Statistical Analysis Plan

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

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SIGNATURES

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

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7/11/2018

Date

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10 July 2018

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Date

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1 LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase (SGPT/serum glutamic-pyruvic transaminase)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT/serum glutamic oxaloacetic transaminase)
ATC	Anatomical Therapeutic Chemical Classification
AUC $_{0\text{-inf}}$	Area under the concentration–time curve from hour 0 to infinity
AUC $_{0\text{-t}}$	Area under the concentration–time curve from time 0 up to the last measurable sampling time
BID	Twice daily
Cmax	Maximum plasma drug concentration
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP 450	Cytochrome P450
DCR	Disease control rate
dL	Deciliter
DLT	Dose limiting toxicity
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EOT	End of treatment
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
iCCA	Intrahepatic cholangiocarcinoma

kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	Millimeter
MTD	Maximum tolerated dose
ORR	Overall response rate
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PS	Performance status
QD	Once daily
QOD	Every other day
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
STDM	Study data tabulation model
$t_{1/2}$	Elimination half-life
T_{max}	Time to maximum plasma concentration
TEAE	Treatment emergent adverse event

2 INTRODUCTION

This document describes the detailed statistical methodology applied in analyzing data of the study ARQ 087-101. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock.

The material presented in this section is based on the trial protocol version 5.0, dated 10 April, 2015. This plan may be revised during the study to accommodate protocol amendments.

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective 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 intrahepatic cholangiocarcinoma (iCCA) with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding).

2.1.2 Secondary Objective

- 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.

2.1.3 Exploratory Objective

- 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.

2.2 Overview of Study Design

2.2.1 Dose Schemes

This is an open-label phase 1/2 study of ARQ 087 in adult subjects with advanced solid tumors that has been in enrolled in two parts. Part 1 enrolled subjects with solid tumors and Part 2 only enrolled subjects with FGFR genetic alterations, including intrahepatic cholangiocarcinoma with FGFR2 gene fusion. Treatment will be initiated at a dose level of 25 mg/QOD (every other day).

Part 1: Dose Escalation Cohorts

In cohorts 1-4, treatment consisted 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).

Given the long half-life (about 1 week) of ARQ 087 in human subjects and the length of time (about 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 consisted of a single treatment period of continuous dosing that ceased at the subject's discontinuation from the study.

The Maximum tolerated dose (MTD) was defined as the dose level at which no more than one subject with a DLT was observed among six subjects. Once the MTD was determined, up to six additional subjects might be treated at this dose level of ARQ 087. If the MTD was not reached, dose escalation would have to proceed with the purpose of determining a RP2D of ARQ 087.

Part 2: Expanded Cohort

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. Approximately 50-60 subjects with advanced solid tumors with FGFR genetic alterations, including iCCA with FGFR2 gene fusion planned to be enrolled in expanded cohort. The tumor type eligibility was to 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) was not achieved, such tumor sub-cohort would have to be closed for further enrollment.

There were 11 dose cohorts (Part 1 and Part 2) as listed below (see Table 1).

Table 1: Dosing Guidelines for ARQ 087

Part/Period	Cohort	Total Daily Dose [a]	Dose per Administration	Number of Subjects
Part 1/Period 1	1[a]	25 mg	1 cap x 25 mg x qod	3-6[b]
Part 1/Period 1	2	25 mg	1 cap x 25 mg x qd	3-6[b]
Part 1/Period 1	3	50 mg	2 caps x 25 mg x qd	3-6[b]
Part 1/Period 1	4	100 mg	1 caps x 100 mg x qd	3-6[b]
Part 1/Period 2	5*	150 mg	2 caps x 25 mg & 1cap x 100 mg x qd	3-6[b]
Part 1/Period 2	6	200 mg	2 caps x 100 mg x qd	3-6[b]
Part 1/Period 2	7	250 mg	2 caps x 25 mg & 2 caps x 100 mg x qd	3-6[b]
Part 1/Period 2	8	325 mg	1 cap x 25 mg & 3 caps x 100 mg x qd	3-6[b]
Part 1/Period 2	9	425 mg	1 cap x 25 mg & 4 caps x 100 mg x qd	3-6[b]
Part 1/Period 2	Food-effect[a]	400 mg	4 caps x 100 mg qd	at least 6
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 followed a modified Fibonacci scheme (increase by 50%, 30%, and 25%). To avoid potential non-compliance due to capsule burden, the dose escalation was supposed to be stopped at the dose level of 550 mg/daily

