REPORT SYNOPSIS

Name of Sponsor/Company: **ArQule, Inc.**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***
Name of Test Product: **ARQ 197 (AQ 3227197)**		
Name of Active Ingredient: (-)-*trans*-3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione		

Title of Study:	A Phase II Study of ARQ 197 in Patients with Microphthalmia Transcription Factor Associated Tumors
Phase of Development:	2
Study Period:	First patient first visit date: 05 Jan 2008 Last patient last follow-up date: 31 Aug 2010
Investigator(s):	University of California San Francisco, San Francisco, CA Steven DuBois, M.D. Cincinnati Children's Hospital Medical Center, Cincinnati, OH James Geller, M.D. University of Miami, Miami, FL John Goldberg, M.D. Princess Margaret Hospital-University Health Network, Toronto, ON Dr. David Hogg Premier Oncology, Santa Monica, CA Lee Rosen, M.D. Mary Crowley Medical Research Center, Dallas, TX Neil Nathan Senzer, M.D. Texas Children's Cancer Center, Houston, TX Patrick Thompson, M.D. Alberto S. Pappo, M.D. Institute of Cancer Research, London, UK Professor Ian Judson, M.A., M.B., B.Chir., M.D., F.R.C.P. Dana-Farber Cancer Institute, Boston, MA Andrew J. Wagner, M.D., Ph.D.
Study Center(s):	Cincinnati Children's Hospital Medical Center Division of Hematology/Oncology 3333 Burnett Avenue, MLC #7015 Cincinnati, OH 45229

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	University of California San Francisco 505 Parnassus Avenue, M647 San Francisco, CA 94143-0106 University of Miami Department of Pediatrics 1611 N.W. 12th Avenue ACC West 5th Floor Miami, FL 33136
Publication (reference):	Goldberg J, Demetri GD, Choy E, et al. Preliminary results from a phase II study of ARQ 197 in patients with microphthalmia transcription factor family (MiT)-associated tumors. J Clin Oncol 2009;27:abstr 10502. Wagner A, Demetri G, Choy E, et al. Preliminary results from a phase 2 study of ARQ 197 in patients with microphthalmia transcription factor family (MiT) associated tumors. Presented at the Annual Meeting of the 2009 Connective Tissue Oncology Society Meeting; November 26; Miami, FL; Oral presentation 39313. Available at http://www.ctos.org/meeting/2009/presentations/friday/39313.ppt. Accessed June 14 2011.
Study Objectives/Hypothesis:	Primary Objective: • Determine the overall response rate (ORR) in patients (Microphthalmia transcription factor associated [MiT] tumors) treated with ARQ 197. Secondary Objectives: • Evaluate progression-free survival (PFS) time in patients treated with ARQ 197. • Evaluate 6-month and 1-year overall survival (OS) rates in patients treated with ARQ 197 • Further characterize the safety of ARQ 197 in adolescent and young adult patients with MiT tumors. Exploratory Objective: • Assess biological tumor response using [^{18} F] fluorodeoxyglucose positron emission tomography (FDG-PET) scanning following treatment with ARQ 197. • Evaluate the pharmacodynamic change of phosphorylated c Met, total c-Met and downstream markers of c-Met signaling including apoptosis (TUNEL) and phosphorylated FAK in tumor tissue correlated with the administration of ARQ 197 (Deleted with Amendment 1, August 1, 2008)

