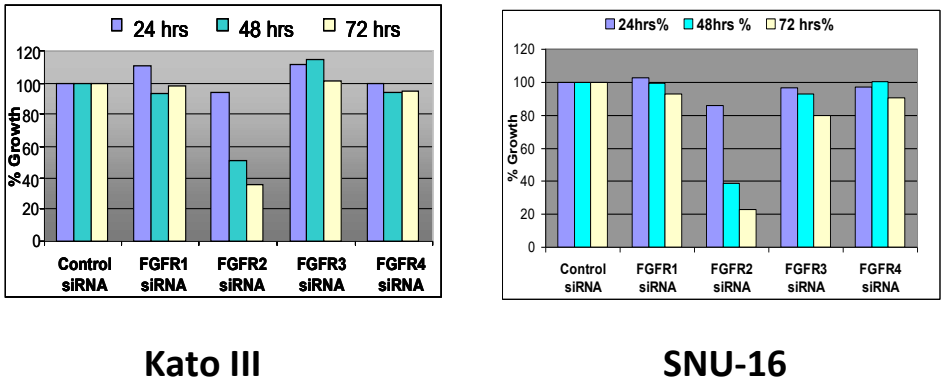


[redacted]

The gastric cancer cell lines Kato III and SNU-16 have been shown to express high levels of FGFR2 protein.[21] Small-interfering RNAs (siRNAs) specific against individual FGFR isoforms were utilized to determine whether Kato III and SNU-16 cells are dependent on FGFR2 signaling for cellular proliferation. While treatment with control, FGFR1, FGFR3, and FGFR4 siRNA had little effect on cell growth, as shown in A[14], treatment with FGFR2 siRNAs significantly reduced the growth of both Kato III and SNU-16 cells after 48 and 72 hrs of treatment. In addition, the reduction of FGFR2 protein in these two cell lines resulted in decreased phosphorylation levels of the downstream proteins MEK and AKT (B[14]). These observations were consistent with data reported in the literature.[21]

Figure 1.3 Kato III and SNU-16 Cells Dependent on FGFR2 Signaling for Proliferation

A.



B.

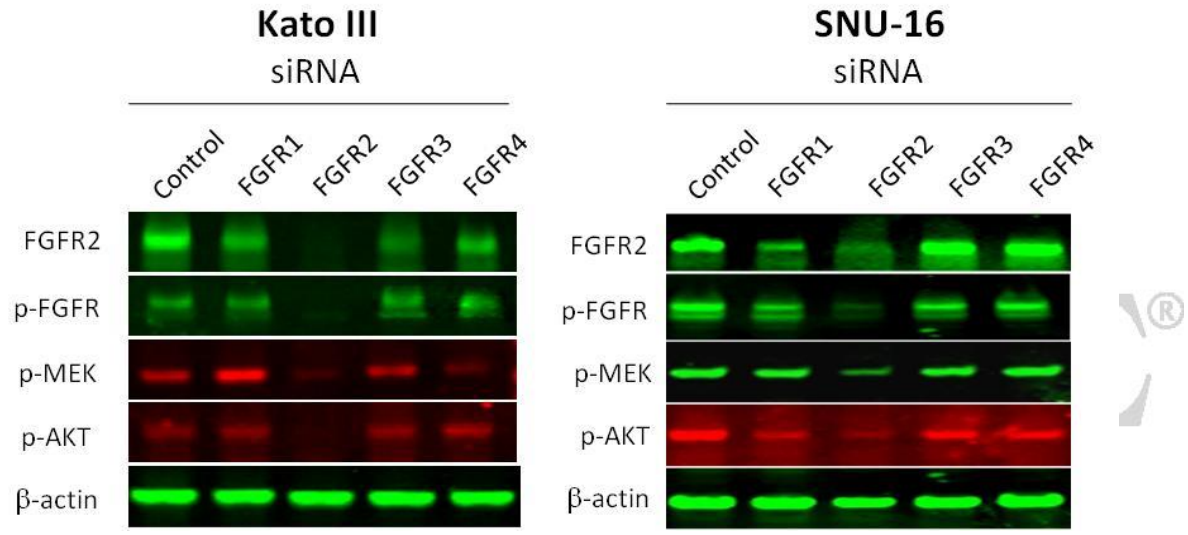


Figure 1.3: Dependency of Kato III and SNU-16 cells on FGFR2 signaling for proliferation.

(A) Kato III and SNU-16 cells were treated with the indicated siRNA for 24, 48, or 72 hrs. Cell growth was assessed by MTS assay.

(B) Kato III and SNU-16 cells were treated with the indicated siRNA for 48 hrs followed by stimulation with 100 pM of FGF7 for 15 min.

Cell lysates were subjected to Western blot analysis to determine expression levels of FGFR2, phospho-FGFR2 (these cell lines predominantly express FGFR2, thus phospho-FGFR indicates phospho-FGFR2), phospho-MEK, phospho-AKT, and β-actin. (The membranes were then scanned using the Odyssey infrared scanner (LiCor). These methods were developed in our laboratory and are described in detail elsewhere.[22]

The ability of ARQ 087 to inhibit the FGFR2 pathway was assessed in Kato III and SNU-16 cells. ARQ 087 inhibited the phosphorylation of FGFR2, and the phosphorylation of its immediate downstream substrate FRS2α, as well as the phosphorylation of further downstream components MEK, ERK, and AKT (Figure 1.4). The IC_{50} values for inhibition of FGFR2 phosphorylation were 92 ± 25 nM (Mean ± SD) and 52 ± 15 nM (Mean ± SD) for

Kato III and SNU-16, respectively. Based on these results, it was concluded that ARQ 087 inhibited the FGFR2 pathway in FGFR2-dependent cancer cells.

Figure 1.4 Inhibition of FGFR2 Pathway by ARQ 087

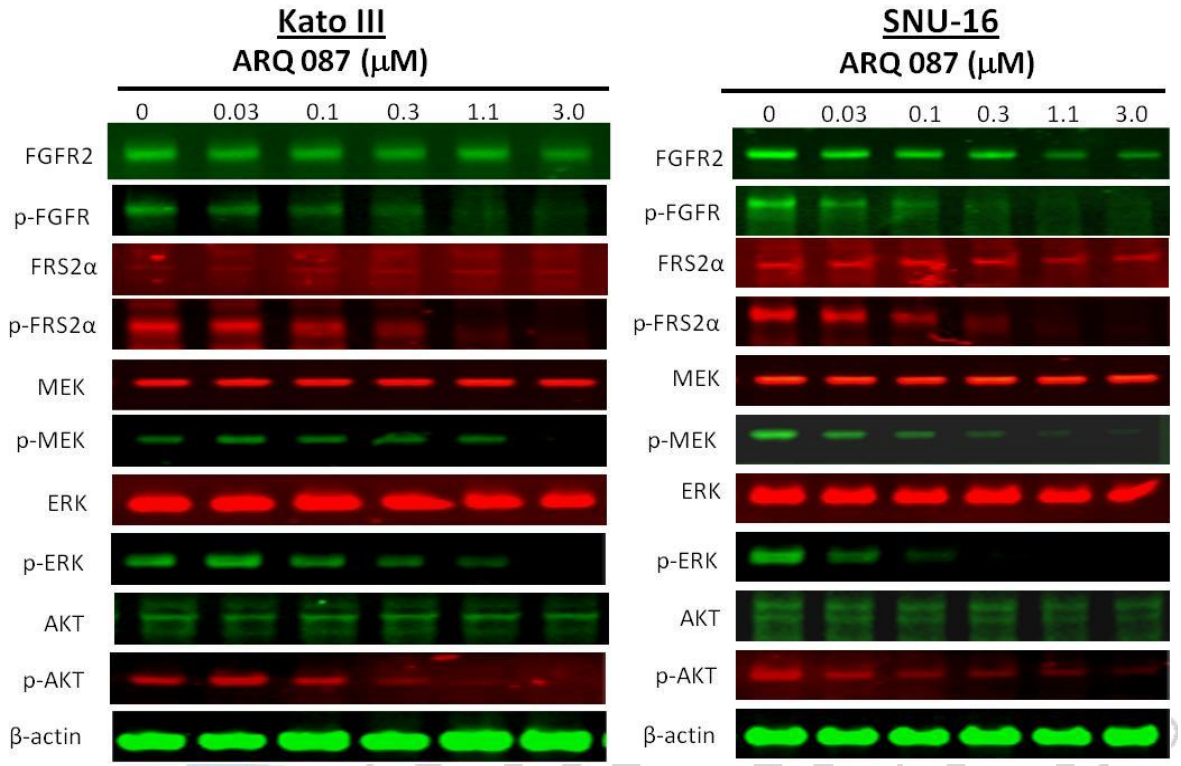


Figure 1.4: Inhibition of FGFR2 Pathway by ARQ 087

Kato III and SNU-16 cells were treated with indicated concentrations of ARQ 087 for 2 hrs followed by stimulation with 100 pM of KGF for 15 min. Cell lysates were subjected to Western blot analysis with the indicated antibodies as described in

Figure 1.3.

1.4 In Vivo Pharmacology

1.4.1 Evaluation of ARQ 087 in Human and Murine Xenografts of Various Histological Types in Athymic Mice

ARQ 087 is a pan-FGFR inhibitor which demonstrated potent inhibition of cell proliferation in cancer cells with FGFR2 amplification (e.g. Kato-III and SNU-16) or in cells possessing an FGFR2 activating mutation (AN3CA).

The *in vivo* anti-tumor efficacy of ARQ 087 was assessed in athymic mice harboring human gastric (SNU-16)[23,24], endometrial (AN3CA)[25] carcinomas, or a murine B cell lymphoma (BaF3)[26] stably transfected with FGFR2. ARQ 087 was formulated in DMA: Cremophor EL: propylene glycol: 0.2M acetate buffer, pH 5 (10:10:30:50) for all *in vivo* experiments and administered orally. Robust *in vivo* activity for ARQ 087 is illustrated in Figure 1.5 through Figure 1.7. Two SNU-16 xenograft studies were conducted for ARQ 087. In the first SNU-16 xenograft study (Figure 1.5), drug treatment was initiated with a mean tumor size range of ~150 mg. In this study, 75 mg/kg and 50 mg/kg groups achieved 80% and 64% tumor growth inhibition (TGI), respectively. Partial regressions were observed in both of these dose groups. Additionally, at 75 mg/kg, one complete regression (CR) was observed. In the second SNU-16 xenograft study, drug treatment was initiated with mean tumor size range ~400 mg. Tumor regression in the second study was observed in the 75 mg/kg group while minimal tumor growth inhibition was observed in both the 25 mg/kg (30% TGI) and 50 mg/kg (28% TGI) groups. Additionally, ARQ 087 demonstrated significant tumor shrinkage in the BaF3/FGFR2 model (Figure 1.6). The 100 mg/kg group resulted in 94% TGI accompanied by 3 CRs (complete regressions) and the 50 mg/kg group had 63% TGI. The mean net body weight loss on Day 14 was 3.9% and on Day 19 was 10.4%. There was no body weight loss or complete/partial regressions in the 50 mg/kg dose level group. Adverse body weight loss was observed at the highest dose of 150 mg/kg, resulting in dosing suspension on Day 7. ARQ 087 did not slow tumor progression in a BaF3/INSR (insulin receptor) model, demonstrating selectivity of this compound towards FGFR2. Fifty four percent TGI was observed in the AN3CA xenograft model on a daily (QD) schedule at 75 mg/kg and on an every other day (Q2D) schedule at 150 mg/kg (Figure 1.7). All doses of ARQ 087 were well tolerated with no evidence of body weight loss.

Figure 1.5 Inhibition of SNU-16 Human Gastric Tumor Xenograft Growth by ARQ 087

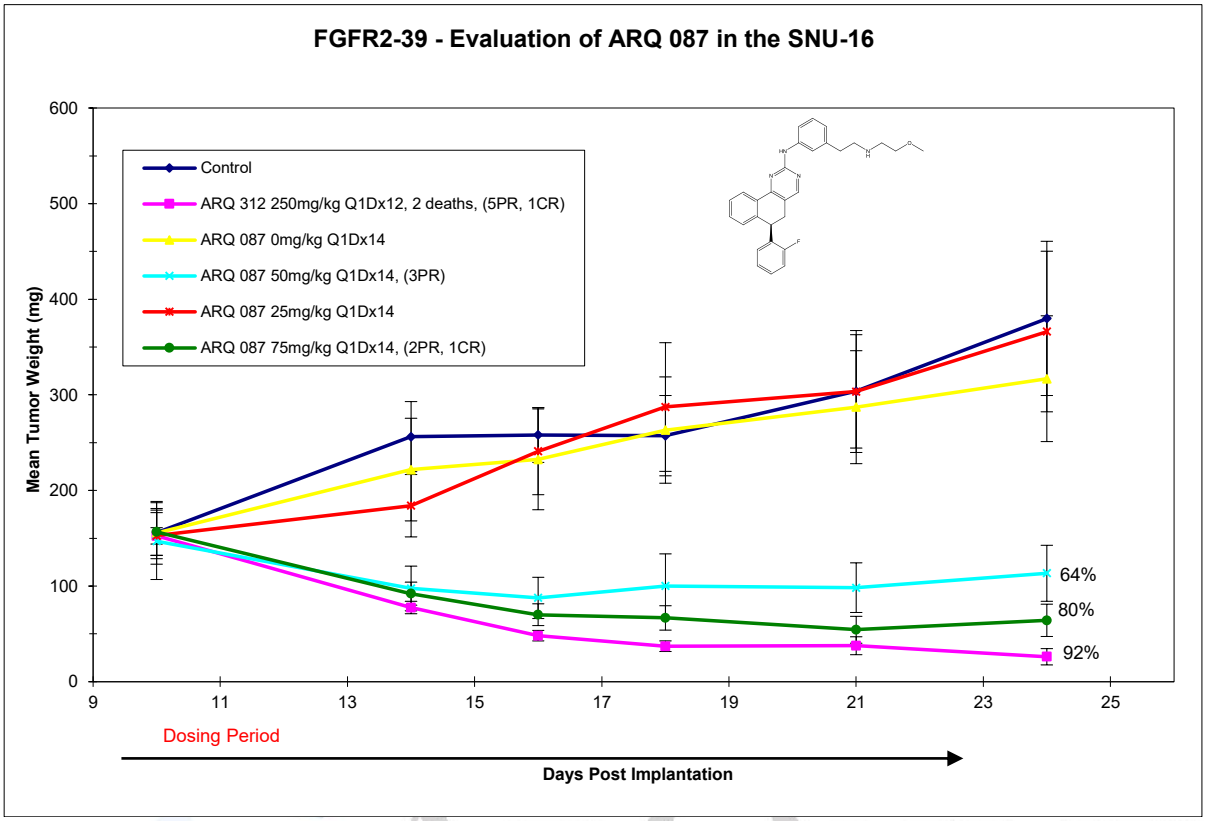


Figure 1.5: ARQ 087 Inhibits Tumor Growth in the SNU-16 Xenograft Model.

Treatment with ARQ 087 was initiated with mean tumor size range ~150 mg. Partial (7) and complete regressions (1) were observed in the 75 mg/kg dose group. ARQ 312 is a first generation pan-FGFR inhibitor previously identified at ArQule.

Error bars represent SD.

Figure 1.6 Inhibition of BaF3/FGFR2 Tumor Xenograft Growth by ARQ 087

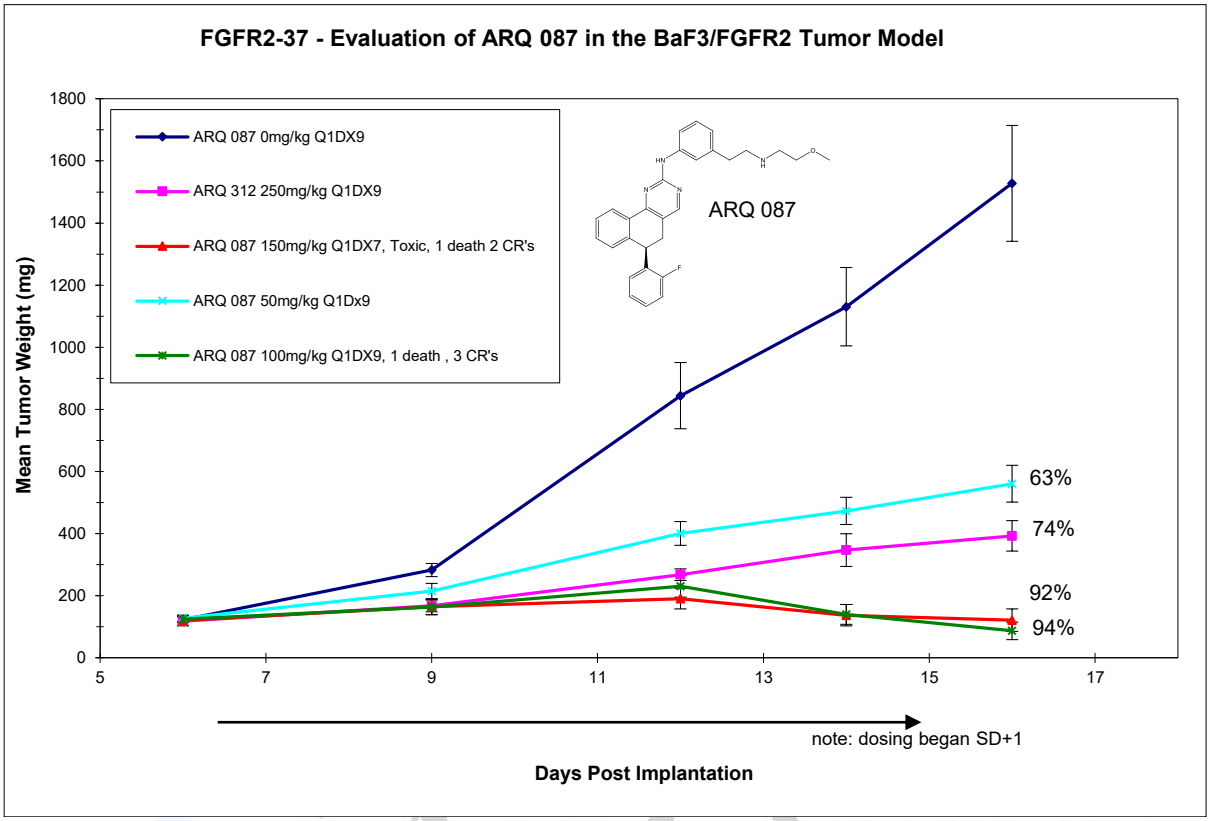


Figure 1.6: ARQ 087 Inhibits Tumor Growth in the BaF3/FGFR2 Xenograft Model.