[a] Total daily dose must be administered one hour prior 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 were further evaluated in the Expanded Cohort.

2.2.2 Schedule of Assessments

Safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ARQ 087 were assessed for the duration of the study.

Detailed assessment plans are listed in table 2 (Part 1: Cohort 1-4), table 3 (Part 1: Cohorts 5-10 and Food-effect Cohort) and table 4 (Part 2: Expanded Cohort).

Table 2: 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				
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

Table 3: Schedule of Assessments (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	
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 Section 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 Cohort 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

Table 4: Schedule of Assessments (Part 2: Expanded 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**	**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	
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	
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	
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 Section 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 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

3 DEFINITIONS AND DATA PROCESSING RULES

3.1 Definitions

3.1.1 Study Drug and Treatment Group

Study drug refers to ARQ 087.

11 cohorts with different dose and frequency are designed and used in this study, for analyses, cohorts will be grouped into four treatment groups as below:

- Low Dose Group (25 mg QOD – 200 mg QD)
- Middle Dose Group (250 mg QD – 325 mg QD)
- High Dose Group (400 mg QD – 425 mg QD)
- Expanded Cohort Group (300 mg QD)

3.1.2 Study Day

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

For days on or after start date of study drug:

Study day = the date of the event (visit date, onset date of an event, assessment date etc.) - start date of study drug + 1.

The first day of study drug is therefore study Day 1. Example: If the start of study drug is on 01JAN2013 and start date of an adverse event is on 05JAN2013, then the study day of the adverse event onset is 5.

For days prior to start date of study drug the study day is negative:

Study Day = event date - start date of study drug.

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

3.2 Analysis Variables

3.2.1 Demographic and Baseline Variables

Demographics and baseline characteristics will include but not limit to:

- Demographics
- Baseline disease characteristics

- Clinically significant medical history, including surgeries
- Prior therapies
- Concomitant medications and treatments

3.2.2 Safety Variables

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

3.2.3 Pharmacokinetics and Pharmacodynamic Variables

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

PD parameters include phosphate, glucose, FGF, 19, 21, and/or 23 from blood sample.

3.2.4 Efficacy Variables

Best Overall Response (BOR)

The best overall response is determined once all the data for the subject is known. No confirmatory measurement for CR or PR is required in this study. The best overall response is defined as the best response (in the order of CR, PR, SD, and PD) among all overall responses recorded from the start of treatment until the last radiographic tumor assessment (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, 8 weeks (±3). 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 first assessment, PD at second and not meeting minimum duration of SD will have a best response of PD. The same subject lost to follow-up after the first assessment would be considered non-evaluable.

Objective Response Rate (ORR)

For purposes of determining the objective response rate (ORR), tumor response will be based on the best overall response recorded for each subject from the date of first dose. The ORR will be calculated as the number of subjects with a complete or partial response divided by the total number of subjects [ORR= (CR+PR)/# subjects].

Disease Control Rate (DCR)

Disease Control Rate (DCR) is defined as the proportion of subjects with the best overall responses of CR, PR and SD [DCR= (CR+PR+SD)/# subjects].

Duration of Objective Response

Duration of objective response is defined as the time from the date of the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is documented.

If a subject is discontinued, dies, or is lost to follow-up with no documentation of progressive disease, duration of response is defined as the time from the date of the first documentation of objective response to the date of the last tumor assessment as a censored value. Duration of response will be measured for responding subjects (PR or CR) only.