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Study Design/Methodology:	This was a multi-center, single arm, two-stage phase II study in patients with MiT tumors. The study had a Simon 2-stage design. Under the original protocol dated 15 Aug 2007, during the first stage of the study, approximately 23 patients were to be enrolled and treated. If a partial response (PR) or a complete response (CR) was observed in more than one patient in the stage, the study was to be continued to the second stage, where an additional 22 patients were to be enrolled. Otherwise the study was to be stopped. The original protocol was amended (Amendment 1 dated August 1,2008) after a maximum tolerated dose (MTD) of ARQ 197 had been reached in a phase I study and a new recommended phase 2 dose (RP2D) of 360 mg BID was established. Under Amendment 1 dated August 1, 2008, sample size and stop rule were adjusted, thirty-nine evaluable patients (23 in first stage and 16 in second stage) were to be enrolled under this Amendment from up to 12 study sites. To account for a 10% dropout rate, 26 patients were to be enrolled during the first stage and 18 patients during the second stage. Among the 23 evaluable patients enrolled in the first stage of the study under this Amendment, if a PR or a CR was observed in one or more patients, the study was to be continued to the second stage, where an additional 16 evaluable patients were to be enrolled. Otherwise the study was to be stopped. Under the original protocol, eligible patients were treated with oral ARQ 197 at the dose of 120 mg twice daily (BID) until implementation of Amendment 1. Under Amendment 1, eligible patients were treated with oral ARQ 197 twice daily at dose of 360 mg BID. For patients enrolled under the original protocol, intra-patient dose escalation from 120 mg BID to 360 mg BID could occur. Patients could continue treatment at the current dose or the dose could be increased stepwise (from 120 mg BID to 240 mg BID, then to 360 mg BID after one cycle of treatment at a low dose in the absence of ≥ Grade 3 drug-related adverse events) if, in the opinion of the investigator, it was in the best interest of a patient, and the ArQule Medical Monitor was consulted.
Duration of Treatment for Individual Patient:	For an individual patient, treatment with ARQ 197 could continue until unacceptable toxicity, disease progression (clinical or radiological) or another discontinuation criterion was met. It was expected that most patients would receive between three and six cycles (28 days each) of ARQ 197 for a treatment period of 12 to 24 weeks. The duration of exposure ranged from 13 to 899 days.

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Number of Patients:	Planned: 26-44 Screened/Enrolled: 47 Treated: 47 Treatment Discontinued: 47
Diagnosis and Main Criteria for Study Entry:	The study enrolled adolescent and adult patients with confirmed MiT tumors. Patients had to meet all eligibility criteria to be enrolled. Main inclusion criteria: 1. Histologically or cytologically confirmed unresectable locally advanced or metastatic alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS) or translocation associated renal cell carcinoma (TLA-RCC) 2. ≥ 13 years old 3. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.0) 4. ECOG performance status 0 to 1 5. Adequate bone marrow, liver and renal functions Main exclusion criteria: 1. Received anti-cancer therapy including surgery, chemotherapy, radiotherapy and investigational drug within four weeks prior to first dose of ARQ 197 2. Pregnant or lactating 3. Central nervous system metastasis unless it was stable for ≥ 3 months after treatment and the patient had no neural symptoms 4. Significant gastrointestinal disorder(s), that in the opinion of the Investigator, could interfere with the absorption of ARQ 197 (e.g. Crohn's disease, ulcerative colitis, extensive gastric or small bowel resection) 5. Unable or unwilling to swallow ARQ 197 capsules daily 6. Any other significant co-morbid conditions that in the opinion of the Investigator would impair study participation or cooperation 7. Bradycardia at baseline or known history of arrhythmia (added with Amendment 1, August 1, 2008) 8. Received ARQ 197 previously (added with Amendment 1, August 1, 2008)

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Investigational Product and Comparator Information:

ARQ 197 Dosage Form: Capsule

Route of Administration: Oral

Lot No.:

8C022-P1	60 mg	Crystalline Form B
8H090-P1	60 mg	Crystalline Form B
8H091-P1	60 mg	Crystalline Form B
8M138-P1	60 mg	Crystalline Form B
7G092-P1	120 mg	Crystalline Form A
7K128-P1	120 mg	Crystalline Form A
7K128-P2	120 mg	Crystalline Form A

Packaging Information: The drug product was packaged in bottles of either 30 or 90 count capsules in various dosage forms and formulations as provided in the above list and completely described on the bottle labels.

Criteria for Evaluation:

Efficacy: Anti-tumor activity was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0). Objective response rates (ORR) and best overall response rates were determined.

Progression-free survival (PFS) was calculated as the time the patient was alive and progression free from the first date of ARQ 197 administration until disease progression per RECIST 1.0 or death due to any cause.

Overall survival time (OS) was calculated from the first date of ARQ 197 administration until death due to any cause.

Pharmacokinetics: PK of ARQ 197 was assessed through serial blood samples collected during Cycle 1 on Day 1 (prior to initial ARQ 197 dosing) and repeated on Day 22 to 24 of Cycle 1 from patients aged 20 years or younger.

One blood sample was collected at baseline for genotyping for Cytochrome P450 (CYP450) 2C19 from all patients enrolled under Amendment 1. For active patients enrolled under the original protocol, a CYP450 blood sample was collected during their next visit.