Treatment with ARQ 087 was initiated with mean tumor size range ~150 mg. ARQ 087 demonstrated significant tumor shrinkage in the BaF3/FGFR2 model. ARQ 312 is a first generation pan-FGFR inhibitor previously identified at ArQule.

Error bars represent SD.

Figure 1.7 Inhibition of AN3CA Tumor Xenograft Growth by ARQ 087

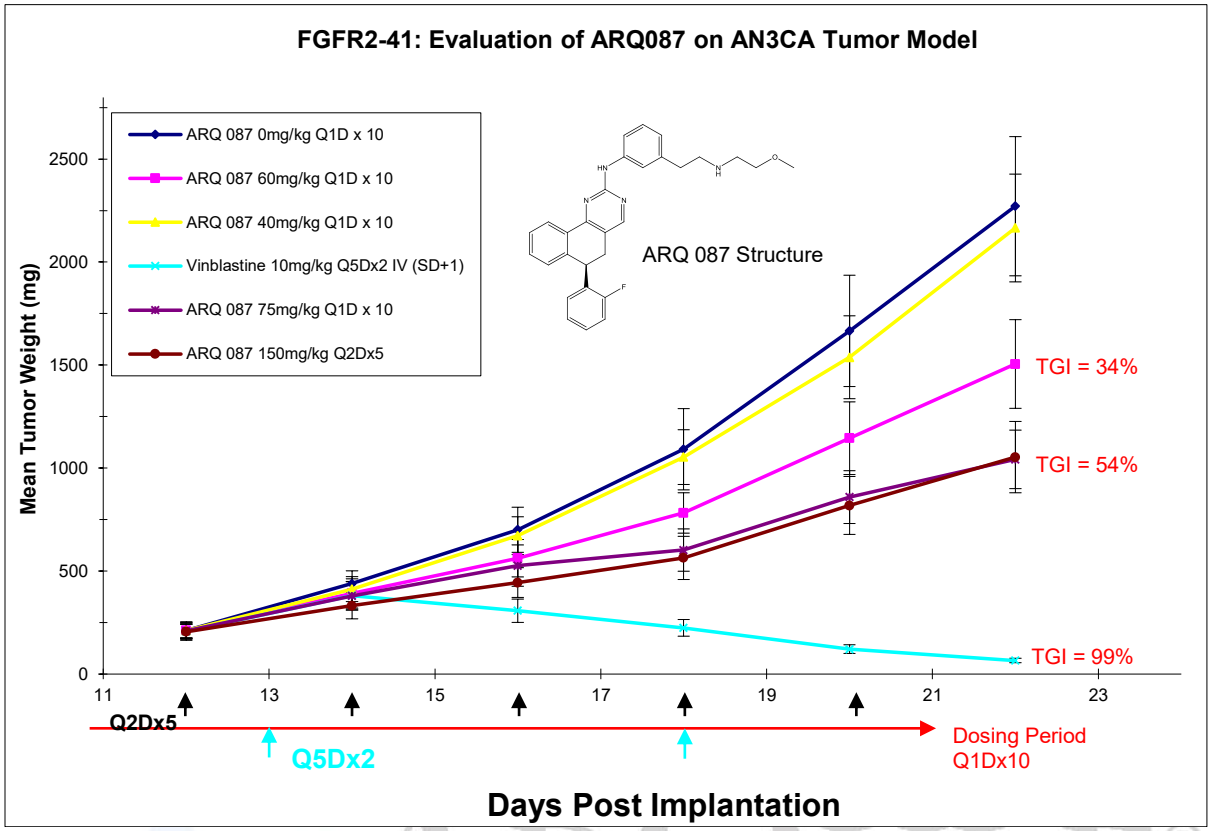


Figure 1.7: ARQ 087 Inhibits Tumor Growth in the AN3CA Xenograft Model.

Treatment with ARQ 087 was initiated with mean tumor size range ~200 mg. ARQ 087 administered orally at 150 mg/kg on a Q2Dx5 schedule and ARQ 087 administered orally at 75 mg/kg on a Q1Dx10 schedule resulted in significant inhibition of tumor progression.

Vinblastine=Positive control

A patient derived xenograft screen was conducted with ARQ 087 in 23 endometrial tumor models.[27] Animals were dosed with 75 mg/kg ARQ 087 po: Q1Dx14 and the mean tumor volume was measured. Figure 1.8 shows two models where there was an effect on tumor growth following the 14 day ARQ 087 treatment.

Figure 1.8 Inhibition of Tumor Progression in ST413 and ST328 Endometrial Patient-derived Xenograft Models

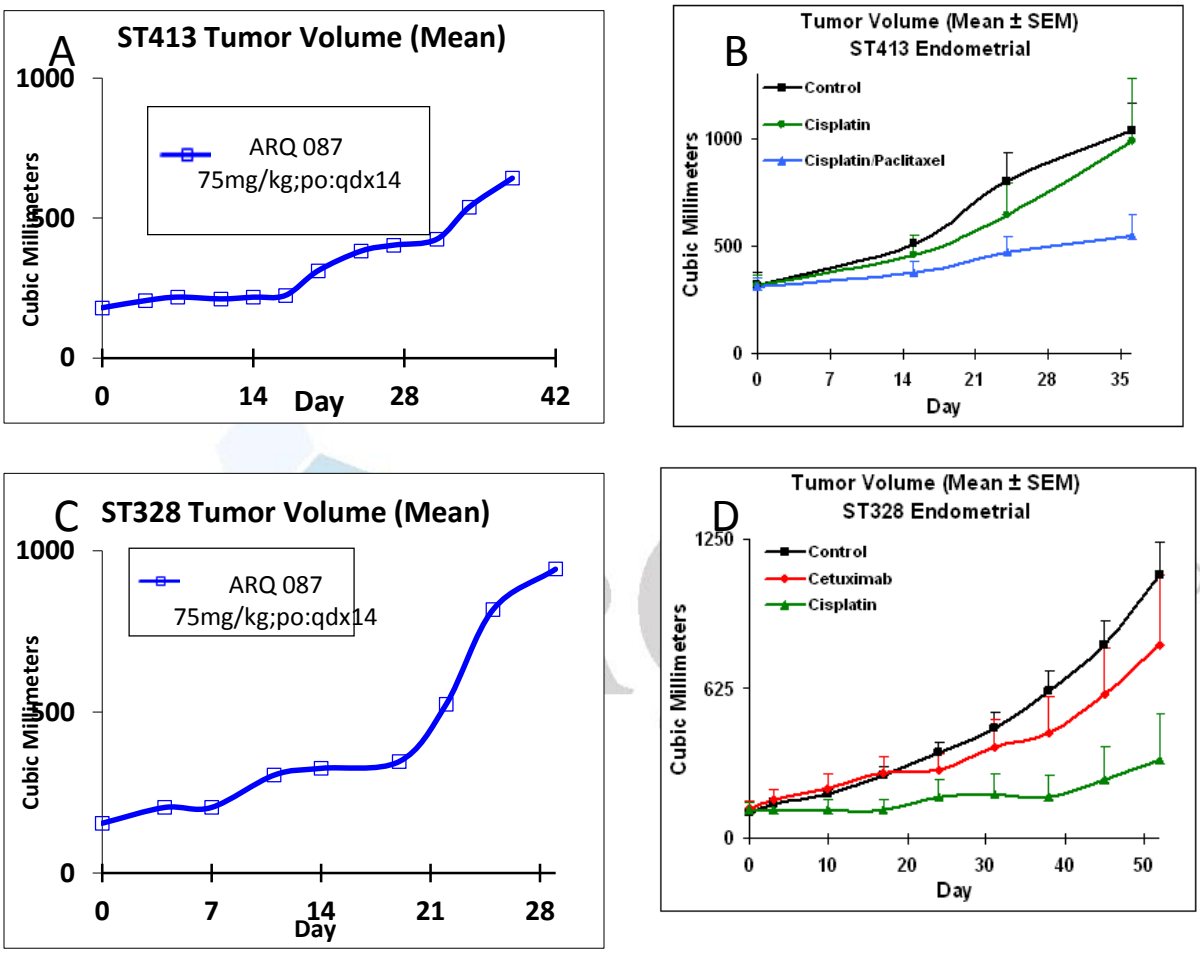


Figure 1.8: ARQ 087 Inhibits Tumor Progression in the ST413 and the ST328 Patient-derived Xenograft Models.

ARQ 087 was administered orally at 75 mg/kg on a Q1Dx14 schedule. The effect of ARQ 087 on tumor volume for ST413(A) and ST328(C) are shown along with the historical control data for the models (B and D).

In summary, ARQ 087 demonstrated biological activity in several *in vivo* xenograft models. PRs and CRs were observed in two models dependent upon FGFR2 signaling (the human gastric [SNU-16] and murine transfected cell line [BaF3/FGFR2]) (Figure 1.5 and Figure 1.6). In addition, data obtained using patient-derived endometrial cancer xenograft models has demonstrated that ARQ 087 slowed tumor progression during the 14-day treatment period.

1.5 Pharmacodynamic Biomarkers

1.5.1 *In Vivo* Pharmacodynamics

Evidence of ARQ 087 target engagement can be detected by measuring the inhibition of phosphorylation of ARQ 087 target receptor tyrosine kinase (RTKs) as well as key downstream signaling proteins. The pharmacodynamic effects of ARQ 087 on the FGFR pathway were confirmed both *in vitro* and *in vivo*. The effects were most evident in FGFR2-overexpressing cell lines such as the gastric carcinoma cell lines SNU-16 and Kato III. In preclinical xenograft tumor models, inhibition of phosphorylation of FGFR, FRS2α, and ERK was observed using IHC on SNU-16 tumors at the efficacious dose of 75 mg/kg (Figure 1.9)[28]. By Western blotting analysis, MEK and ERK phosphorylation levels were reduced by 68% and 82%, respectively. This dose resulted in plasma levels of ARQ 087 of 4.9 ± 2.3 μM.[28]

Figure 1.9 Inhibition of FGFR2 Pathway in SNU-16 Gastric Carcinoma Xenograft Tumors by ARQ 087

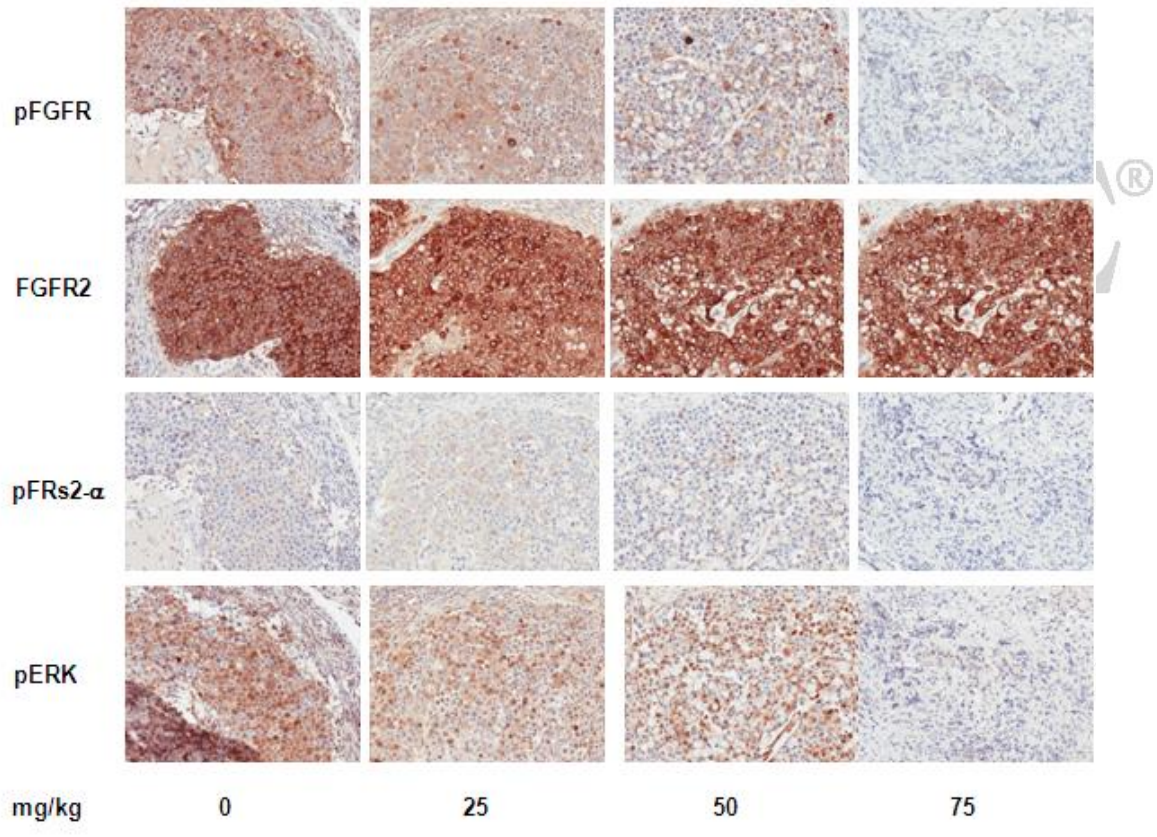


Figure 1.9: Target engagement study for ARQ 087 in SNU-16 tumor xenograft model (mean tumor size of ~400 mg at drug treatment initiation). Female NCr nu/nu mice with established subcutaneous SNU-16 tumors were treated with indicated doses of ARQ 087 or vehicle control. Tumor samples were collected 4 hrs after the last dose. Mice in the group dosed with 75 mg/kg were sacrificed on Day 9 after treatment initiation in order to

obtain sufficient quantities of tumor tissue. The remaining groups were sacrificed at Day 21. IHC staining of pFGFR, total FGFR2, pFRS2α, and pERK were performed on tumor tissues. Representative photomicrographs are shown.[28]

Changes in plasma levels of FGF19, FGF21, and FGF23 as well as soluble FGFR, collagen IV, phosphate, glucose, and calcium either have been observed with other FGFR inhibitors or represent viable blood-based biomarkers to assess pharmacodynamic action of ARQ 087. In cell-based systems, ARQ 087 inhibited endogenously expressed FGFR2 and ectopically expressed FGFR1, 2, and 3 in COS-1 cells. ARQ 087 demonstrated potent inhibition of FGFR2 phosphorylation in Kato III and SNU-16 human gastric carcinoma cells with comparable antiproliferative potencies in the MTS assay. Cell proliferation studies suggested a correlation of FGFR2 mRNA amplification in gastric and other cancers with associated sensitivity to treatment with ARQ 087. Concentration-dependent inhibition of phosphorylation of downstream FGFR pathway signals (FRS2α, MEK, ERK, and AKT) was evident in response to ARQ 087 treatment in both *in vitro* and *in vivo* pharmacodynamic assays. Correspondingly, ARQ 087 induced regressions in FGFR2-driven xenograft models (SNU-16 and BaF3/FGFR2) and inhibited tumor progression in a model harboring a FGFR2-activating mutation (AN3CA).

1.5.2 Pharmacokinetic Characteristics

The oral bioavailability of ARQ 087 in rats was 37%, and in dogs ranged from 38 to 46% (solution or powder filled capsule, respectively), and indicated that ARQ 087 may have slightly higher bioavailability in dogs.

Cross-species NADPH-dependent metabolism studies revealed that ARQ 087 was highly stable in mouse, rat, dog, monkey, and human liver microsomes with half-life values ≥ 56 min. Consistent with these data, half-life values for all individual CYP450 human isoforms tested were ≥ 53 min. In human liver microsomes, ARQ 087 showed no significant liability against 3A4, 2C8, 2C9, and 2C19. However, ARQ 087 showed potential to inhibit CYP 1A2 with an IC_{50} of 12.1 μM, and 2D6 with an IC_{50} of 18.6 μM. ARQ 087 did not significantly induce CYP3A and CYP1A2 activity in fresh human hepatocytes. In one of four independent donors, ARQ 087 induced CYP2B6 activity >40% of control at 5 μM. Caco-2 studies conducted with ARQ 087 showed high permeability and no significant efflux, suggesting ARQ 087 is not a P-gp substrate. However, data from *in vitro* ATPase assays in human P-gp and human mutant (Thr482) BCRP membranes suggested that ARQ 087 may be a potential substrate and/or inhibitor of P-gp and mutant (Thr482) BCRP. Protein binding in rat, dog, and human plasma was > 99.0%. ARQ 087 was stable in human, rat, dog, and mouse whole blood and plasma for at least 2 hours at room temperature. Additionally, ARQ 087 was stable (> 80% remaining) for at least 240 minutes at 37°C.

1.6 Nonclinical Toxicology

Studies were conducted in rats to evaluate the toxicokinetics after oral gavage of ARQ 087. The results indicate that exposure to ARQ 087 generally increased as the dose was increased from 5 to 50 mg/kg/day. After reaching C_{max}, ARQ 087 concentrations readily declined with $t_{1/2}$ values ranging from 5.56 to 8.84 hours on Day 1 and 5.61 to 9.32 hours on Day 28, although determination of $t_{1/2}$ was limited due to the lack of a distinct elimination phase in some groups. Values for C_{max} and AUC_{0-24} were generally higher on Day 28 than on Day 1

indicating accumulation of ARQ 087 after multiple dosing at 5 and 15 mg/kg/day. The accumulation ratio for AUC_{0-24} ranged from 1.64 to 2.94. Sex differences were less than 2-fold in ARQ 087 C_{max} and AUC_{0-24} values, although females generally had higher exposures than males. Values for CL/F and V_z/F generally appeared dose independent.

Studies were also conducted in dogs to evaluate the toxicokinetics after oral capsule dosing of ARQ 087. The results show that exposure to ARQ 087 increased as the ARQ 087 dose level increased from 3 to 30 mg/kg/day. After reaching C_{max}, ARQ 087 concentrations readily declined with the mean $t_{1/2}$ values ranging from 4.80 to 7.43 hours on Day 1 and from 6.41 to 10.8 hours on Day 28, although determination of $t_{1/2}$ was limited due to the lack of a distinct elimination phase in some animals. Values for mean C_{max} and AUC_{0-24} were generally higher after multiple dosing on Day 7 and 28 than on Day 1, indicating accumulation of ARQ 087 in dogs. The mean accumulation ratio (AR) for AUC_{0-24} ranged from 2.79 to 3.46 on Day 7 at the 30 mg/kg/day dose level and from 2.04 to 3.59 on Day 28 for the 3 and 10 mg/kg/day dose levels. Sex differences were less than 2-fold in ARQ 087 mean C_{max} and AUC_{0-24} values. Values for CL/F and V_z/F generally appeared to be dose independent.