Duration of Stable Disease

Duration of stable disease is defined as the time from the start of the treatment until the criteria for disease progression are met.

If a subject is discontinued or dies, or is lost to follow-up with no documentation of progressive disease, duration of stable disease is defined as the time from the date of first dose to the date of the last tumor assessment as a censored value. Duration of stable disease is measured for any subject who has best overall response of SD.

Progression-Free Survival (PFS)

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

If a subject is discontinued from study due to reasons other than radiographic disease progression or death, PFS is censored as the time from the date of first dose to the date of the last tumor assessment. Only assessments with CR, PR SD or NE as overall tumor response are treated as last tumor assessment.

If a subject has no baseline tumor assessment and/or has no post baseline tumor assessment, this subject is to be censored at the date of first dose for PFS.

4 STATISTICAL ANALYSIS POPULATIONS

Four populations are considered in the statistical analysis of the study. The treatment cohort assignment for analyses on all populations will be based on the dose they received.

4.1 Enrolled Population

Subjects who enrolled in ARQ 087-101 study are included in the enrolled population.

4.2 Safety Population

Subjects who received any amount of ARQ 087 are included in the safety population.

4.3 Pharmacokinetic Population

Subjects who received at least one dose of ARQ 087 and who had an evaluable ARQ 087 pharmacokinetic profile on first day (Week 0 Day 1/Cycle 1 Day 1) and/or last day (Cycle 1 Day 22/23) in treatment cycle 1 are included in PK population.

4.4 Evaluable Population

Subjects who have received at least one cycle of study treatment and have at least one post-baseline tumor evaluation are included in the evaluable population.

5 STATISTICAL METHODS AND DATA ANALYSIS

5.1 Determination of Sample Size

No formal statistical tests of hypotheses will be performed in this study. The exact number of subjects estimated for this study depends on the number of cohorts investigated based on the toxicity encountered. It is expected that approximately 60-120 subjects will be enrolled in this study.

5.2 General Statistical Considerations

All summary tables will include all subjects from cohort 1 to the last cohort enrolled and be presented by treatment groups, including low dose group (25 mg QOD – 200 mg QD), middle dose group (250 mg QD – 325 mg QD), high dose group (400 mg QD - 425 mg QD), expanded (RP2D) cohort (300 mg QD) and Overall.

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.

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

5.3 Visit Window Rules

If there are multiple measurements/samples within the same post-baseline visit, the last measurement/sample within the visit (sorted by date and as available by time or repeat measurements) will be used in the analysis by visit or overall. For any analyses, only scheduled visits will be included except for using value form unscheduled visit as baseline if needed.

5.4 Statistical Method

5.4.1 Subject Disposition

The number and percentage of subjects will be presented for enrolled population, safety population, PK population and evaluable population.

Subject disposition information and reasons for discontinuation (as reported on eCRF) will be summarized per treatment groups and overall for all enrolled subjects. A listing will be presented for data relevant to subject disposition.

5.4.2 Demographic and Baseline Characteristics

Demographic Characteristics

Demographic characteristics will be summarized per treatment groups and overall in the safety population. Demographic characteristics include age, age groups (<65, ≥65), gender, race, ethnicity, ECOG performance status, height, weight.

Baseline Disease Characteristics

For current cancer history, including cancer type, cancer stage at diagnosis and study entry, summary statistics will be presented for safety population by each treatment group and overall. Current cancer types will be categorized into Adrenal Cortical Carcinoma, Lung Cancer, Colorectal Cancer, Ovarian Cancer, Breast Cancer, Intrahepatic Cholangiocarcinoma, Urothelial Carcinoma and other. In additional, the 95% confidence interval for percent of subjects in each cancer type will be estimated from binomial distribution.

Prior Cancer Therapies

Prior cancer therapies for current cancers are composed of prior surgery, systemic therapy and radiotherapy. Descriptive summary statistics on prior cancer therapies, including any prior cancer therapies (surgery/radiotherapy/systemic therapy) and regiment number of systemic therapy will be presented for safety population by each treatment group and overall. Individual subject listings for prior surgery, systemic therapy and radiotherapy will also be presented.