To explore biological responses of tumors to ARQ 197 treatment, FDG-PET scanning was performed at baseline within 14 days prior to treatment. If PET standardized uptake value (SUV) was equal to or greater than 4 for at least one tumor lesion at baseline, two follow-up scans were performed on Day 8 (± 2 days) of Cycle 1 and after two cycles of treatment coinciding with tumor measurement added with Amendment 1, August 1, 2008). If PET SUV was less than 4 for all lesions measured at baseline, no follow-up scan was performed. Note that by administrative letter dated October 28, 2008, FDG-PET scanning was discontinued since after 20 patients had been enrolled and evaluated by FDG-PET, “most

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lesions evaluated did not show much metabolic activity from the onset or remained largely unchanged."

Biomarkers: Information on patients' tumor gene translocation/fusion status was desirable for this study. Investigators were to use best efforts to collect patients' archival tissue specimens at baseline. If a patient had accessible tumor that was safely amenable to tumor biopsy, the procedure could be conducted at baseline and post-treatment on Day 9 (± 1 day), one day after the first post-treatment FDG-PET scan (Day 8, Cycle 1), with the patient's consent.

Safety: Adverse events observed by the investigator, or reported by the patient, and any remedial action taken, were recorded throughout the study. Each event was assessed for severity, relationship to study drug, need for remedial therapy and event outcome by the investigator. In addition, serious treatment-emergent adverse events (serious TEAEs) were reported through a phone/fax system to the sponsor's designee, ICON.

Hematology with differential, liver function tests, blood chemistry and electrolytes were assessed at baseline and Days 1, 8, 15 and 22 of Cycle 1 and Day 1 of each subsequent cycle, and at the End of Treatment evaluation.

Complete physical examination including vital signs was completed at baseline, Day 1 of Cycle 1 and each subsequent treatment cycle and at the End of Treatment evaluation. Vital signs were also assessed at Day 8, 15 and 22 of Cycle 1. With Amendment 1, August 1, 2008, patients were to take the morning dose of ARQ 197 in the clinic on scheduled visit days. Vital signs were measured prior to, 0.5 to 1 and 2 to 3 hours after morning dosing on Days 1, 8, 15 and 22 of Cycle 1 and on Day 1 of each subsequent cycle.

A 12-lead electrocardiogram (ECG) was performed at baseline and the End-of Study Evaluation. Per Amendment 1, August 1, 2008, ECG was performed during the pre-study visit and prior to, 0.5, to 1 and 2 to 3 hours post dosing on Days 1, 8, 15 and 22 of Cycle 1. One ECG was to be conducted on Day 1 of each subsequent cycle and in addition, ECG(s) could be conducted if clinically indicated.

Other: Eastern Cooperative Oncology Group (ECOG) status was assessed at baseline, Day 1 of Cycle 1 and each subsequent treatment cycle and at the End of Treatment evaluation.

Tumor markers, if applicable, were to be evaluated at baseline and post-treatment on Day 9 (± 1 day), one day after the first post-treatment FDG-PET scan (Day 8, Cycle 1)

Statistical Methods:

In original protocol, the sample size of 45 patients (23 in stage 1, 22 in stage 2) was determined to provide 90% power to detect a significant difference between an ARQ 197 observed response rate of 20% and a fixed uninteresting response rate of 5% with a two-sided type-I error rate of 5% (i.e., α=0.05).

Under Amendment 1, the sample size of 39 evaluable patients (23 in stage 1, 16 in stage 2) calculated using Simon 2-Stage Optimal method was determined to provide 90% power to detect a significant difference between an assumed ARQ 197 response rate of 11% and a fixed uninteresting response rate of 1% with a 1-sided type-I error rate of 5% (i.e., α=0.05). Efficacy of ARQ 197 was only to be evaluated in patients enrolled under this Amendment.

The demographics and efficacy summary tables display data by ARQ 197 dosing cohort and overall. In

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addition, baseline and efficacy tables were presented by cancer type and overall where applicable. Dosing cohorts for patient disposition, demographics and baseline characteristics, extent of exposure, and efficacy analysis included patients taking 120 mg BID ARQ 197 only, patients dose escalated from 120 mg BID to 360 mg BID and patients enrolled at 360 mg BID ARQ 197.