Studies were conducted in dogs to evaluate the effects of different formulations (solution and solid) on the oral bioavailability of ARQ 087 relative to IV administration. Capsule formulations, dosed with ARQ 087 at a dose of 50 mg/kg, resulted in AUC_{0-24} values for ARQ 087 ranging from 14524 to 18659 h•ng/mL, C_{max} values ranging from 1050 to 1324 ng/mL, and %F values ranging from 38 to 46. A separate study evaluating capsule formulations dosed at 25 mg ARQ 087/kg resulted in AUC_{0-inf} values for ARQ 087 ranging from 3388 to 6666 h•ng/mL, C_{max} values ranging from 166 to 296 ng/mL.

ARQ 087 was reasonably well tolerated over the course of the 28-day GLP toxicity studies with a NOAEL dose of 20 mg/kg/day (18 days)[i] in dog and a non-severely toxic dose in rats of 15 mg/kg/day. The severely toxic dose in rats was determined to be 50 mg/kg/day.

The toxicity profile of orally administered ARQ 087 in rat and dog studies was characterized principally by decreases in body weight and/or body weight gain, an effect generally correlated to a decrease in food consumption. Trends in reversibility during the recovery phase were observed for decreases in body weight and/or body weight gain and decreased food consumption in dogs but not in rats. Target organ toxicities based on the results of the 28-day rat and dog studies were associated to those involving gastrointestinal (rat, dog), hematological (rat, dog), liver (rat, dog), bone (rat), and lung (rat) function.

In the 28-day rat study, all control, low, and mid dose (0, 5, and 15 mg/kg) animals survived to the scheduled terminal necropsy. All high dose (50 mg/kg) animals, excluding those designated for recovery, were sacrificed and/or necropsied between Days 12 and 14 of the dosing phase. ARQ 087-related clinical observations were limited to animals given 50 mg/kg/day, which made necessary the suspension of further dosing and an unscheduled terminal necropsy. These clinical observations, along with decreases in body weight/body weight gain and food consumption included hunched appearance and swelling of the

[i] Animals in the 30/20 mg/kg/day group were dosed on Days 1 through 7 at 30 mg/kg/day at which point this dose level was not tolerated and they were put on dosing holiday on Days 8 through 11. Dosing was resumed on Day 12 at 20 mg/kg/day.

abdomen (noted in one female), thinness, nasal and oral discharge, fecal abnormalities (few and nonformed), squinting of the eyes, and pelage/skin abnormalities. Clinical observations associated with thinness and decreases in body weight/body weight gain that did not resolve following the 2-week recovery phase were noted for animals given 50 mg/kg/day of ARQ 087.

Additionally, in the 28-day rat study, ARQ 087 administration was associated with several effects on clinical pathology test results. The most toxicologically important effects included reduced erythropoiesis at ≥ 15 mg/kg/day, suspected lymphoid tissue injury at 50 mg/kg/day (females), and liver injury at ≥ 15 mg/kg/day. Specifically, reduced erythropoiesis was associated with decreased red cell mass and absolute reticulocyte counts as well as changes in erythrocytic indices. Decreased lymphocyte counts were observed in females given 50 mg/kg/day. Increased alanine aminotransferase (ALT) activity was first observed in males given 5 mg/kg/day, followed by increased ALT and alkaline phosphatase (ALP) activity in animals given 15 mg/kg/day. At dose levels of 50 mg/kg/day, increased ALT, aspartate aminotransferase (AST), ALP, and gamma glutamyltransferase (GGT) activities were observed. A few less specific test article-related effects, especially changes in electrolyte values, were observed during the recovery phase in animals given 50 mg/kg/day. These changes may have been associated with mild dehydration. No macroscopic findings were attributed to the test article at the terminal or recovery necropsy. In animals sacrificed in moribund condition or at the terminal sacrifice, test article-related microscopic findings were observed in the femur and sternum bone and marrow, alimentary canal (tongue, esophagus, nonglandular stomach, duodenum, ileum, and jejunum), spleen, and lung. Most findings were limited to the 50 mg/kg/day dose level. Exceptions were the lung and spleen, where findings were also observed at 15 mg/kg/day. All test article-related microscopic findings observed at the terminal necropsy and in animals sacrificed at an unscheduled interval were reversed at the recovery necropsy, excluding femur and sternum physeal hypertrophy, increased splenic extramedullary hematopoiesis, and lung vacuolated macrophage infiltrates. Tongue and esophageal ulcers observed at 50 mg/kg/day were considered severely toxic.

In shorter duration 7-day repeat dose toxicity studies, minimally longer prothrombin time and activated partial thromboplastin time was observed in male rats dosed at 150 mg/kg/day.

In the 28-day dog study, oral capsule administration of ARQ 087 was tolerated in dogs at 3 and 10 mg/kg/day for 29 days and at 20 mg/kg/day for 18 days; however, it was not tolerated at 30 mg/kg/day for 7 days. Animals given 30 mg/kg/day had vomitus, abnormal feces, body weight loss, and/or markedly reduced food consumption during the first week of dosing. One male given 30 mg/kg/day was sacrificed on Day 6 of the dosing phase in moribund condition that included clinical observations of vomitus, limited use of the hind quarters, ataxia, rigid stance, hypoactivity, dilated and minimally responsive pupils, excessive salivation, occasional tonic front limbs, and postictal and close to seizure threshold. The male had clinical pathology findings consistent with inflammation/stress, dehydration, and lower serum potassium and chloride that likely resulted from vomiting. Potentially adverse, test article-related microscopic findings of acute inflammation and ulceration of the esophagus were also noted, and the moribund condition of the male is partially attributed to these microscopic findings. All other animals survived to their scheduled sacrifices. Due to adverse findings observed at 30 mg/kg/day, dosing was

suspended on Day 8 and resumed on Day 12 of the dosing phase at 20 mg/kg/day. Abnormal feces observed for most animals given 20 mg/kg/day was not adverse because it did not impact the health of the animals. Animals given 30/20 mg/kg/day had white discolored haircoat of the entire head during the dosing and recovery phases; however, this observation was not adverse, and no corresponding microscopic finding was present. No test article-related changes in ECG parameters or ophthalmic examinations were observed. No test article-related clinical pathology effects were observed at 3 or 10 mg/kg/day. A few minor, potentially test article-related findings in animals given 30/20 mg/kg/day were minor and not considered adverse or toxicologically important. Potentially adverse, test article-related microscopic findings of acute inflammation and ulceration of the esophagus occurred in one male given 30/20 mg/kg/day. Test article-related microscopic findings noted during the dosing phase were not present in recovery animals.

The hERG IC_{50} for ARQ 087 was greater than 3 μM. No effect on QT was observed in dogs in the cardiovascular study (60 mg/kg) or in the ECG in the 28-day toxicity study (up to 30/20 mg/kg).

Additionally, the hemodynamic and electrocardiographic effects of ARQ 087 were examined in telemeterized dogs. A slight, transient increase in mean arterial pressure and its components (~15% compared to vehicle) was observed 40 to 120 minutes after dosing with 60 mg/kg ARQ 087. A concomitant increase in heart rate was also noted, and was on average ~20% higher compared to heart rates observed after vehicle dosing within this timeframe. There were no notable effects of ARQ 087 on pulse pressure, PR interval, QRS duration, QTcVDW interval, or arrhythmogenesis.

ARQ 087 was found to have phototoxic potential in the 3T3 Neutral Red Uptake Phototoxicity Test.

Transient effects on clinical chemistry such as increased glucose levels and phosphorous levels were observed in rats and/or dogs in shorter duration 7-Day repeat dose toxicity studies and may be characteristic of FGFR kinase inhibitors.[31,32,33]

Based on the findings from the 4-week toxicity studies, the rat is considered as the more sensitive of the two species and will be evaluated for purposes of estimating a safe starting dose for a First in Human (FIH) study conducted in subjects with advanced malignancies. As described in the ICH guidance document: *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, a safe human starting dose based on assessment of toxicity in rodent species is 1/10 of the severely toxic dose in 10% of the animals (STD 10). The STD 10 for ARQ 087 was determined to be 50 mg/kg/day, however, due to the need to sacrifice the 50 mg/kg/day animals between Days 12 and 14 of the dosing phase (except those designated for recovery), the 15 mg/kg dose was used to select the safe starting dose in humans. From this dose, the Phase 1 starting dose is calculated to be 9 mg/m^2/day or 15.3 mg/day (BSA 1.7). For the purpose of this FIH study the starting dose is suggested to be 25 mg every other day (QOD) to conform to available capsule dosage strengths (25 and 100 mg) and minimize capsule consumption burden for subjects.

In summary, the pre-clinical data support that ARQ 087 has the potential to exert significant anti-tumor effects on human tumors driven by oncogenic FGFR with an acceptable therapeutic window.

1.7 Clinical Experience

The initial safety and tolerability of ARQ 087 have been established in the open-label, Dose Escalation part (Part 1) of the ongoing ARQ 087-101 study in adult subjects with advanced solid tumors. A total of 61 subjects with different types of solid tumors have been enrolled and treated with ARQ 087.

As of 31-Mar-2015, in the Dose Escalation/Food-effect Cohorts, in two out of three subjects with iCCA, a significant reduction in tumor burden (assessed per RECIST v. 1.1) has been observed. Both subjects have confirmed FGFR2 fusion (BICC1 and KIAA1217, respectively), one subject has had a partial response (PR) (with 35% tumor reduction after 8 weeks of treatment; the subject completed 24 weeks of treatment) and another subject has demonstrated a durable stable disease (SD) (with maximum 26% tumor reduction; currently, the subject is at Week 34 of treatment). The subject with the durable SD received four regimens of prior chemotherapy including gemcitabine plus cisplatin. The subject with the PR did not receive any prior systemic therapy. The third subject with unknown FGFR status was discontinued from the treatment after 8 weeks due to lack of clinical benefit.

Overall, the drug has demonstrated a favorable safety profile with manageable toxicities. The most common (≥ 5%) drug-related adverse events (AE) reported to date include fatigue (50.0%), nausea (46.7%), aspartate aminotransferase increased (30.0 %,), diarrhoea (25.0%), vomiting (21.7%), constipation, decreased appetite (20.0%, each), dysgeusia (15.0%), alanine aminotransferase increased (11.7%), anaemia, dyspepsia, blood creatinine increased, dry skin (8.3%, each), dry mouth, blood alkaline phosphatase increased (6.7%, each), and gastrooesophageal reflux disease, rash maculo-papular (5.0%, each).

The RP2D has been defined as 300 mg qd under fasting conditions.

Based on the non-clinical and clinical literature data, early efficacy results observed in the Dose Escalation part of this study, and known unmet need for new, effective treatments for iCCA patients, it seems reasonable to further evaluate ARQ 087 in subjects with iCCA with FGFR2 fusion.

Detailed non-clinical and clinical data can be found in the ARQ 087 Investigator's Brochure (IB).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this first-in-human (FIH) study is to assess the safety and tolerability of ARQ 087 in subjects with advanced solid tumors (Part 1; Dose Escalation/Food-effect Cohorts) or with advanced solid tumors with FGFR genetic alterations, including iCCA with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding).

2.2 Secondary and Exploratory Objectives

The secondary objectives of this study are:

- To assess the pharmacokinetic profile of ARQ 087 in subjects enrolled in Part 1 (Dose Escalation/Food-effect Cohorts) of the study
- To assess the pharmacodynamic activity of ARQ 087 in blood and tumor biopsy specimens obtained from subjects with advanced solid tumors
- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ARQ 087 (Part 1)
- To further evaluate the RP2D of ARQ 087 in subjects with FGFR genetic alterations, including subjects with iCCA with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding)
- To generate preliminary evidence of anti-tumor activity
- To generate preliminary biomarker evidence of target inhibition
- To identify specific target subject (patient) population, e.g., subjects with iCCA with FGFR2 gene fusion or with other solid tumors with FGFR genetic alterations

The exploratory objectives of this study are:

- To validate and assess FGFR family members (specifically FGFR2 and potentially those harboring activating mutations) as predictive biomarkers
- To evaluate the association between known markers of the FGF signaling pathway, toxicity, and clinical activity

3 SELECTION OF STUDY POPULATION

Adult subjects with advanced solid tumors whose cancer has progressed following standard therapy, or who have been unable to tolerate standard therapy, and/or for whom no standard treatment is available will be enrolled.

The exact number of subjects estimated for this study is dependent on the number of subject cohorts investigated based on the toxicity encountered. It is expected that approximately 60-120 subjects at five to fifteen sites in the United States and Italy will be enrolled in this study. Once the MTD/RP2D level is determined, an Expanded Cohort will be enrolled. Subject accrual will occur over a period of time dependent upon the number of cohorts enrolled.

The Food-effect Cohort (Part 1) will enroll at least six subjects with luminal breast A or B, endometrial, urothelial, gastric, or lung cancer with known and/or confirmed *FGFR1-3* high level amplification, mutation or gene rearrangement (fusion, translocation), or with adrenocortical carcinoma, cholangiocarcinoma, or sarcomas, independent from FGFR1-3 status. All subjects enrolled in the Food-effect Cohort should agree to and be eligible for paired biopsy.

The Expanded Cohort (Part 2) of approximately 50-60 subjects with advanced solid tumors with FGFR genetic alterations, including iCCA with FGFR2 gene fusion will be enrolled. The tumor type eligibility should be confirmed by the Sponsor's Medical Monitor or designee prior to enrollment. If at the time of the first restaging (C3D1), in two out of the first five enrolled subjects with the same tumor type, objective response (significant, ≥ 15%, reduction in tumor size) is not achieved, such tumor sub-cohort may be closed for further enrollment. If the objective response in the first 10 subjects with iCCA is observed in ≤30% of the enrolled subjects, the enrollment will be stopped for lack of efficacy.

3.1 Inclusion Criteria

Each prospective subject must meet ALL of the following inclusion criteria in order to be eligible for this study:

1. Signed written informed consent granted prior to initiation of any study-specific procedures
2. Male or female subjects of ≥ 18 years of age
3. Histologically or cytologically confirmed locally advanced, inoperable, or metastatic solid tumors. All subjects eligible for enrollment in the Expanded Cohort must have documented and/or confirmed FGFR genetic alterations, including iCCA with FGFR2 gene fusion.
4. Failure to respond to standard therapy, or for whom standard therapy does not exist.
    - Subjects enrolled in the Expanded Cohort should have no more than two prior systemic regimens with confirmed disease progression.
    - If the subject is refractory or has disease progression within 6 months of adjuvant treatment, then the previous treatment should be considered as a line of treatment rather than adjuvant therapy.

- Subjects who did not receive prior systemic therapy for locally advanced and/or metastatic iCCA with confirmed FGFR2 gene fusion and for whom, in the opinion of the Investigator, treatment with ARQ 087 is appropriate may be enrolled

5. Evaluable or measurable disease
6. Archival and/or fresh biopsy tissue samples must be available prior to the first dose of the study drug.
   - All subjects eligible for enrollment in the Expanded Cohort (Part 2) must have known (documented and/or confirmed) FGFR genetic alterations.
   - Archival tumor samples should be collected for all subjects enrolled in the Expanded Cohort. Paired fresh tumor biopsy is optional for subjects enrolled in the Expanded Cohort. Both archival and pre-treatment fresh tumor samples (optional) should be collected prior to the first dose of the study drug
   - All subjects eligible for enrollment in the Food-effect Cohort must have the following tumor types: luminal breast A or B, endometrial, urothelial, gastric, or lung cancer with known and/or confirmed *FGFR1-3* high level amplification, mutation or gene rearrangement (fusion, translocation), or adrenocortical carcinoma, cholangiocarcinoma, or sarcomas, independent from *FGFR1-3* mutation status
   - All subjects eligible for enrollment in the Food-effect Cohort should agree to and be eligible for paired biopsy
7. Life expectancy ≥ 12 weeks
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 (Appendix 2)
9. Hemoglobin (Hgb) ≥ 9.0 g/dL
10. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
11. Platelet count ≥ 100 x 10^9/L
12. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (≤ 2 ULN for subjects with cholangiocarcinoma)
13. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 ULN (≤ 5 x ULN for subjects with liver metastases)
14. Serum creatinine ≤ 1.5 x ULN or creatinine clearance > 60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal
15. Albumin ≥ 2.8 g/dL
16. INR 0.8 to ULN or ≤ 3 for subjects receiving anticoagulant therapy such as Coumadin or heparin
17. Male or female subjects of child-producing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of ARQ 087
18. Women of childbearing potential must have a negative serum pregnancy test during Screening Period and within 48 hours of the first dose of ARQ 087. “Women of childbearing potential” is defined as sexually mature women who have not undergone a

hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months prior to the first dose of ARQ 087.