Prior and Concomitant Medications

Prior medication is defined as any medication taken within 30 days of the stating of ARQ 087 and ending prior to the start of study treatment.

Concomitant medication is defined as any medication besides the study treatment that was administered to a subject coinciding with the study assessment period.

Descriptive summary statistics on the prior and concomitant medications will be presented for safety populations by each treatment group and overall in ATC class and preferred term.

In addition, the related listings will be presented.

5.4.3 Pharmacokinetic Analysis

Pharmacokinetic analysis of ARQ 087 plasma concentrations will be performed separately from this analysis plan, a separate PK report will be generated.

PK parameters of ARQ 087 (AUC0-t, AUC0-inf, Cmax and $t_{½}$) may be summarized using mean, standard deviation, median, coefficient of variation, minimum and maximum for the full PK assessments. For single PK time point assessments, only plasma concentrations of ARQ 087 will be presented.

If appropriate, logistic regression will be performed on tumor response (CR, PR and SD combined vs. PD) with each PK parameter (Cmax and AUC0-t at cycle 1 day 22/23) and assigned dose level as independent variable for safety and evaluable population; the logarithmic transformation will be applied to AUC and Cmax when conducting the logistic regression. The odds ratio and 95% confidence interval will be estimated for each covariate from logistic regression.

Separate sample collection listings for PK full assessment and single assessment of plasma by subject will also be provided for safety population.

5.4.4 Pharmacodynamic Analyses

Analysis of biomarkers FGF 19, 21, and/or 23 is performed outside of this statistical analysis plan. Separate report will be prepared.

Summary statistics including mean, standard deviation, median, minimum and maximum for baseline, each post-baseline measurement, and change from baseline will be performed for glucose and phosphate levels for safety population.

5.4.5 Efficacy Analyses

Efficacy analysis will be performed based on both safety and evaluable populations.

Objective Response Rate and Disease Control Rate

The best overall tumor response (CR, PR, SD, PD and not evaluable), objective response rate and disease control rate will be tabulated by treatment group and overall on the safety population and evaluable population. The percent of subjects in each treatment group will be provided along with the 95% confidence interval of the percentage. In addition, the related listings will also be presented.

Percent change from the minimum sum of longest diameters (including baseline, if that is the minimum value, up to the preceding tumor assessment) and the percent change from baseline for the sum of longest diameters will be computed in the listings for target lesions. A waterfall plot will also be utilized to display the relationship between minimum sum of longest diameters change and current cancer types.

Progression Free Survival

Progression free survival will be estimated based on Kaplan-Meier estimate (product limit) for both safety and evaluable population. The median PFS and the 95% confidence interval will be estimated, and the corresponding Kaplan-Meier plots will be also presented.

5.4.6 Exposure Analyses

Dosing and Extent of Exposure

Duration of exposure is defined as the total number of days on the study drug. The following algorithm will be used to calculate the duration of study treatment exposure for subjects who took at least one dose of ARQ 087:

Duration of exposure (days) = [(date of last administration of study treatment) – (date of first administration of study treatment) + 1]

Temporary drug discontinuation will be ignored. If the date of the last administration is unknown, the date until which the dispensed drug should last without counting any extra drug provided will be used.

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 safety of ARQ 087, replacement of non-compliant subjects will be allowed during the first 28 days of dosing.

Compliance will be calculated using the following equation:

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

This treatment compliance will be summarized for safety population per treatment groups and overall.

5.4.7 Analyses of Safety Variables

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

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

Adverse Events

Adverse events will be evaluated for severity using NCI-CTCAE, version 4.03. AE summaries will include treatment-emergent adverse events (TEAEs).

A TEAE is defined as:

- an AE which is not present prior to the first dose of ARQ 087 and started after taking the study drug during the treatment period or within 30 days after the last dose of the study drug;
- an AE which is present prior to the first dose of ARQ 087 and increased in severity after taking study drug during the treatment period or within 30 days after the last dose of study drug;
- an AE which is considered study drug-related regardless of the start date of the event.

All TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) Version 15.1 and summaries will be presented by system organ class and preferred term. Separate TEAE summaries will be generated for the following categories:

- All TEAEs
- Severe TEAEs (Grade 3 or higher)
- SAEs
- TEAEs related to study drug
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to treatment interruption then dose reduction
- TEAEs resulting in death
- TEAEs listed according to maximum severity
- TEAEs classified as DLTs

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

Separate TEAE summaries will be presented by system organ class, preferred term, and maximum CTCAE 4.03 grade. A subject with multiple CTCAE grades for the same TEAE will be summarized under the maximum CTCAE grade recorded for the event.

Laboratory Test

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

Toxicities will be graded according to the NCI CTCAE, Version 4.03. Shift table of toxicity grade for NCI CTCAE specified laboratory tests will also be presented in the safety population per treatment groups and overall.

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

If lab results contain symbols like "<", ">", "≥" or "≤", extract the numeric value as the limit, Example: if result is ">0.1", "0.1" will be used for analysis.

Vital Signs

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

Individual absolute vital sign values and the change from baseline will be summarized descriptively for each treatment group and overall, by schedule of assessments.

ECOG Performance Status

Number and percentage of subjects having each ECOG performance status level will be presented for baseline and each post-baseline measurement, per treatment groups and overall.

In addition, the shift table comparing post baseline to baseline will also be presented per treatment groups and overall.

12-lead ECG

12-lead ECG absolute individual parameters [PR interval, QRS interval, QT interval, QTcF interval, QTcB interval and Summary (Mean) Ventricular Rate] and the change from baseline will be summarized per treatment groups and overall per assessment. All ECG measurements will be presented in the data listings.

Physical Examination

Data from physical examinations will be presented in the data listings as per subject per visit per body system, using safety population.

6 CONVENTION FOR HANDLING PARTIAL AND MISSING DATES

6.1 Handling Partial Dates

6.1.1 Partial Tumor Assessment Dates for PFS

All dates for tumor assessment must be completed with day, month and year.

If one or more measurement dates (e.g. X-ray, CT-scan for target and non-target tumor lesions) are partial but other measurement dates are available, this/these partial date(s) are not considered for calculation of the assessment date.

6.1.2 Partial Dates for Clinical Events

Imputation will be only performed for partial dates in concomitant medication and prior cancer therapy, missing dates (date element is totally unknown) will not be imputed.

The following rules will be used to impute incomplete start and end date:

- Incomplete start date: assign 1 to missing day, January to missing month.
- Incomplete end date: assign the last date of the month (28/29/30/31) to missing day, December to missing month.
- If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be replaced with the start date.

6.1.3 Partial Dates for Adverse Events

No imputation will be applied for adverse events. AE with partial or missing dates will be categorized as treatment emergent unless there was sufficient specificity to the onset date to document that the event began before the first dose of study treatment. Incomplete AE start date as reported will be used to compare with the first dose date of study treatment to distinguish if it is a TEAE. Example: If the first dose date is 01FEB 2013 and incomplete start date for an AE is JAN2013, then this AE will not be treated as TEAE.

7 INTERIM ANALYSIS

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, otherwise, the enrollment will be stopped for lack of efficacy.

8 MULTIPLICITY

Since the interim analysis will be performed to determine if the trial should be stopped for futility only, there will be no adjustment for multiplicity.

9 CHANGES TO THE PLANNED ANALYSES

N/A.

10 REFERENCES

1. ARQ 087-101 Protocol Amendment 5 dated on 10 April, 2015.
2. RECIST 1.1 Eisenhauer et. al. (2009). New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) European Journal of Cancer 45 (2009) 228-24
3. NCI CTCAE version 4.03 http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

11 MOCK-UP TABLES AND LISTINGS OF APPENDICES

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

LIST OF FIGURE

LIST OF TABLES

LIST OF LISTINGS