3.2 Exclusion Criteria

Prospective Subjects who meet ANY of the following criteria will not be eligible for enrollment into this study:

1. Anti-cancer therapy, such as chemotherapy, immunotherapy, hormonal, targeted therapy, or investigational agents within four weeks or five times of the drug half-life, whichever is **LONGER**, of the first dose of ARQ 087
2. Major surgery or radiation therapy within four weeks of the first dose of ARQ 087
3. Previous treatment with FGFR inhibitors (e.g., ponatinib, dovitinib, nintedanib, AZD4547, NVP-BGJ398, LY2784455, BAY1163877)
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition as ARQ 087
5. Unable or unwilling to swallow the complete daily dose of ARQ 087
6. Clinically unstable central nervous system metastasis (to be eligible, subjects must have stable disease ≥ 3 months, confirmed by MRI or CT scan, and/or have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications)
7. History of myocardial infarction (MI) or congestive heart failure defined as Class II to IV per the New York Heart Association (NYHA) classification within 6 months of the first dose of ARQ 087 (MI that occurred > 6 months prior to the first dose of ARQ 087 will be permitted)
8. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of ARQ 087 (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection)
9. History and/or current evidence of clinically relevant ectopic mineralization/calcification including but not limited to the soft tissue, kidneys, intestine, myocardium, and lung with the exception of calcified lymph nodes, asymptomatic nephrolithiasis, and asymptomatic coronary calcification (If indicated, standard CT or MRI may be used to assess ectopic mineralization/calcification.)
10. Previous malignancy within 2 years of the first dose of ARQ 087, except curatively treated non-melanoma skin cancer, carcinoma in-situ of the breast or cervix, superficial bladder tumors
11. Known human immunodeficiency virus (HIV) infection
12. Concurrent uncontrolled illness not related to cancer, including but not limited to:
    - Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements
    - Uncontrolled diabetes mellitus
13. Blood transfusion within 5 days of the blood draw being used to confirm eligibility
14. Pregnant or breastfeeding

3.3 Number of Subjects

The exact number of subjects estimated for this study is dependent on the number of subject cohorts investigated based on the toxicity encountered. It is expected that approximately 60 to 120 subjects will be enrolled in the Dose Escalation/Food-effect Cohorts (Part 1) and the Expanded Cohort (Part 2).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

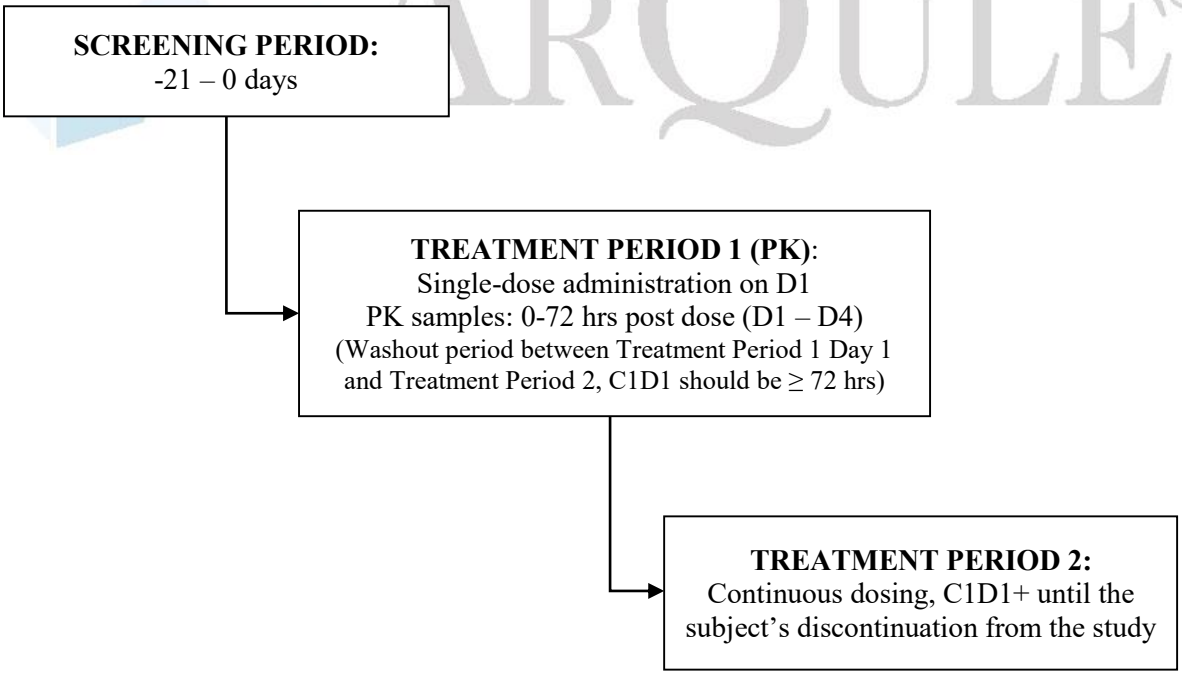
This is an open-label, Phase 1/2, dose escalation and signal finding study of ARQ 087 administered to subjects with advanced solid tumors. The study is designed to explore the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of ARQ 087 and to define a RP2D of ARQ 087.

4.1.1 Part 1: Dose Escalation Cohorts

Treatment will be initiated at a dose level of 25 mg/qod (every other day). All cycles/cohorts of therapy will consist of the oral administration of ARQ 087 at dose levels and administration schedules specified for their respective dose cohorts; the drug should be taken one hour prior to or two hours after the meal. In Cohorts 1-4, treatment will consist of two treatment periods: Treatment Period 1 (single dose administration for 72-hour PK assessment) and Treatment Period 2 (continuous dosing that will cease at the subject's discontinuation from the study).

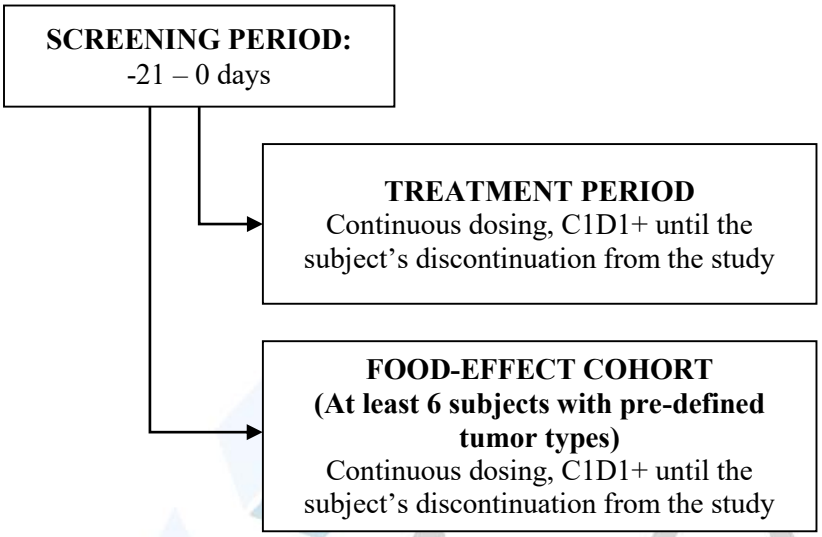
To assess safety of ARQ 087, a minimum of three subjects will be enrolled in each cohort. To assess pharmacodynamic changes, enrollment of additional subjects from whom paired (pre- and post-treatment) biopsies may be obtained will be allowed in each cohort. Each dose escalation cohort may enroll up to six subjects.

Cohorts 1 – 4 (Part 1)



Given the long half-life (~ 1 week) of ARQ 087 in human subjects and hence the length of time (~35 days) to reach steady state, it was determined that it was reasonable to eliminate the single dose phase. Hence, starting with Cohort 5, treatment will consist of a single treatment period of continuous dosing that will cease at the subject's discontinuation from the study.

Cohort 5 and all Subsequent Dose Escalation/Food-effect Cohorts (Part 1)



Tumor assessments (CT scan, MRI, or PET scan) will be performed at Baseline, and every eight weeks during Treatment Period 2 (e.g., on Day 1 of every odd cycle, Cycle 3 Day 1, Cycle 5 Day 1, or Week 8, Week 16, etc.) or as otherwise clinically indicated.

Dose escalation will be performed after three or six subjects are evaluated in each cohort (see Table 4.1). If a DLT is observed in one of the three subjects in a cohort in the first 28 days of therapy, the additional three subjects will be enrolled in the cohort sequentially.

If no DLT is seen in the first three evaluable subjects in the first 28 days of therapy, dose escalation will occur and another three subjects will be enrolled and treated at the next ARQ 087 dose level. If two or more subjects experience a DLT at Dose Level 1, subsequent subjects will be enrolled at a lower dose or at a less frequent drug administration schedule (e.g., 25 mg twice a week). If a subject withdraws from study treatment for any reason other than a DLT during the first 28 days (first cycle), that subject will be replaced.

The MTD is defined as the dose level at which no more than one subject with a DLT is observed among six subjects. Once the MTD is determined, up to six additional subjects may be treated at this dose level of ARQ 087. If the MTD is not reached, dose escalation will proceed with the purpose of determining a RP2D of ARQ 087.

In the first four cohorts, the dose may be doubled, and in the next cohorts, the dose escalation will follow a modified Fibonacci scheme (increase by 50%, 30%, and 25%) until RP2D or MTD is determined.

Subjects enrolled in the Food-effect Cohort will be asked to take ARQ 087 (400 mg qd) with or immediately after their morning meals (moderate-fat meal) and to keep a food diary (breakfast). The moderate-fat breakfast should contain approximately 550 kcal, with approximately 25% of the calories from fat. The Food-effect Cohort will enroll at least six subjects with luminal breast A or B, endometrial, urothelial, gastric, or lung cancer with known and/or confirmed *FGFR1-3* amplification, mutation or gene rearrangement (fusion, translocation), or with adrenocortical carcinoma, cholangiocarcinoma, or sarcomas, independent from FGFR1-3 status. All subjects enrolled in the Food-effect Cohort should agree to and be eligible for paired biopsy. Once the MTD/RP2D level is determined, the Expanded Cohort (Part 2) will enroll approximately 50-60 subjects with advanced solid tumors with documented (known/confirmed) FGFR genetic alterations, including iCCA with FGFR2 gene fusion.

Based on the drug safety profile and the Food-effect Cohort PK data, 300 mg qd under fasted condition (1 hour prior or 2 hours after the meal) has been defined as a RP2D and is recommended for further evaluation in the Expanded Cohort. Also, in two out of three subjects with iCCA enrolled in the Food-effect cohort, an objective response (assessed per RECIST) was observed. Both subjects had confirmed FGFR2 gene fusion, one subject had PR (with 34% tumor reduction) after 8 weeks of treatment and another subject demonstrated a durable SD after 28 weeks on treatment (with maximum 26% tumor reduction).

Table 4.1 Dosing Guidelines

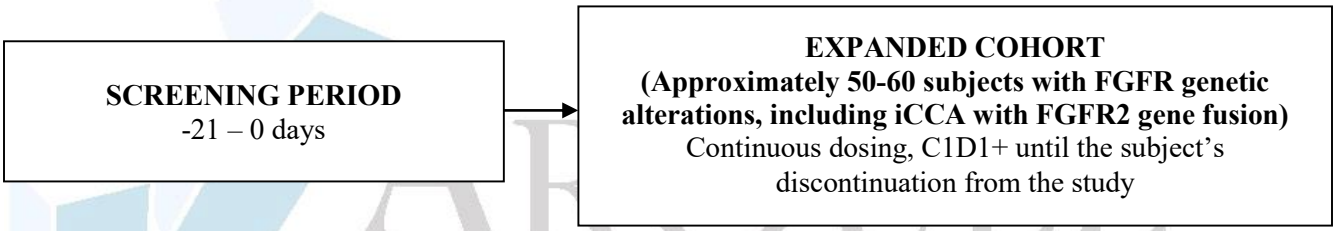
Cohort	Total Daily Dose[a]	Dose per Administration	Number of Subjects
Dose Escalation Cohorts: Part 1			
	25 mg	1 cap x 25 mg x twice a week	3-6[b]
1[a]	25 mg	1 cap x 25 mg x qod	3-6[b]
2	25 mg	1 cap x 25 mg x qd	3-6[b]
3	50 mg	2 caps x 25 mg x qd	3-6[b]
4	100 mg	1 caps x 100 mg x qd	3-6[b]
5*	150 mg	2 caps x 25 mg & 1cap x 100 mg x qd	3-6[b]
6	200 mg	2 caps x 100 mg x qd	3-6[b]
7	250 mg	2 caps x 25 mg & 2 caps x 100 mg x qd	3-6[b]
8	325 mg	1 cap x 25 mg & 3 caps x 100 mg x qd	3-6[b]
9	425 mg	1 cap x 25 mg & 4 caps x 100 mg x qd	3-6[b]
10	550 mg	2 caps x 25 mg & 5 caps x 100 mg x qd	3-6[b]
Food-effect[a]	400 mg	4 caps x 100 mg qd	at least 6
Expanded Cohort: Part 2			
Expanded[c]	300 mg	3 caps x 100 mg x qd under fasting conditions	approx. 50-60

*Starting from Cohort 5, the dose escalation will follow a modified Fibonacci scheme (increase by 50%,

30%, and 25%)
To avoid potential non-compliance due to capsule burden, the dose escalation may be stopped at the dose level of 550 mg/daily
[a]Total daily dose must be administered one hour prior to or two hours after the meal [Exceptions: 1) Cohort 1 is dosed every other day and 2) Food-effect Cohort]
[b]If a DLT is seen in one of three treated subjects, an additional three subjects will be treated at the same dose level
[c]Based on the safety profile and PK results of the Food-effect cohort, the dose of 300 mg qd under fasting conditions has been defined as MTD/RP2D and should be further evaluated in the Expanded Cohort

Preliminary PK results reported in subjects enrolled in Cohorts 1-3, have shown that ARQ 087 has a long half-life (~ 1 week) and accumulates with continuous dosing in human subjects (~4 to 14 fold across all cohorts, 4 to 8 fold in cohorts dosed at ≥ 100 mg qd). Additionally, preliminary PK results showed that Day 22 exposure (AUC and C_{max}) remained essentially the same when increasing the dose from 250 to 425 mg qd, suggesting that drug exposure has reached a plateau at dose levels above 250 mg qd. The ArQule Medical Monitor and Investigator(s) will review all significant ARQ 087-related toxicities and PK data to determine if the dose escalation schedule requires modification. Intermediate doses or different drug administration schedules (e.g., 2 weeks on/1 week off) may be investigated after agreement between ArQule's Medical Monitor and the Investigator(s).

4.1.2 Part 2: Expanded Cohort



Approximately 50-60 subjects with advanced solid tumors with FGFR genetic alterations, including iCCA with FGFR2 gene fusion will be enrolled. The tumor type eligibility should be confirmed by the Sponsor's Medical Monitor or designee prior to enrollment. If, at the time of the first restaging (C3D1), in two out of the first five enrolled subjects with the same tumor type, an objective response (significant, ≥ 15%, reduction in tumor size) is not achieved, such tumor sub-cohort may be closed for further enrollment.

Interim monitoring for futility will be incorporated after response data from 10 subjects with iCCA are available. If objective response is observed in ≥ 30% of enrolled subjects, up to 20 additional subjects with iCCA with FGFR2 fusion will be enrolled.

4.2 Rationale for Study Design

4.2.1 Part 1: Dose Escalation/Food-effect Cohorts

This is the FIH, open-label clinical study with ARQ 087. This study will be conducted to evaluate the safety, tolerability, pharmacodynamic, and pharmacokinetics of ARQ 087 in subjects with advanced solid tumors.

The principal objective of Phase 1 studies is the assessment of the safety, tolerability, pharmacokinetics, and pharmacodynamics as well as determination of the RP2D of a new drug. For traditional chemotherapeutic agents that show limited selectivity for cancer cells over normal cells, RP2D is generally set at the MTD. However, for targeted agents, such as ARQ 087, the RP2D range may be below the MTD. For such therapies, it is important to collect pharmacokinetic and pharmacodynamic data to establish the dosing regimen that achieves the desired plasma concentration required for the intended pharmacologic effect.

Although pharmacokinetic and pharmacodynamic results may ultimately lead to selection of a lower dose, it is considered important to establish the clinical toxicity, including DLT as part of a thorough clinical evaluation of anticancer drugs. Therefore, in the current study dosing may be escalated beyond what is expected to produce therapeutic levels.

4.2.2 Part 2: Expanded Cohort

Once the MTD/RP2D is determined, subjects with advanced solid tumors with FGFR genetic alterations, including iCCA with FGFR2 gene fusion, will be enrolled in Part 2, the signal finding Expanded Cohort.

4.3 Selection of Initial Dose

Based on the findings from the 4-week toxicity studies, the rat is considered as the more sensitive of the two species and will be evaluated for purposes of estimating a safe starting dose for a First in Human (FIH) study conducted in subjects with advanced malignancies. As described in the ICH guidance document: *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, a safe human starting dose based on assessment of toxicity in rodent species is 1/10 of the severely toxic dose in 10% of the animals (STD 10). The STD 10 for ARQ 087 was determined to be 50 mg/kg/day, however, due to the need to sacrifice the 50 mg/kg/day animals between Days 12 and 14 of the dosing phase (except those designated for recovery), the 15 mg/kg dose was used to select the safe starting dose in humans. From this dose, the Phase 1 starting dose is calculated be 9 mg/m^2/day or 15.3 mg/day (BSA 1.7). For the purpose of this FIH study the starting dose is suggested to be 25 mg every other day (QOD) to conform to available capsule dosage strengths (25 and 100 mg) and minimize capsule consumption burden for subjects.

4.4 Criteria for Dose Escalation and Determination of Dose-Limiting Toxicity

Evaluable subjects are defined as having been exposed to at least 28 days of continuous administration of ARQ 087 (e.g., qod, qd, 2 weeks on/1 week off, etc.). Based on the tolerability and safety of ARQ 087 evaluable subjects, enrollment at the next dose level and/or additional subjects into the ongoing cohort will occur according to the following:

- If zero of three initially treated subjects experience a DLT by Day 29 of continuous dosing, then dose escalation will occur
- If one of three initially treated subjects experiences a DLT by Day 29 of continuous dosing, then an additional three subjects will be enrolled for a total of six subjects treated

at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort.

- If two or more of three initially treated subjects at a dose level experience a DLT by Day 29 of continuous dosing, dose escalation will stop and the prior dose level will be considered the MTD. If the first dose results in MTD, subsequent subjects will be enrolled at a lower dose or at a less frequent drug administration schedule (e.g., 25 mg/twice a week).

The MTD is defined as the dose level at which no more than one out of six subjects has an observable DLT.

Preliminary PK results reported in subjects enrolled in Cohorts 1-10 and the Food-effect Cohort have shown that ARQ 087 has a long half-life (~ 1 week) and accumulates (~4 to 14 fold across all cohorts, 4 to 8 fold in cohorts dosed at ≥ 100 mg qd) with continuous dosing. To determine MTD or RP2D and drug administration schedules, clinical PK parameters will be continuously monitored and assessed throughout the study.

Based on the drug safety profile and preliminary Food-effect Cohort PK data, 300 mg qd under fasting conditions has been defined as the RP2D and is recommended for further evaluation in the Expanded Cohort.

4.5 Dose-Limiting Toxicity

Dose-limiting toxicities will be determined during the first four weeks/28 days (first cycle) of Treatment Period 2 (Cohorts 1-4) or during Cycle 1 (Cohort 5 and all subsequent cohorts). A DLT is defined by the occurrence of any of the following toxicities related to ARQ 087 within the first 28 days of continuous treatment (Treatment Period 2 or Cycle 1 of Continuous Dosing) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:

- Grade 4 anemia
- Grade 4 neutropenia
- Grade 4 thrombocytopenia
- Grade 3 neutropenia with fever (≥ 38°C/100.4°F)
- Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
- Grade 3 thrombocytopenia in the presence of bleeding
- ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with metformin)
- ≥ Grade 3 non-hematological toxicity of any duration, except for the following:
    - Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours
    - Alopecia
- Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject

Note: During the dose escalation phase, if the subject experienced a DLT, such subject should be permanently discontinued from the treatment.

4.6 Study Duration

Subjects will receive treatment with ARQ 087 until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criterion is met (see Section 5.8). It is expected that most subjects will receive between one and six cycles of ARQ 087 for a treatment period of four to 24 weeks.

5 STUDY VISITS

Before the start of any study required procedures, the Investigator or designee must obtain a signed written informed consent form (ICF) for the study from each prospective study subject or his/her legal representative.

Study visits will consist of Pre-study Visit(s), during which the subject's eligibility for the study and baseline disease state will be evaluated; four Daily Visits during Treatment Period 1 (Cohorts 1-4); four Weekly Visits during Cycle 1; and Bi-weekly Visits thereafter (Cycle 2+) during which the subject will be evaluated. Additionally, an End of Treatment Visit(s) and 30-day Safety Follow-up(s) Visit will be performed (see Appendix 1 for the Schedule of Assessments).

Following the Pre-study evaluation and a determination by the Investigator and ArQule's Medical Monitor that the subject meets all inclusion/exclusion criteria, the subject will be considered entered into the study.

5.1 Informed Consent

A sample 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 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) 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.

5.2 Pre-Study Evaluations (Baseline) (Within 21 Days Prior to the First Dose of ARQ 087)

After written informed consent is obtained, the subject's eligibility for the study and baseline disease state will be assessed.

The following will be evaluated and documented within 21 days prior to the first dose of ARQ 087 (Day -21 – Day 0):

- Obtain written informed consent from the subject or subject's legal representative
- Medical history (see Section 6.1)
- Physical examination, including mucous membranes and skin (see Section 6.2)
- ECOG PS (see Appendix 2)
- Vital signs (height, weight, temperature, blood pressure, respiration rate, and pulse)
- Fasting clinical blood tests (see Section 6.4)*

- Urinalysis (see Section 6.4)
- Serum pregnancy test, if applicable (see Section 6.4)
- 12-lead electrocardiogram (ECG) (see Section 6.3)
- Echocardiography or Multiple Gated Acquisition (MUGA) scan, if applicable (see Section 6.3)
- Blood samples for tumor markers, if applicable (to be tested at study site)
- Collect archival and/or fresh tissue biopsy samples (see Section 6.8)
    - For subjects enrolled in the Expanded Cohort, archival samples should be collected for all enrolled subjects, paired biopsy is optional. Both archival and pre-treatment fresh tumor samples should be collected prior to the first dose of the study drug
    - For subjects enrolled in the Food-effect Cohort, both archival and paired biopsy should be collected. If archival tissue is not available, paired fresh tumor biopsy should be performed to confirm the subjects' FGFR1-3 or KIT/PDGFR status.
- Record prior and concomitant medications (medications used within 30 days prior to the first dose of ARQ 087)
- Tumor measurement and staging [e.g., computed tomography (CT) scan, magnetic resonance imaging (MRI) or positron emission tomography (PET)] (see Section 6.7, Appendix 6) **Note:** CT, PET, and MRI scans can be used as a Baseline assessment if they were performed within four weeks (28 days) prior to the first dose of ARQ 087.

* Fasting clinical blood tests obtained during the Pre-study Visit can be used for Day 1 if they are performed within 72 hours prior to the first dose of the study drug (Cycle 1, Day 1 visit).

Subjects who satisfy all inclusion and exclusion criteria may be enrolled in the study.

5.3 Treatment Period 1 (PK): Single-Dose Administration of ARQ 087; Cohorts 1-4

The approximate duration of Treatment Period 1 will be 4 days.

5.3.1 Day 1 (Day of the Single Dose of ARQ 087 Administration)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate, and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Blood sample for pharmacokinetics (see Section 6.5; blood samples will be collected immediately prior to the first dose of ARQ 087 and will continue through 72 hours after study drug administration.)
- Blood samples for pharmacodynamics (see Section 6.6)

- Tumor biopsy (if applicable, see Section 6.8)
- Record concomitant medications
- Administer a single dose of ARQ 087
- Assess adverse events (AE; after study drug administration)

* If Baseline fasting clinical blood tests are obtained more than 72 hours prior to the first dose of ARQ 087, then Day 1 fasting clinical blood tests should be repeated, however, they may be obtained within 24 hours prior to the first dose of study drug.

5.3.2 Day 2 (24 Hours; ± 2 Hours, Post-Dose on Day 1)

The following assessments will be made during this visit:

- Vital signs (temperature, blood pressure, respiration rate, and pulse)
- Blood sample for pharmacokinetics (see Section 6.5)
- Blood samples for pharmacodynamics (see Section 6.6)
- Assess AEs
- Record concomitant medications

5.3.3 Day 3 (48 Hours; ± 2 Hours, Post-Dose on Day 1)

The following assessments will be made during this visit:

- Vital signs (temperature, blood pressure, respiration rate, and pulse)
- Blood sample for pharmacokinetics (see Section 6.5)
- Blood samples for pharmacodynamics (see Section 6.6)
- Assess AEs
- Record concomitant medications

5.3.4 Day 4 (72 Hours; ± 2 Hours, Post-Dose on Day 1)

The following assessments will be made during this visit:

- Vital signs (temperature, blood pressure, respiration rate, and pulse)
- Blood sample for pharmacokinetics (see Section 6.5)
- Blood samples for pharmacodynamics (see Section 6.6)
- Assess AEs
- Record concomitant medications

The washout time between Treatment Period 1 and Treatment Period 2 should be at least 72 hours. If the subject continues to be eligible, the treatment with ARQ 087 per the Treatment Period 2 schedule may be initiated immediately after the 72-hour PK sample is drawn.

5.4 Continuous Administration of ARQ 087: Dose Escalation/Food-effect Cohorts and Expanded Cohort

After completion of the Treatment Period 1 Day 4 (Cohorts 1-4) assessments or if the subject is enrolled in the Dose Escalation/Food-effect and Expanded cohorts, the subject will continue treatment according to the schedule of visits and assessments described below.

5.4.1 Cycle 1, Weekly Evaluations

5.4.1.1 Week 1 (Day 1)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Urinalysis (see Section 6.4)
- Blood sample for pharmacokinetics (except Expanded Cohort, see Section 6.5)
- Blood samples for pharmacodynamics (see Section 6.6)
- Blood samples for tumor marker(s), if applicable (to be tested at the study site)
- 12-lead ECG (see Section 6.3)
- Record concomitant medications
- Dispense ARQ 087
- Assess AEs (after study drug administration)

* Fasting clinical blood tests may be obtained within 24 hours of the visit.

5.4.2 Week 2 (Day 8; ± 3 Days)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Blood sample for pharmacokinetics (except Expanded Cohort, see Section 6.5)
- Blood sample for pharmacodynamics (except Expanded Cohort, see Section 6.6)
- Assess AEs
- Record concomitant medications
- Dispense ARQ 087

* Fasting clinical blood tests may be obtained within 24 hours of the visit.

5.4.3 Week 3 (Day 15; ± 3 Days)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Urinalysis (see Section 6.4)
- 12-lead ECG (see Section 6.3)
- Blood sample for pharmacokinetics (except Expanded Cohort, see Section 6.5)
- Blood sample for pharmacodynamics (except Expanded Cohort, see Section 6.6)
- Assess AEs
- Record concomitant medications
- Dispense ARQ 087

* Fasting clinical blood tests may be obtained within 24 hours of the visit.

5.4.4 Week 4 (Day 22; ± 3 Days)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Blood samples for pharmacokinetics (except Expanded Cohort, see Section 6.5)
- Blood sample for pharmacodynamics (except Expanded Cohort, see Section 6.6)
- Tumor biopsy if applicable (see Section 6.8)
- Assess AEs
- Record concomitant medications
- Dispense ARQ 087

* Fasting clinical blood tests may be obtained within 24 hours of the visit.

5.4.5 Week 4 (Day 23; except Expanded Cohort)

The following assessments will be made during this visit:

- Vital signs (temperature, blood pressure, respiration rate and pulse)
- Blood sample for pharmacokinetics (see Section 6.5)

- Assess AEs
- Record concomitant medications

Note: Because the Cycle 1 Day 22 and Day 23 visits are days when the full PK is performed, subjects enrolled in **Cohort 1** (25 mg every other day) Cycle 1 Week 4 visits should be scheduled on the day of ARQ 087 administration and the next consecutive day, when drug is not taken, e.g., Cycle 1 Day 21 and Day 22 or Cycle 1 Day 23 and Day 24.

5.5 Cycle 2 and Following Cycles, Bi-weekly Evaluations

5.5.1 Week 1 (Day 1; ± 3 Days)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Blood samples for tumor marker(s), if applicable (to be tested at study site)
- Blood samples for pharmacokinetics (except Expanded Cohort, see Section 6.5)
- Blood samples for pharmacodynamics (see Section 6.6)
- Urinalysis (see Section 6.4)
- Tumor measurement and staging (see Section 6.7, Day 1 of every odd cycle or every 8 weeks, e.g. C3D1, C5D1, etc.)
- 12-lead ECG (see Section 6.3)
- Echocardiography or MUGA scan to measure LVEF, if applicable and clinically indicated (see Section 6.3)
- Assess AEs
- Record concomitant medications
- Dispense ARQ 087

* Fasting clinical blood tests may be obtained within 24 hours of the visit.

5.5.2 Week 3 (Day 15; ± 3 Days)

The following assessments will be made during this visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate and pulse)
- Fasting clinical blood tests (see Section 6.4)*
- Blood samples for pharmacokinetics (except Expanded Cohort, see Section 6.5)

- Assess AEs
- Record concomitant medications
- Dispense ARQ 087

* Fasting clinical blood tests may be obtained within 24 hours of the visit.

Note: Subjects who do not experience Grade 3/4 toxicity after four cycles (16 weeks) at the same dose level can be evaluated every four weeks (monthly) upon agreement between the Investigator and the ArQule Medical Monitor. The schedule of assessment should follow the Cycle 2 Week 1 schedule.

5.6 End of Treatment Visit (7 [+3] Days after the Last Dose of ARQ 087)

If possible, the End of Treatment Visit should be performed 7 [+3] days after the last dose of ARQ 087. The following assessments will be made during the End of Treatment Visit:

- Physical examination, including mucous membranes and skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate, and pulse)
- Fasting clinical blood tests (see Section 6.4)
- Urinalysis (see Section 6.4)
- Serum pregnancy test, if applicable (see Section 6.4)
- 12-lead ECG (see Section 6.3)
- Echocardiography or MUGA scan to measure LVEF, if applicable (see Section 6.3)
- Blood samples for tumor marker(s), if applicable (to be tested at study site)
- Blood samples for pharmacokinetics (except Expanded Cohort, see Section 6.5)
- Tumor measurement and staging if not done within four weeks (28 days) prior to the end of treatment visit (see Section 6.7)
- AEs assessment
- Record concomitant medications

5.7 30-day (± 3 Days) Safety Follow-Up Visit

All subjects will be followed for a minimum of 30 days after the last dose of ARQ 087. If a subject is removed from the study treatment due to drug-related AEs, the subject will be followed until drug-related AEs occurring during the study or within 30 days after the last dose of ARQ 087 have resolved to baseline, CTCAE Grade 1, stabilized, or are deemed irreversible. 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.

Note: The visit can be done either as an office visit or over the telephone.

5.8 Discontinuation from the Treatment/Study

Subjects will be removed from the study treatment at any time if they meet any of the following criteria:

- Documented radiographic or clinical progression of disease*
- Noncompliance with any part of the study, as evaluated by the Investigator and Medical Monitor
- Clinically unacceptable toxicities despite optimal treatment or dose reduction
- Withdrawal of consent
- Investigator's decision (in agreement with the Sponsor/Medical Monitor or designee)
- Lost to Follow-up
- Death

* Subjects may remain on treatment if, in the opinion of the Investigator and with the agreement of ArQule's Medical Monitor, they continue to derive benefit from the treatment.

Subjects will be removed from the study if they meet any of the following criteria:

- Safety follow-up visit is completed per protocol and drug-related AEs have resolved to baseline, CTCAE Grade 1, stabilized, or are deemed irreversible.
- Withdrawal of consent
- Lost to Follow-up
- Death

5.9 Study Discontinuation

The Sponsor reserves the right to temporarily or permanently discontinue the study at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice (GCP) guidelines, or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority
- Discontinuation of product development
- Manufacturing difficulties/concerns

The Sponsor and/or designee will promptly inform all Investigators and the appropriate regulatory authorities if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

6 STUDY PROCEDURES

6.1 Medical History

Medical history will include but not be limited to the following:

- Demography: date of birth, sex, ethnic origin, height, and weight
- Clinically significant prior diagnoses, surgeries, and current medications
    - Medications used within 30 days prior to the first dose of ARQ 087 should be reported
- Prior cancer history, current cancer diagnosis, tumor stage at time of diagnosis and screening, previous anti-cancer therapy, including dates, duration and outcome of treatment, previous radiation therapy, including anatomic site, dose and dates of treatment, previous cancer-related surgical procedures, including type of the procedure and dates

6.2 Physical Examination

Complete physical examination of the major body systems, including mucous membranes, skin, height (Baseline visit only), weight (Baseline visit, Cycle 1 Day 1 and Day 15, on Day 1 of all subsequent cycles, and End of Treatment visit), vital signs (blood pressure, heart rate, respiratory rate, temperature [oral, axillary, or tympanic]), and ECOG PS (Appendix 2).

6.3 12-Lead ECG, Echocardiography, and MUGA Scan

Twelve-lead ECG should be conducted at the Baseline Visit, on Day 1 and Day 15 of Cycle 1, on Day 1 of all subsequent cycles (e.g., Cycle 2, Cycle 3, etc.), and at the End of Treatment Visit. Additional ECG(s) may be conducted if clinically indicated.

For subjects previously treated with anthracyclines (e.g., epirubicin [Ellence, Pharmorubicin]; idarubicin [Idamycin]; doxorubicin [Adriamycin, Rubex]; and daunorubicin [Cerubidine]), an echocardiography or MUGA scan to measure LVEF should be performed at Baseline, and, if clinically indicated, every eight/twelve weeks (e.g., Day 1 Cycle 3, Day 1 Cycle 6, Day 1 Cycle 9, Day 1 Cycle 12, etc.), and at the End of Treatment Visit.

For the individual subject, the same method of measuring LVEF should be used throughout the study.

6.4 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, liver function tests, coagulation tests, and urinalyses. All laboratory tests required during the study must be obtained at a local laboratory designated by the Investigator. Fasting clinical blood tests obtained during the Pre-study Visit can be used for Day 1 if they are performed within 72 hours prior to the first dose of the study drug (Treatment Period 1, Day 1 in Cohorts 1-4 or Cycle 1 Day 1 visit in Cohort 5 and all subsequent cohorts). During Treatment Period 2 (Cohorts 1-4) or the Continuous Treatment Administration (Cohort 5 and all subsequent cohorts), clinical blood tests can be obtained within 24 hours prior to the scheduled visit.

Chemistry samples should be taken in a fasting state (fasting at least 8 hours) prior to administration of the morning dose of ARQ 087*.

- Hematology: complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count (WBC) with 5-part differential, red blood cell (RBC), platelet, and reticulocyte count
- Blood chemistry: albumin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, glycated hemoglobin (HbA1c)**, magnesium, phosphate, potassium, total protein, sodium, uric acid
- Liver function tests (LFT): alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total and direct bilirubin, lactate dehydrogenase (LDH)
- Thyroid function tests (at Baseline and End of Treatment, and if clinically indicated): thyroid stimulating hormone (TSH), triiodothyronine (total T3), thyroxine (free T4)
- Coagulation tests (at Baseline and End of Treatment, and if clinically indicated): prothrombin time (PT), international normalized ratio (INR), and partial prothrombin time (PTT)
- Routine urinalysis: dipstick and microscopy (only if clinically indicated or dipstick is not done) including protein, specific gravity, glucose and blood
    - To assess ARQ 087 metabolism, the Sponsor may request collection of 24-hour urine samples
- Serum pregnancy test (at Baseline and End of Treatment only): for female subjects of childbearing potential

*ARQ 087 should be administered in the fasted state, except to subjects enrolled in the Food-effect Cohort.
**HbA1c should be done at Baseline and End of Treatment, and if clinically indicated

6.5 Pharmacokinetic Assessments

Pharmacokinetic variables will include C_{max}, AUC, and half-life. To assess single dose PK, blood samples will be collected for four consecutive days during Treatment Period 1 (Cohorts 1-4), on Day 1 (full assessment), Day 2 (24 hrs post-dose), Day 3 (48 hrs post-dose), and Day 4 (72 hrs post-dose). The washout period between Treatment Period 1, Day 1 and Treatment Period 2, Day 1 Cycle 1 should be at least 72 hours. During Treatment Period 2 (continuous administration of ARQ 087), PK samples will be collected on Day 8, Day 15, Day 22 (full assessment), and Day 23 (24 hrs post-dose on Day 22) of Cycle 1 (see Appendix 3). However, for subjects enrolled in **Cohort 1** (25 mg every other day), Cycle 1 Week 4 visits should be scheduled on the day of ARQ 087 administration and the next consecutive day, when drug is not taken, e.g., Cycle 1 Day 21 and Day 22 or Cycle 1 Day 23 and Day 24. Also, a Cycle 1 Day 1 pre-dose sample should be collected if the Cycle 1 Day 1 visit differs from the Treatment Period 1, Day 4 visit (72 hours).

During continuous administration of ARQ 087 (Cohort 5 and all subsequent cohorts, including ALL subjects enrolled in the Food-effect Cohort, and for up to 10 subjects enrolled in the Expanded Cohort at selected sites), PK samples will be collected on Day 1 (full assessment), Day 2, Day 8 (pre-dose), Day 15 (pre-dose), Day 22 (full assessment), and

Day 23 (pre-dose) of Cycle 1; and on Day 1 and Day 15 of all subsequent cycles (pre-dose), and End of Treatment (see Appendix 3).

The blood sampling date and time and the time of the last dose of ARQ 087 administration prior to PK blood draw should be recorded on the eCRF.

Detailed instructions for collection and shipment of plasma PK samples will be provided in the laboratory manual.

6.6 Pharmacodynamic Assessments

The goal of the proposed biomarker study is to evaluate the tumoral and serum- or plasma-based pharmacodynamic response in subjects treated with ARQ 087.

Information on tumor FGFR protein expression, gene copy number and mRNA amplification, and/or mutational/gene re-arrangement (fusion, translocation) status is required for this study. If these are not known, tumor biopsy should be done to assess these parameters prior to the first dose of ARQ 087. All baseline samples (archival or newly acquired) will be evaluated by immunohistochemistry (IHC), FISH (gene copy number), ISH or qNPA (mRNA amplification), and/or DNA sequencing (mutational/gene re-arrangement [fusion, translocation] status assessment).

Pathology specimens (pre- and post-treatment tumor biopsies) will be evaluated for changes in total FGFR1, total FGFR2, pFGFR, pFRS2α, and/or pERK status by either IHC, mesoscale, or immunoprecipitation/Western blot analysis. A post-treatment tumor biopsy should be collected between Cycle 1 Day 22 and Cycle 2 Day 1 at least 1 hour post-dose. In subjects who have been on treatment ≥8 weeks and with the subject's agreement, additional post-treatment biopsies may be collected.

Blood samples (pre-dose) will be collected during Treatment Period 1 on Day 1, Day 2, Day 3, and Day 4 (Cohorts 1-4), and during Treatment Period 2 Cycle 1 (Cohort 5 and all subsequent Dose Escalation cohorts) on Day 1, Day 8, Day 15, and Day 22, and on Day 1 of Cycles 2-5 for evaluations of pharmacodynamic changes of factors including phosphate, glucose, FGF 19, 21, and/or 23 utilizing standard blood chemistry methodologies and ELISA-based assays.

For subjects enrolled in the Expanded Cohort, blood samples for evaluations of pharmacodynamic changes of FGF 19, 21, and 23 will be collected on Day 1 of the first six cycles.

Samples for pharmacokinetic and pharmacodynamic assessments will be labeled by personnel from the institution with subjects' study ID; subjects' identity will not be made known to employees from the Sponsor, additional collaborators, or other investigators. Samples will only be used for the purposes of the protocol and will only be used by ArQule's personnel or by an external laboratory chosen by ArQule to outsource the analyses according to internal guidelines. Samples will be kept until all protocol-related analyses are completed, for a period not exceeding 10 years or as required by local law.

Detailed instructions for collection, testing, and shipment of tissue, plasma, or serum pharmacodynamic samples will be provided in the laboratory manual.

6.7 Tumor Evaluation

Tumor assessments (CT scan, PET scan, or MRI) will be performed at Baseline, and every eight weeks (e.g., on Day 1 of every odd cycle, Day 1 Cycle 3, Day 1 Cycle 5, or Week 8, Week 16, etc.) or as otherwise clinically indicated.

For subjects who do not experience disease progression and continue to benefit from the treatment after 11 cycles, tumor evaluation may be performed every 3 months (e.g., Day 1 of Cycle 14, Day 1 of Cycle 17, Day 1 of Cycle 20, etc.) upon agreement between the Investigator and ArQule's Medical Monitor.

Standard imaging studies should be performed according to institutional procedures and/or standard of care. Tumor response will be evaluated using relevant guidelines (see Appendix 6 for RECIST 1.1 guidelines).

6.8 Tumor Biopsy

All enrolled subjects should agree to provide archival tissue and to have a fresh tumor biopsy.

- For ALL subjects, archival tissue biopsy samples should be collected
- For subjects enrolled into the Expanded Cohort, samples will be tested for genetic alterations, that may include FGFR genetic alterations, FGFR gene fusions, and KIT/PDGFR mutations
- For subjects enrolled in the Dose Escalation and Food-effect Cohorts, samples will be tested to assess protein expression levels of FGFR family members (FGFR1 and FGFR2) and/or to confirm the tumor's genomic profile, e.g., KIT/PDGFR mutation or *FGFR1-3* amplification, mutations/gene rearrangement (fusion, translocation) status
- If archival samples are not available, a fresh core needle biopsy or fine needle aspiration (FNA) may be collected during the Screening Period. Core needle biopsy samples collected within 30 days prior to the first dose of ARQ 087 are considered fresh.
- If allocated slots are available, for subjects eligible for enrollment in the Dose Escalation cohorts, paired (pre- and post-treatment) tumor biopsy is optional. The paired tumor biopsy will be done only if, in the Investigator's opinion, a minimally invasive biopsy may be performed.
- For all subjects enrolled in the Food-effect Cohort, a paired tumor biopsy is mandatory.
- In Cohorts 1-4, tumor samples will be collected at Baseline/archival and 4-6 hours after ARQ 087 administration on Day 1 of Treatment Period 1 or on Day 1 of Cycle 1 of Treatment Period 2. Starting with Cohort 5, a post-treatment tumor biopsy should be collected between Cycle 1 Day 22 and Cycle 2 Day 1 at least 1 hour post-dose. (Additionally, optional post-treatment biopsies may be collected at any time during treatment at least 1 hour post-dose.)
- For subjects enrolled in the Expanded Cohort pre- and post-treatment (paired) biopsy is optional. If a paired biopsy is deemed safe and with the subject's consent, the biopsy may be performed at Baseline, at any time point between Cycle 1 Day 22 and Cycle 2

Day 1 visits, and an additional optional biopsy may be performed at any time during the treatment including the End of Treatment Visit.

Prior to a subject's enrollment, the Investigator should establish availability of suitable pathology specimens and/or evaluate the subject's eligibility for tumor biopsy.

The testing may include assessment of FGFR1 and FGFR2 protein levels, pFGFR, pFRS2α, and pERK expression levels.

Fresh tumor biopsy samples must be frozen immediately after the samples are obtained. Detailed instructions for collection, shipment, and testing of tissue samples will be provided in the laboratory manual.

7 TREATMENT

7.1 ARQ 087

ARQ 087 capsules (multiple strengths of 25 mg and 100 mg) will be supplied to the research pharmacy at the clinical site. Study drug will be labeled as an investigational agent according to relevant Federal laws and regulatory guidelines.

7.1.1 Investigational Product Accountability

ArQule will provide study drug and drug accountability documentation required for completion of this study. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced.

Drug Accountability Records (logs) will be maintained. These records should record quantities of study drug received and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the drug. Accurate records of all study drug dispensed from and returned to the study site are to be maintained. 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 monitor or designated representative, all unopened drug is to be returned to ArQule or designee in the original containers.

7.1.2 Storage and Handling

At a study site, ARQ 087 should be stored refrigerated (2°-8°C; 35°-46°F) or at controlled room temperature (15°-30°C; 59°-86°F) depending on the storage instructions provided on the label of the container in which the capsules are shipped to the site and dispensed to the subject. Until dispensed to the subject, the study drug should be stored in a secure locked area accessible to authorized personnel only.

7.1.3 ARQ 087 Administration

ARQ 087 will be administered once a day, orally. ARQ 087 must be administered in the fasted state, except for subjects who are enrolled in the Food-effect Cohort. Subjects in the Food-effect Cohort will be asked to take ARQ 087 with their morning meals and to keep a food diary (breakfast).

For administrative reasons, during continuous dosing, the treatment period is divided into 4-week cycles (28 days).

The dose of ARQ 087 to be administered depends on the dose level cohort to which the subject is enrolled, with the initial dose level of 25 mg qod, see Section 4.1 for details.

For individual subjects, treatment will continue until unacceptable toxicity, disease progression (clinical or radiological), or other discontinuation criterion is met. It is expected that most subjects will receive ARQ 087 for one to six treatment cycles (4 to 24 weeks).

7.2 Missed or Vomited Doses

A missed or vomited dose should not be replaced. The subject should be instructed to take the next scheduled dose at the regularly scheduled time. If the subject vomited the very first dose of study drug, the subject may be re-challenged per discretion of the Investigator.

7.3 Dose Modifications

In general, once the dose of ARQ 087 has been modified for a subject, all subsequent cycles should be administered to that subject at the modified dose. The modified dose will be considered the maximum dose for all subsequent cycles for that subject.

When a drug-related toxicity is observed, dose delays and/or reductions in ARQ 087 administration are allowed. If dose reduction is indicated, a subject should be assigned to the previous (lower) cohort dose (dose re-escalation is not permitted). In the event of a dose modification, the dose change(s) must be captured in the electronic data capture (EDC) system. If questions or considerations regarding dose modification arise or a specific dose modification is needed, ArQule's Medical Monitor or designee should be consulted.

If the subject experienced a DLT, such subject should be permanently discontinued from the treatment. During the dose escalation period, intra-subject dose escalation is not allowed. Once the MTD/RP2D is reached, intra-subject dose escalation may be considered to optimize the dose level taking into consideration the available dosage strengths. A maximum of one intra-subject dose escalation per subject may be considered.

Table 7.1 Dose Delays/Reductions for Drug-Related Toxicity

Event Grade	Action
Grade 1 or 2, including significant increase in LFTs (as assessed by the Investigator) and alopecia	Continue current dose level, unless dose interruption/modification may be clinically indicated, e.g., due to significant increase in LFTs
Grade 3-4 nausea, vomiting or diarrhea lasting < 24 hours	Withhold ARQ 087 until recovery to Grade 1 or baseline. If recovery occurs within 24 hours, restart ARQ 087 at the current dose level.
Grade 3-4 toxicity, including nausea, vomiting or diarrhea lasting ≥ 24 hours	Withhold ARQ 087 until recovery to Grade 1 or baseline. - If recovery occurs within 14 days, restart ARQ 087 at the dose and schedule of the previous cohort for all subsequent cycles, unless further dose reduction is required. - If recovery occurs within 21 days of the drug hold, ARQ 087 may be restarted upon agreement between the Investigator and the Sponsor's Medical Monitor. Treatment should be restarted at the dose and schedule of the previous cohort for all subsequent cycles, unless further dose reduction is required. - If recovery occurs after more than 21 days of the drug hold, ARQ 087 should be permanently discontinued

Table 7.2 ARQ 087 Dose Reduction Schema

Current Dose	Dose after Reduction
Dose Level 1: 3 capsules qd (300 mg daily)	Dose Level 2: 2 capsules qd (200 mg daily)
Dose Level 2: 2 capsules qd (200 mg daily)	Dose Level 3: 1 capsule qd (100 mg daily)
Dose Level 3: 1 capsule qd (100 mg daily)	

7.4 Treatment Compliance

A subject is considered compliant with the study protocol when study medication is administered at a compliance level of ≥ 80%. In order to evaluate the safety of ARQ 087, replacement of non-compliant subjects will be allowed during Cycle 1 of Treatment Period 2/Continuous Dosing.

Compliance will be calculated using the following equation:

(Number of capsules actually ingested / number of capsules that should have been ingested per dose level) x 100 = % compliance

7.5 Blinding

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

7.6 Prior Treatment

Reasonable efforts will be made to determine all relevant prior treatments received by the subject within 30 days prior to the first ARQ 087 dose. All relevant information must be recorded on the appropriate subject's electronic case report form (eCRF). All surgical procedure history, prior chemotherapy, and radiation therapy must be recorded on the appropriate eCRF.

7.7 Concomitant Treatments

All information regarding concomitant treatments (medications or procedures) must be recorded on the subject's eCRF (including the name of the medication or procedure and duration of treatment). Complete information of analgesic consumption should be obtained and recorded.

7.7.1 Permitted Treatment

Palliative and supportive care for disease-related symptoms will be offered to all subjects.

In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
    - If active hepatitis B virus (HBV) replication is discovered, the subject must be immediately treated with conventional anti-viral therapy (excluding interferon) per standard of care

- Erythropoietin Stimulating Agents (ESA): Please follow the American Society of Clinical Oncology (ASCO), the American Society of Hematology, MEDICARE guidelines for the use of epoetin in subjects with cancer and FDA alerts dates 09 March 2007, 08 November 2007, 12 March 2008, 31 July 2008, and 02 December 2008.
- Hematopoietic growth factors, including filgrastim (Neupogen®), or other granulocyte colony stimulating factors (G-CSF). Please follow ASCO guidelines for the use of white blood cell growth factors. http://jco.ascopubs.org/content/24/19/3187.full
- Prophylactic antiemetics may be administered according to standard practice
- Megestrol acetate (Megace®)
- Use of topical corticosteroids, topical and systemic antibiotics according to SOC or institutional guidelines

7.7.2 Prohibited Treatment/Treatment to Be Avoided or Used with Caution

The following treatments are not allowed during the study:

- Any concurrent anti-cancer therapy including chemotherapy, radiotherapy, hormonal, targeted therapy, or immunotherapy
    - Palliative radiotherapy for local pain-control may be allowed, provided the subject does not meet criteria of progressive disease and treated lesions will not be included in the target/non-target lesion assessment
- 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, for CNS metastases management or as premedication for imaging studies)

The following treatments should be avoided, if possible or used with caution during the study:

- ARQ 087 may inhibit CYP1A2 or CYP2D6 metabolism, hence co-administration of ARQ 087 with drugs known to be substrates of CYP1A2 or CYP2D6 should be avoided or used with caution (see Appendix 4)
- ARQ 087 may be a substrate and inhibitor of human P-glycoprotein (P-gp), therefore co-administration of ARQ 087 with drugs known to be P-gp substrates with narrow therapeutic index should be avoided or used with caution (see Appendix 5)
- Drugs with known liver toxicity, e.g., clotrimazole, should be avoided or used with caution; if such drugs need to be administered, LFT should be done every 4-5 days during the drugs' co-administration

7.8 Potential Risks for Study Subjects

Based on pre-clinical data it has been suggested that ARQ 087 may cause a phototoxic reaction in some subjects exposed to the sunlight while being treated with the drug. The amount of ARQ 087 that may be required to cause such reaction is unknown. All subjects should be instructed to avoid sunlight exposure, to use sunscreen to protect exposed areas of

the body (e.g., forehead, nose, lips, and hands), and to immediately report symptoms that may be associated with phototoxic reaction (redness, pruritus, swelling, blister formation).

8 SAFETY ASSESSMENTS

8.1 Definitions

8.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigational subject administered a pharmaceutical product that does not necessarily have a causal relationship with study-drug 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.

8.1.2 Serious Adverse Event

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening
- Requires new inpatient hospitalization defined as a hospital admission lasting > 24 hours (not including emergency room visit without hospital admission), or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event 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 above. An important medical event may be considered an SAE based upon appropriate medical judgment.

8.1.3 Unexpected Adverse Event or Serious Adverse Event

An unexpected AE or SAE is one for which the nature or severity of the event is not consistent with the applicable product information, as summarized in the Investigator's Brochure.

8.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All adverse events that are determined by the Investigator or by the Sponsor as having a reasonable suspected causal relationship to a study drug and that are both unexpected and serious are considered to be SUSARs and are subject to expedited regulatory reporting.

8.1.5 Inpatient Hospitalization

An inpatient hospitalization is a hospital admission that lasts more than 24 hours.

8.1.6 Study Drug-related Adverse Event or Serious Adverse Event

Study drug-related AE or SAE is defined as an AE or SAE that is related to the treatment with ARQ 087

8.1.7 Further Adverse Event and Serious Adverse Event Defining

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE.

Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Scheduled hospitalizations or elective surgical procedures will not be considered as AEs or SAEs.

Prolongation of a scheduled hospitalization can be considered an SAE.

Complications associated with scheduled procedures are considered AEs or SAEs.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE or a SAE unless its outcome is death.

Adverse events including SAEs that occur following the execution of the ICF but prior to dosing will not be recorded as AEs or SAEs.

Adverse events including SAEs that occur after subjects receive any anticancer therapy other than the study-defined treatments will not be recorded as AEs or SAEs.

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 AE and SAE they experience.

Investigators capture, evaluate, and document all AEs and SAEs occurring during a subject's enrollment in the trial, commencing with the first day of treatment and including the protocol-defined 30-day post-treatment follow-up period (Code of Federal Regulations [CFR] 21 §312.64[b]) as source documents and on designated eCRF pages. These AEs/SAEs must be recorded in the EDC system of this study.

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 (see Section 8.4).

In cases of SUSARs, Investigators 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 Event and Serious Adverse Event Assessment Criteria

Adverse events and SAEs are evaluated and graded using NCI CTCAE guidelines, version 4.03.

8.4 Serious Adverse Event Reporting

The Investigators are obligated to immediately report to Global Safety Surveillance, Inc. (Telerx Healthcare ConneXions), the drug safety designee of the Sponsor, each SAE that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related. All requested supplementary documents (e.g., discharge letter, autopsy report, etc.); relevant data (e.g., electrocardiograms, lab tests, discharge summaries, post mortem results, etc.) must be faxed or e-mail within 24 hours after available. If any questions or considerations regarding an SAE arise, the ArQule Medical Monitor or designee should be consulted.

Healthcare ConneXions SAE Fax number for US reports: 888-314-7557

ArQule Medical Monitor

Julia Kazakin, M.D.
Telephone: (781) 994-0478
e-mail: jkazakin@arqule.com

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

If all 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 ARQ 087 trials in an expedited manner (within 7 days or 15 days of knowledge) and to all Investigators involved in ARQ 087 clinical trials.

The Investigators 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 occurring during the study period from the time of the first dose of study drug administration 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. All subjects should be instructed to reported AEs or SAEs occurring during the 30-day post-treatment safety follow-up period.

Unresolved study drug related (see Section 8.1.6 for definition) AEs and SAEs at the time of treatment discontinuation or new study drug related AEs and SAEs that occur during the 30-day safety follow-up period will be followed until they have, in opinion of the Investigator, resolved to baseline, have stabilized, or are deemed to be irreversible.

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.

8.6 Grading of Severity

Each AE or SAE will be graded for severity according to NCI CTCAE (version 4.03). The criteria can be found at http://ctep.cancer.gov/reporting/ctc.html.

For AEs not listed in the NCI CTCAE version 4.03, a similar grading system should be used as follows:

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

For AEs that can be described by the NCI CTCAE guidelines, 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.

8.7 Assessment of Causality

The relationship between an adverse event and the study product (ARQ 087) will be determined by the Investigator on the basis of his/her clinical judgment and the following definitions.

8.7.1 Related Adverse Events

- 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, concomitant diseases, 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, a known reaction to agent, or chemical group.

8.7.2 Not Related Adverse Events

- The AE does not follow a reasonable temporal 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).

9 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the Sponsorship of ArQule. Study drug ARQ 087, clinical supplies, and eCRFs will be supplied by ArQule or its representative. Representatives of ArQule will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCPs and other applicable regulations and guidelines.

10 PLANNED STATISTICAL METHODS

The material presented in this section will serve as the basis for the statistical analysis plan. This plan may be revised during the study to accommodate protocol amendments. Because of the nature of this study, no formal statistical analysis is planned. Evaluation of the data will consist primarily of summary displays (e.g., descriptive statistics and graphs).

In addition, for the iCCA sub-cohort of the Expanded Cohort (Part 2), statistical analysis will include interim monitoring for futility. After response data from 10 subjects with iCCA are available, the response rate will be assessed. If the objective response is observed in ≤ 30% of enrolled subjects, the enrollment will be stopped for lack of efficacy.

10.1 Determination of Sample Size

The exact number of subjects estimated for this study is dependent on the number of subject cohorts investigated based on the toxicity encountered. It is expected that approximately 60-120 subjects at five to fifteen sites in the United States and Italy will be enrolled in this study.

10.2 Analysis Variables

10.2.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will include:

- Demographics
- Baseline disease characteristics
- Clinically significant medical history, including surgeries
- Prior therapies
- Baseline concomitant medications and treatments

10.2.2 Safety

Safety variables include the reported AEs, laboratory tests, vital signs, ECOG performance status, and physical examination.

10.2.3 Efficacy

Response rate/disease control rate and progression free survival will be used to determine preliminary evidence of activity.

Progression Free Survival (PFS) is defined as time from first dose until documented radiographic disease progression or death, whichever occurs first.

10.2.4 Pharmacokinetics

Pharmacokinetics parameters include C_{max}, AUC, and half-life.

10.3 Statistical Methods

All subjects receiving at least one daily dose of ARQ 087 will be considered evaluable for safety analyses. Subjects who have received at least one cycle of ARQ 087 and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response.

10.3.1 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be descriptively summarized. 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.

10.3.2 Extent of Treatment Exposure

Duration of exposure is defined as the total number of days of study drug administration, ignoring any temporary drug discontinuation. If the date of last administration is unknown, the date until which the dispensed drug would have lasted without counting the extra drug provided should be used.

10.3.3 Analyses of Safety Variables

10.3.3.1 Adverse Events

Adverse events will be evaluated for severity using NCI CTCAE, version 4.03. Adverse Event summaries will include the incidence of TEAEs. All TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) and summaries will present data by 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 leading to treatment discontinuation
- TEAEs resulting in death
- TEAEs listed according to maximum severity

10.3.3.2 Laboratory Test

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for each hematology, serum chemistry, liver function test, electrolyte, and urinalysis parameter.

10.3.3.3 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.

10.3.3.4 ECOG Performance Status

Number and percent of subjects having each ECOG performance status level will be presented for baseline and each post-baseline measurement.

10.3.3.5 Physical Exams

Data from physical exams will be presented in the data listings.

10.3.4 Analysis of Efficacy Variables

10.3.4.1 Progression Free Survival

Progression Free Survival (PFS) will be estimated based on a Kaplan-Meier estimate. Median PFS time and the 95% confidence interval will be estimated.

10.3.4.2 Response Rate

Analyses on the ORR will be performed in evaluable subject population. The 95% confidence interval will be estimated.

The 95% confidence interval for percent of subjects in each RECIST response category (e.g., CR, PR, SD, and PD) and disease control rate will also be estimated.

10.3.5 Pharmacokinetics and Pharmacodynamics

10.3.5.1 Pharmacokinetics

Pharmacokinetics parameters include C_{max}, AUC, and half-life; summary statistics will be performed.

10.3.5.2 Pharmacodynamics

Summary statistics including mean, standard deviation, median, coefficient of variation, minimum and maximum for baseline, each post-baseline measurement, and change from baseline will be performed on the specified tumoral biomarkers (FGFR1-2 protein, pFGFR, pFRS2α, and pERK levels) and blood biomarkers (e.g., phosphate, glucose, FGF 19, 21, and/or 23 utilizing standard blood chemistry methodologies and ELISA-based assays).

To explore the association of blood concentration with clinical outcome, the above descriptive statistics will also be presented separately for each response category (CR, PR, and SD combined vs. PD). Logistic regression will also be utilized if appropriate.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS

11.1 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 trial, 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.

11.2 Compliance with Good Clinical Practice 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.

11.3 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 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 US federal regulations (21 CFR §50) and the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance." 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.

12 STUDY MANAGEMENT AND MATERIALS

12.1 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 eCRFs and original source documents for accuracy of data recording, study drug accountability, and correspondence. The extent and frequency of monitoring visits will be determined by the Sponsor or designee based on the status of the trial and the performance of the site. 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.

12.2 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 ARQ 087 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.

12.3 Electronic Case Report Forms

An 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.

12.4 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 ARQ 087. 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

Part 1: Cohorts 1-4											
Tests & Procedures	**Pre-Study Visit(s)**	**Treatment Period 1: Single-dose (PK)[1]**		**Treatment Period 2: Continuous Dosing Weekly Visits[1]**						**End of Treatment Visit**	**30-day Safety Follow-up**
	Baseline			**Cycle 1**				**Cycle 2+**			
Week		**0**	**0**	**1**	**2**	**3**	**4**	**1**	**3**	**7 days after the last dose of ARQ 087**	**30 days after the last dose of ARQ 087**
Day	**0**	**Day 1**	**Day 2, 3, 4**	**1**	**8**	**15**	**22**	**1**	**15**		
Window	**-21 – 0**	**0**	**0**	**0**	**± 3 days**			**± 3 days**		**+3 days**	**± 3 days**
Written Informed Consent	X										
Medical History	X										
Physical Examination[2]	X	X		X	X	X	X	X	X	X	
ECOG PS	X	X		X	X	X	X	X	X	X	
Vital Signs, Weight[3]	X	X	X	X	X	X	X	X	X	X	
Hematology[4]	X	X		X	X	X	X	X	X	X	
Blood Chemistry[4]	X	X		X	X	X	X	X	X	X	
Liver Function Tests[4]	X	X		X	X	X	X	X	X	X	
Coagulation tests[4]	X									X	
Thyroid function tests[4]	X									X	
Urinalysis[4]	X			X		X		X		X	
Serum Pregnancy Test[4]	X									X	
Tumor Markers, if applicable	X			X				X		X	
12-Lead ECG[5]	X			X		X		X		X	
Echocardiography or MUGA, if applicable[5]	X							X		X	
Pharmacokinetics[6]		X	X		X	X	X				

Part 1: Cohorts 1-4											
Tests & Procedures	**Pre-Study Visit(s)**	**Treatment Period 1: Single-dose (PK)[1]**		**Treatment Period 2: Continuous Dosing Weekly Visits[1]**						**End of Treatment Visit**	**30-day Safety Follow-up**
	Baseline			**Cycle 1**				**Cycle 2+**			
Week		**0**	**0**	**1**	**2**	**3**	**4**	**1**	**3**	**7 days after the last dose of ARQ 087**	**30 days after the last dose of ARQ 087**
Day	**0**	**Day 1**	**Day 2, 3, 4**	**1**	**8**	**15**	**22**	**1**	**15**		
Window	**-21 – 0**	**0**	**0**	**0**	**± 3 days**			**± 3 days**		**+3 days**	**± 3 days**
Pharmacodynamics[6]		X	X		X	X	X	X		X	
Archival and/or Fresh Tumor Biopsy[7]	X	X		X							
FGFR mutation, if unknown, Expanded Cohort only[7]	X										
Tumor Measurement and Staging[8]	X[9]							X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X
ARQ 087 Dispensation		X		X	X	X	X	X	X		

1. Washout period between Treatment Period 1 Day 1 and Treatment Period 2 Cycle 1 Day 1 should be at least 72 hrs
2. Physical examination, including mucous membrane and skin
3. Weight at Baseline visit, on Day 1 and Day 15 of Cycle 1, on Day 1 of each subsequent cycle, and End of Treatment visit.
4. Refer to Section 6.4 for description of laboratory assessments
5. Refer to Section 6.3 for detailed description of assessments (Echocardiography or MUGA should be performed at Baseline, C3D1, C5D1, etc., and End of Treatment)
6. Refer to Sections 6.5 and 6.6.for pharmacokinetic and pharmacodynamic blood samples collection schedules. **Note**: Because Cycle 1 Day 22 and Day 23 visits are days when the full PK is performed, subjects enrolled in **Cohort 1** (25 mg every other day) Cycle 1 Week 4 visits should be scheduled on the day of ARQ 087 administration and next consecutive day, when drug is not taken, e.g., Cycle 1 Day 21 and Day 22 or Cycle 1 Day 23 and Day 24.
7. Refer to Section 6.8 for detailed description of tumor tissue samples collection. If archival tissue is not available, baseline tumor biopsy will be performed to confirm FGFR mutation (the Expanded Cohort only).
8. Refer to Sections 6.7 and Appendix 6 for tumor evaluation description (Baseline, C3D1, C5D1, etc., and End of Treatment)
9. Unless tumor evaluation/measurement has been performed within 28 days prior to the first dose of ARQ 087

Appendix 1: Schedule of Assessments continued

Part 1: Cohorts 5-10 and Food-effect Cohort											
Tests & Procedures	**Pre-Study Visit(s)**	**Continuous Dosing Weekly Visits**								**End of Treatment Visit**	**30-day Safety Follow-up**
	Baseline	**Cycle 1**						**Cycle 2+**			
Week		**1**		**2**	**3**	**4**		**1**	**3**	**~7 days after the last dose of ARQ 087**	**~30 days after the last dose of ARQ 087**
Day	**0**	**1**	**2**	**8**	**15**	**22**	**23**	**1**	**15**		
Window	**-21 – 0**	**0**		**± 3 days**				**± 3 days**		**+3 days**	**±3 days**
Written Informed Consent	X										
Medical History	X										
Physical Examination[1]	X	X		X	X	X		X	X	X	
ECOG PS	X	X		X	X	X		X	X	X	
Vital Signs, Weight[2]	X	X	X	X	X	X	X	X	X	X	
Hematology[3]	X	X		X	X	X		X	X	X	
Blood Chemistry[3]	X	X		X	X	X		X	X	X	
Liver Function Tests[3]	X	X		X	X	X		X	X	X	
Coagulation tests[3]	X									X	
Thyroid function tests[3]	X									X	
Urinalysis[3]	X	X			X			X		X	
Serum Pregnancy Test[3]	X									X	
Tumor Markers, if applicable	X	X						X		X	
12-Lead ECG[4]	X	X			X			X		X	
Echocardiography or MUGA, if applicable[4]	X							X		X	
Pharmacokinetics[5]		X	X	X	X	X	X	X	X	X	

Part 1: Cohorts 5-10 and Food-effect Cohort											
Tests & Procedures	**Pre-Study Visit(s)**	**Continuous Dosing Weekly Visits**								**End of Treatment Visit**	**30-day Safety Follow-up**
	Baseline	**Cycle 1**						**Cycle 2+**			
Week		**1**		**2**	**3**	**4**		**1**	**3**	**~7 days after the last dose of ARQ 087**	**~30 days after the last dose of ARQ 087**
Day	**0**	**1**	**2**	**8**	**15**	**22**	**23**	**1**	**15**		
Window	**-21 – 0**	**0**		**± 3 days**				**± 3 days**		**+3 days**	**±3 days**
Pharmacodynamics[5]		X		X	X	X		X		X	
Archival and/or Fresh Tumor Biopsy[6]	X					X					
Tumor's genomic status, if unknown, Food-effect & Expanded Cohorts[6]	X										
Tumor Measurement and Staging[7]	X[8]							X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X
ARQ 087 Dispensation		X		X	X	X		X	X		

1. Physical examination, including mucous membrane and skin
2. Weight at Baseline visit, on Day 1 and Day 15 of Cycle 1, on Day 1 of each subsequent cycle, and End of Treatment visit.
3. Refer to Section 6.4 for description of laboratory assessments
4. Refer to Section 6.3 for detailed description of assessments (Echocardiography or MUGA should be performed at Baseline, C3D1, C6D1, C9D1, etc., and End of Treatment)
5. Refer to Sections 6.5 and 6.6.for pharmacokinetic and pharmacodynamic blood samples collection schedules.
6. Refer to Section 6.8 for detailed description of tumor tissue samples collection. If archival tissue is not available, baseline tumor biopsy should be performed. Paired biopsy is mandatory for subjects enrolled in the Expanded and Food-effect Cohorts.
7. Refer to Sections 6.7 and Appendix 6 for tumor evaluation description (Baseline, C3D1, C5D1, etc., and End of Treatment)
8. Unless tumor evaluation/measurement has been performed within 28 days prior to the first dose of ARQ 087

Appendix 1: Schedule of Assessments continued

Part 2: Expanded Cohort									
Tests & Procedures	**Pre-Study Visit(s)**	**Weekly Visits**						**End of Treatment Visit**	**30-day Safety Follow-up**
	Baseline	**Cycle 1**				**Cycle 2+**			
Week		**1**	**2**	**3**	**4**	**1**	**3**	**~7 days after the last dose of ARQ 087**	**~30 days after the last dose of ARQ 087**
Day	**0**	**1**	**8**	**15**	**22**	**1**	**15**		
Window	**-21 – 0**	**0**	**± 3 days**			**± 3 days**		**+3 days**	**±3 days**
Written Informed Consent	X								
Medical History	X								
Physical Examination[1]	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	
Vital Signs, Weight[2]	X	X	X	X	X	X	X	X	
Hematology[3]	X	X	X	X	X	X	X	X	
Blood Chemistry[3]	X	X	X	X	X	X	X	X	
Liver Function Tests[3]	X	X	X	X	X	X	X	X	
Coagulation tests[3]	X							X	
	X							X	
Urinalysis[3]	X	X		X		X		X	
Serum Pregnancy Test[3]	X							X	
Tumor Markers, if applicable	X	X				X		X	
12-Lead ECG[4]	X	X		X		X		X	
Echocardiography or MUGA, if applicable[4]	X					X		X	
Pharmacodynamics[5]		X	X	X	X	X		X	

Part 2: Expanded Cohort									
Tests & Procedures	**Pre-Study Visit(s)**	**Weekly Visits**						**End of Treatment Visit**	**30-day Safety Follow-up**
	Baseline	**Cycle 1**				**Cycle 2+**			
Week		**1**	**2**	**3**	**4**	**1**	**3**	**~7 days after the last dose of ARQ 087**	**~30 days after the last dose of ARQ 087**
Day	**0**	**1**	**8**	**15**	**22**	**1**	**15**		
Window	**-21 – 0**	**0**	**± 3 days**			**± 3 days**		**+3 days**	**±3 days**
Archival and/or Fresh Tumor Biopsy(optional)[6]	X				X				
Tumor's genomic status, if unknown[6]	X								
Tumor Measurement and Staging[7]	X[8]					X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	
Adverse Events Assessment		X	X	X	X	X	X	X	X
ARQ 087 Dispensation		X	X	X	X	X	X		

1. Physical examination, including mucous membrane and skin
2. Weight at Baseline visit, on Day 1 and Day 15 of Cycle 1, on Day 1 of each subsequent cycle, and End of Treatment visit.
3. Refer to Section 6.4 for description of laboratory assessments
4. Refer to Section 6.3 for detailed description of assessments (if applicable, Echocardiography or MUGA should be performed at Baseline and End of Treatment. If clinically indicated the test may be done at any time during the study treatment.)
5. Refer to Sections 6.6 for pharmacodynamic blood samples collection schedules.
6. Refer to Section 6.8 for detailed description of tumor tissue samples collection. If archival tissue is not available, baseline tumor biopsy should be performed. Paired biopsy is optional for subjects enrolled in the Expanded Cohort.
7. Refer to Sections 6.7 and Appendix 6 for tumor evaluation description (Baseline, C3D1, C5D1, etc., and End of Treatment)
8. Unless tumor evaluation/measurement has been performed within 28 days prior to the first dose of ARQ 087

APPENDIX 2: PERFORMANCE STATUS

ECOG Performance Status Scale	
Grade	Descriptions
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: PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING SCHEDULES

Blood Collection Schedule for Pharmacokinetic Assessment: Cohorts 1-4			
DAY	**Procedure**	**Sample**	**Desired Time**
TREATMENT PERIOD 1: DAY 1 (single dose administration)			
1	Draw blood sample	PK	0 hour (prior to ARQ 087 administration)
1	Draw blood sample	PK	1 (±10 min) hour
1	Draw blood sample	PK	2 (±15 min) hours
1	Draw blood sample	PK	4 (±15 min) hours
1	Draw blood sample	PK	6 (±15 min) hours
1	Draw blood sample	PK	8 (±15 min) hours
1	Draw blood sample	PK	10 (±15 min) hours
1	Draw blood sample	PK	12 (±15 min) hours
TREATMENT PERIOD 1: DAY 2 (single dose administration)			
2	Draw blood sample	PK	24 hours (±2 hrs) (post ARQ 087 administration)
TREATMENT PERIOD 1: DAY 3 (single dose administration)			
3	Draw blood sample	PK	48 hours (±2 hrs) (post ARQ 087 administration)
TREATMENT PERIOD 1: DAY 4 (single dose administration)			
4	Draw blood sample	PK	72 hours (±2 hrs) (post ARQ 087 administration)
TREATMENT PERIOD 2: CYCLE 1 DAY 8 (continuous dosing)			
8	Draw blood sample	PK	Prior to ARQ 087 administration on Day 8
TREATMENT PERIOD 2: CYCLE 1 DAY 15 (continuous dosing)			
15	Draw blood sample	PK	Prior to ARQ 087 administration on Day 15
TREATMENT PERIOD 2: CYCLE 1 DAY 22* (continuous dosing)			
22	Draw blood sample	PK	0 hour (prior to ARQ 087 administration)
22	Draw blood sample	PK	1 (±10 min) hour
22	Draw blood sample	PK	2 (±15 min) hours
22	Draw blood sample	PK	4 (±15 min) hours
22	Draw blood sample	PK	6 (±15 min) hours
22	Draw blood sample	PK	8 (±15 min) hours
22	Draw blood sample	PK	10 (±15 min) hours
22	Draw blood sample	PK	12 (±15 min) hours
TREATMENT PERIOD 2: CYCLE 1 DAY 23* (continuous dosing)			
23	Draw blood sample	PK	24 hours (±2 hrs) (post ARQ 087 administration on Day 22 and prior to ARQ 087 administration on Day 23)

* Because Cycle 1 Day 22 and Day 23 visits are days when the full PK is performed, subjects enrolled in **Cohort 1** (25 mg every other day), Cycle 1 Week 4 visits should be scheduled on the day of ARQ 087 administration and next consecutive day, when drug is not taken, e.g., Cycle 1 Day 21 and Day 22 or Cycle 1 Day 23 and Day 24.

Blood Collection Schedule for Pharmacokinetic Assessment: Cohorts 5-10 and Food-effect Cohort*			
CxDx	**Procedure**	**Sample**	**Desired Time**
CYCLE 1 DAY 1			
C1D1	Draw blood sample	PK	0 hour (prior to ARQ 087 administration)
C1D1	Draw blood sample	PK	1 (±10 min) hour
C1D1	Draw blood sample	PK	2 (±15 min) hours
C1D1	Draw blood sample	PK	4 (±15 min) hours
C1D1	Draw blood sample	PK	6 (±15 min) hours
C1D1	Draw blood sample	PK	8 (±15 min) hours
C1D1	Draw blood sample	PK	10 (±15 min) hours collect up through Food-effect Cohort then optional for Expanded Cohort
C1D1	Draw blood sample	PK	12 (±15 min) hours collect up through Food-effect Cohort then omit for Expanded Cohort
CYCLE 1 DAY 2			
C1D2	Draw blood sample	PK	24 hours (±2 hrs) (post ARQ 087 administration on Day 1 and prior to ARQ 087 administration on Day 2) collect up through Food-effect Cohort then omit for Expanded Cohort
CYCLE 1 DAY 8			
C1D8	Draw blood sample	PK	Prior to ARQ 087 administration on Day 8
CYCLE 1 DAY 15			
C1D15	Draw blood sample	PK	Prior to ARQ 087 administration on Day 15
CYCLE 1 DAY 22			
C1D22	Draw blood sample	PK	0 hour (prior to ARQ 087 administration)
C1D22	Draw blood sample	PK	1 (±10 min) hour
C1D22	Draw blood sample	PK	2 (±15 min) hours
C1D22	Draw blood sample	PK	4 (±15 min) hours
C1D22	Draw blood sample	PK	6 (±15 min) hours
C1D22	Draw blood sample	PK	8 (±15 min) hours
C1D22	Draw blood sample	PK	10 (±15 min) hours collect up through Food Effect cohort then optional for Expanded cohort
C1D22	Draw blood sample	PK	12 (±15 min) hours collect up through Food-effect Cohort then omit for Expanded Cohort

Blood Collection Schedule for Pharmacokinetic Assessment: Cohorts 5-10 and Food-effect Cohort*			
CxDx	**Procedure**	**Sample**	**Desired Time**
CYCLE 1 DAY 23			
C1D23	Draw blood sample	PK	24 hours (±2 hrs) (post ARQ 087 administration on Day 22 and prior to ARQ 087 administration on Day 23)
CYCLE 2 DAY 1 (and all subsequent cycles)			
CxD1	Draw blood sample	PK	Prior to ARQ 087 administration on Day 1
CYCLE 2 DAY 15 (and all subsequent cycles)			
CxD15	Draw blood sample	PK	Prior to ARQ 087 administration on Day 15
END OF TREATMENT			
EOT	Draw blood sample	PK	

* 1. Subjects enrolled in the Food-effect Cohort should take ARQ 087 with their morning meal
2. PK samples may be collected from up to 10 subjects enrolled in the Expanded Cohort

TUMOR TISSUE BIOPSY AND BLOOD COLLECTION SCHEDULES FOR PART 1: DOSE ESCALATION

Tumor Tissue Biopsy Schedule for Pharmacodynamic Assessment: Cohorts 1-4			
Day	**Procedure**	**Sample**	**Desired Time**
BASELINE			
-21 – 0 days	Tumor biopsy	TB-01	0 (prior to ARQ 087 administration)
TREATMENT PERIOD 1 DAY 1 or TREATMENT PERIOD 2, CYCLE 1 DAY 1			
Tx Period 1, Day 1 or Tx Period 2, Cycle 1 Day 1	Tumor biopsy	TB-02	Tx Period 1, Day 1 or Tx Period 2, Cycle 1 Day 1 (4-6 hrs after ARQ 087 administration)

Tumor Tissue Biopsy Schedule for Pharmacodynamic Assessment: Cohorts 5-10 and Food-effect Cohort			
Day	**Procedure**	**Sample**	**Desired Time**
BASELINE			
-21 – 0 days	Tumor biopsy	TB-01	0 (Prior to ARQ 087 administration)
CYCLE 1 DAY 22 – CYCLE 2 DAY 1			
C1D22-C2D1 (post-treatment biopsy)	Tumor biopsy	TB-02	At least 1 hr after ARQ 087 administration
Optional (additional) Biopsies			
>C3D1 (post-treatment biopsy)	Tumor biopsy	TB-03	At least 1 hr after ARQ 087 administration

Blood Collection Schedule for Pharmacodynamic Assessment: Cohorts 5-10 and Food-effect Cohort			
CxDx	**Procedure**	**Sample**	**Desired Time**
CYCLE 1 DAY 1			
C1D1	Draw blood sample	PD-01	Prior to ARQ 087 administration
C1D8	Draw blood sample	PD-02	Prior to ARQ 087 administration
C1D15	Draw blood sample	PD-03	Prior to ARQ 087 administration
C1D22	Draw blood sample	PD-04	Prior to ARQ 087 administration
CYCLE 2 DAY 1			
C2D1	Draw blood sample	PD-05	Prior to ARQ 087 administration
CYCLE 3 DAY 1			
C3D1	Draw blood sample	PD-06	Prior to ARQ 087 administration
CYCLE 4 DAY 1			
C4D1	Draw blood sample	PD-07	Prior to ARQ 087 administration
CYCLE 5 DAY 1			
C5D1	Draw blood sample	PD-08	Prior to ARQ 087 administration

TUMOR TISSUE BIOPSY AND BLOOD COLLECTION SCHEDULES FOR PART 2: EXPANDED COHORT

Tumor Tissue Biopsy Schedule for Pharmacodynamic Assessment (optional)			
Day	**Procedure**	**Sample**	**Recommended Time**
ARCHIVAL TISSUE			
-21 – 0 days			Should be collected prior to Cycle 1 Day 1
PAIRED BIOPSY (optional)			
BASELINE			
-21 – 0 days	Tumor biopsy	TB-01	0 (Prior to ARQ 087 administration)
CYCLE 1 DAY 22 – CYCLE 2 DAY 1			
C1D22-C2D1 (post-treatment biopsy)	Tumor biopsy	TB-02	At least 1 hr after ARQ 087 administration
Optional (additional) Biopsies			
> C3D1 (post-treatment biopsy)	Tumor biopsy	TB-03	At least 1 hr after ARQ 087 administration

Blood Collection Schedule for Pharmacodynamic Assessment			
CxDx	**Procedure**	**Sample**	**Desired Time**
CYCLE 1 DAY 1			
C1D1	Draw blood sample	PD-01	Prior to ARQ 087 administration
CYCLE 2 DAY 1			
C2D1	Draw blood sample	PD-02	Prior to ARQ 087 administration
CYCLE 3 DAY 1			
C3D1	Draw blood sample	PD-03	Prior to ARQ 087 administration
CYCLE 4 DAY 1			
C4D1	Draw blood sample	PD-04	Prior to ARQ 087 administration
CYCLE 5 DAY 1			
C5D1	Draw blood sample	PD-05	Prior to ARQ 087 administration
CYCLE 6 DAY 1			
C6D1	Draw blood sample	PD-06	Prior to ARQ 087 administration

APPENDIX 4: EXAMPLES OF IN VIVO SUBSTRATES, INHIBITORS AND INDUCERS FOR SPECIFIC CYP ENZYMES FOR STUDY

CYP1A2 Ligands

Following is a table of selected substrates, inducers and inhibitors of CYP1A2.

Inhibitors of CYP1A2 can be classified by their potency, such as:

- **Strong inhibitor** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate inhibitor** being one that causes at least a 2-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- **Weak inhibitor** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Selected Inducers, Inhibitors, and Substrates of CYP1A2

Substrates	Inhibitors	Inducers

• many antidepressants
  ○ amitriptyline (tricyclic antidepressant)
  ○ clomipramine (tricyclic antidepressant)
  ○ imipramine (tricyclic antidepressant)
  ○ agomelatine
• some atypical antipsychotics
  ○ clozapine
  ○ olanzapine
• haloperidol (typical antipsychotic)
• caffeine (stimulant)
• ropivacaine (local anaesthetic)
• theophylline (xanthine, in respiratory diseases)
• zolmitriptan (serotonin receptor agonist)
• melatonin (antioxidant, sleep-inducer)
• tamoxifen (SERM)
• erlotinib (Tarceva, a tyrosine kinase inhibitor)
• cyclobenzaprine (muscle relaxant, depressant)
• estradiol (in hypoestrogenism)
• fluvoxamine (SSRI antidepressant)
• mexiletine (antiarrhythmic agent)
• naproxen (NSAID)
• ondansetron (5-HT3 antagonist)
• phenacetin (analgesic)
	Strong:
	• ciprofloxacin (fluoroquinolone bactericidal)
	• many other fluoroquinolones (broad-spectrum antibiotics)
	• fluvoxamine (SSRI antidepressant)
	• verapamil (calcium channel blocker)
	Weak
	• cimetidine (H2-receptor antagonist)
	Unspecified potency:
	• amiodarone (antiarrhythmic agent)
	• interferon (antiviral, antiseptic, antioncogenic)
	• methoxsalen (in psoriasis)
	• mibefradil (calcium channel blocker)
	Some foods
	○ grapefruit juice (its bitter flavanone naringenin)
	○ cumin
	○ turmeric
		• tobacco
		• **Some foods**
		  ○ broccoli
		  ○ brussels sprouts
		  ○ chargrilled meat
		  ○ cauliflower
		  ○ cauliflower
		• insulin (in diabetes)
		• methylcholanthrene (carcinogen)
		• modafinil (eugeroic)
		• nafcillin (beta-lactam antibiotic)
		• beta-Naphthoflavone (chemopreventive)
		• omeprazole (proton pump inhibitor)

Substrates	Inhibitors	Inducers
• paracetamol (analgesic, antipyretic) • propranolol (beta blocker) • riluzole (in amyotrophic lateral sclerosis) • tacrine (parasympathomimetic) • tizanidine (α-2 adrenergic agonist) • verapamil (calcium channel blocker) • warfarin (anticoagulant) • zileuton (in asthma)		

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

CYP2D6 Ligands

Following is a table of selected substrates, inducers and inhibitors of CYP2D6. Where classes of agents are listed, there may be exceptions within the class. Inhibitors of CYP2D6 can be classified by their potency, such as:

- **Strong inhibitor** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate inhibitor** being one that causes at least a 2-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- **Weak inhibitor** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Selected Inducers, Inhibitors, and Substrates of CYP2D6

Substrates ↑ = bioactivation by CYP2D6	Inhibitors	Inducers

• All tricyclic antidepressants, e.g.
  ○ imipramine
  ○ amitriptyline
  ○ etc.
• Most SSRIs (antidepressant), e.g.
  ○ fluoxetine
  ○ paroxetine
  ○ fluvoxamine
• venlafaxine (SNRI antidepressant)
• mianserin (tetracyclic antidepressant)
• opioids
  ○ codeine↑ into morphine
  ○ tramadol↑
  ○ oxycodone
• antipsychotics, e.g.
  ○ haloperidol
  ○ risperidone
	Strong:
	• SSRIs
	  ○ fluoxetine
	  ○ paroxetine
	• bupropion (non-SSRI antidepressant)
	• quinidine (class I antiarrhythmic agent)
	• cinacalcet (calcimimetic)
	• ritonavir (antiretroviral)
	Moderate
	• sertraline (SSRI)
	• duloxetine (SNRI
		• dexamethasone (glucocorticoid)
		• rifampicin (bactericidal)
		Strong:
		• glutethimid

Substrates ↑ = bioactivation by CYP2D6	Inhibitors	Inducers
○ perphenazine ○ thioridazine ○ zuclopenthixol ○ iloperidone ○ aripiprazole ○ chlorpromazine ○ levomepromazine ○ remoxipride • minaprine (RIMA antidepressant) • tamoxifen↑ (SERM) • beta-blockers ○ metoprolol ○ timolol ○ alprenolol ○ carvedilol ○ bufuralol ○ nebivolol ○ propranolol • debrisoquine (antihypertensive) • Class I antiarrhythmics ○ flecainide ○ propafenone ○ encainide ○ mexiletine ○ lidocaine ○ sparteine • ondansetron (antiemetic) • donepezil (acetylcholinesterase inhibitor) • phenformin (antidiabetic) • tropisetron (5-HT3 receptor antagonist) • amphetamine (in ADHD, narcolepsy) • atomoxetine (in ADHD) • chlorphenamine (antihistamine) • dexfenfluramine (serotoninergic anorectic) • dextromethorphan (antitussive) into psychoactive dextrorphan • duloxetine (SNRI) • metoclopramide (dopamine antagonist) • Methoxyamphetamine • perhexiline (antianginal agent) • phenacetin (analgesic) • promethazine (antihistamine antiemetic)	• terbinafine (antifungal) **Weak**: • buprenorphine (in opioid addiction) • amiodarone (antiarrhythmic) • cimetidine (H2-receptor antagonist) **Unspecified potency**: • antipsychotics ○ haloperidol ○ perphenazine ○ thioridazine ○ zuclopenthixol ○ risperidone ○ chlorpromazine • bicalutamide • hyperforin (St. Johns Wort) • antihistamines (H1-receptor antagonists) ○ Promethazine ○ chlorphenamine ○ diphenhydramine ○ hydroxyzine ○ tripelennamine • some SSRI antidepressants ○ citalopram ○ escitalopram • clemastine (antihistamine and anticholinergic) • celecoxib (NSAID) • clomipramine (tricyclic antidepressant) • cocaine (stimulant) • doxorubicin (chemotherapeutic) • metoclopramide (antiemetic, prokinetic) • methadone (analgesic and anti-addictive) • moclobemide (antidepressant) • ranitidine (H2-receptor antagonist) • doxepin (tricyclic antidepressant, anxiolytic) • halofantrine (in malaria) • levomepromazine (antipsychotic) • mibefradil (calcium channel blocker) • midodrine (α_1 agonist) • ticlopidine↓ (antiplatelet)	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

APPENDIX 5: EXAMPLES OF IN VIVO SUBSTRATES, INHIBITORS AND INDUCERS OF P-GLYCOPROTEIN

Examples of In Vivo Substrates, Inhibitors and Inducers of P-glycoprotein[1]

Transporter	Substrates	Inhibitors(2)	Inducers(3)
P-gp (Gene *ABCB1*)	Aliskiren ambrisentan colchicine dabigatran etexilate digoxin everolimus fexofenadine imatinib lapatinib maraviroc, nilotinib posaconazole ranolazine saxagliptin sirolimus sitagliptin talinolol tolvaptan topotecan	Amiodarone azithromycin(4) captopril carvedilol clarithromycin conivaptan cyclosporine diltiazem dronedarone erythromycin(5) felodipine itraconazole ketoconazole(4) lopinavir and ritonavir quercetin(4) quinidine ranolazine ticagrelor verapamil	Avasimibe(6) carbamazepine(7) phenytoin rifampin St John's wort(8) tipranavir/ritonavir

Source: Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

(1) Not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

(2) Inhibitors listed for P-gp are those that showed >25% increase in digoxin AUC or otherwise indicated if substrate is other than digoxin.

(3) Inducers listed for P-gp are those that showed >20% decrease in digoxin AUC or otherwise indicated if substrate is other than digoxin.

(4) Inhibitors listed are those that showed >25% increase in fexofenadine AUC.

(5) Inhibitors listed are those that showed >25% increase in talinolol AUC.

(6) Not a marketed drug.

(7) Inducers listed are those that showed >20% decrease in fexofenadine AUC.

(8) Herbal product.

APPENDIX 6: ASSESSMENT OF ANTI-TUMOR ACTIVITY

Assessment of tumor responses may be performed following the revised RECIST guidelines, version 1.1.[34] Some of these definitions and criteria are highlighted below.

Measurability of Tumor Baseline

- CT with IV contrast and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.
- All imaging methods should be performed according to institutional standards with each subject having consistency of methods beginning from baseline through the course of the study.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-Measurable

All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin (nevi) or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm diameter as assessed using calipers (e.g. skin (nevi) nodules). For the case of skin (nevi) lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only subjects with measurable disease at baseline should be included in the study.

Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a *maximum* of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of the diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of Target Lesions

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. In this study, the minimum duration for SD is defined as 8 weeks (± 2 days).

Special Notes on the Assessment of Target Lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each Response Criteria subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as

in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- *Complete Response (CR):* Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *Progressive Disease (PD):* Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special Notes on the Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Evaluation of New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging

modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI of the brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. No confirmatory measurement for CR or PR is required in this study.

The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. The table below provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Time Point Response: Subjects with Target (+/– non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, and NE = not evaluable.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline of 8 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at second the assessment, and does not meet the minimum duration for SD, the subject will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in the size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of 'zero' on the case report form (CRF).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at Baseline, and then in 8-week intervals while the subject is on treatment or as clinically indicated until progression of disease,

withdrawal of consent, death, or loss to follow-up. Tumor measurement will also be performed during the End-of-Treatment visit if it is not done within 28 days of the visit date.

Baseline tumor assessments must be performed within four weeks (28 days) of the first dose of treatment.

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

The radiological 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 sites are evaluated at each time point of tumor assessment.

Confirmatory Measurement/Duration of Response

Confirmation

Confirmation of PR and CR is NOT required in this study.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria that are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). In this study, the minimum duration for SD is defined as 8 weeks (±3 days).

SPONSOR SIGNATURE

Study Title: A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with FGFR Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with FGFR2 Gene Fusion

Study Number: ARQ 087-101

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:

Signed [redacted] Date: 10 APR 2015

VP Regulatory Affairs and Quality Assurance
ArQule, Inc.

Signed: [redacted] Date: 10 Apr 2015

Chief Medical Officer
ArQule, Inc.

INVESTIGATOR'S SIGNATURE

Study Title: A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with FGFR Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with FGFR2 Gene Fusion

Study Number: ARQ 087-101

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: _____