Patient Populations: All patients enrolled under Amendment 1who received at least one dose of ARQ 197 were considered evaluable for safety analysis (Safety [SAF] Population). All patients enrolled under Amendment 1who received at least one dose of ARQ 197 were also defined as the intent-to-treat (ITT) population (per revised SAP dated August 11, 2011). The SAF and ITT populations were the same.

The Evaluable (EVAL) Population was defined as all patients enrolled under Amendment 1 who received at least 75% of doses of ARQ 197 during the first two cycles of treatment and who had at least one post-baseline tumor evaluation performed.

The analysis for the overall ITT population was considered the primary analysis for this study.

Safety: Adverse events (AE) data (coded using Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 and classified by the primary System Organ Class [SOC] and preferred term [PT]) were summarized for the SAF Population. For purposes of creating the summary tables, AEs were assigned to the ARQ 197 dosing regimen the patient was receiving at the time the event started. The data were then summarized two ways: (1) by the dose patients were on at the time of the events and (2) for all doses combined.

In addition to the evaluation and categorization of AEs, listings of laboratory test results collected at baseline and during the study were generated. Descriptive statistics summarizing the changes in those laboratory tests over time were presented.

Patients who received at least one dose of ARQ 197 and who had an evaluable ARQ 197 pharmacokinetic profile on Days 1-3 and/or Days 22-24 of Cycle 1 were included in the pharmacokinetic analysis.

Patients who received at least one dose of ARQ 197 and had at least one post-treatment plasma sample collected were included in the biomarker analysis.

Efficacy: ORR was calculated based on the best tumor response recorded for each patient from the date of their first dose of ARQ 197. Best overall response data were presented as the number and percentage of patients in each RECIST 1.0 response category (CR, PR, stable disease [SD], progressive disease [PD], and not evaluable [NE]). Data were summarized overall and by ARQ 197 dosing cohort and patients were assigned to the regimen they were receiving at the time of their best response. The ORR and best overall response data were summarized for both the EVAL and ITT Patient populations. The analysis for the overall ITT population was considered the primary analysis.

Summary:

Efficacy Results: Forty-seven patients were enrolled in the study and all 47 patients received study treatment. The distribution by cancer diagnosis was: 27 of 47 (57.4%) patients, ASPS; 11 of 47 (23.4%) patients, CCS; 6 of 47 (12.8%) patients, translocational associated renal cell sarcoma (TLA-RCC); 3 of 47 (6.4%) patients, other (papillary renal cell carcinoma, Wilms tumor, high grade clear cell renal cell sarcoma). Thirty-eight of 47 (80.9%) patients enrolled under Amendment 1 received at least 75% of doses of ARQ 197 during the first two cycles of treatment and had at least one post-

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baseline tumor evaluation performed and comprised the EVAL Population. The SAF/ITT Populations included all 47 patients who received at least one dose of ARQ 197.

One patient (tumor type CCS) included in both the ITT (1/47 [2.1%]) and EVAL (1/38 [2.6%]) Populations had a partial response (PR) to treatment. The corresponding ORR response rates by cancer type were 1/11 (9.1% [ITT]) and 1/6 (16.7% [EVAL]) CCS patients and by dosing cohort 1/8 (12.5%, 120 – 360 mg BID [ITT]) and 1/7 (14.3%, 120 – 360 mg BID [EVAL]) patients.

By Cancer type in the ITT Population, 28 out of 47 (59.6%) patients had SD, (22/27 patients [81.5%] in the ASPS cohort, 3/11 patients [27.3%] in the CCS cohort and 3/6 patients [50%] in the TLA-RCC cohort. Sixteen out of 47 patients (34.0%) had PD (4/27 patients [14.8%] in the ASPS cohort, 6/11 patients [54.5%] in the CCS cohort, 3/6 patients [50%] in the TLA-RCC cohort, and 3/3 (100%) in the Other cohort). In the EVAL Population, 26 out of 38 (68.4%) patients had SD, (21/25 patients [84.0%] in the ASPS cohort, 2/6 patients [33.3%] in the clear CCS cohort and 3/5 patients [60%] in the TLA-RCC cohort). Eleven out of 38 patients (28.9%) had PD (4/25 patients [16.0%] in the ASPS cohort, 3/6 patients [50%] in the CCS cohort, 2/5 patients [40%] in the TLA-RCC cohort, and 2/2 (100%) in the Other cohort).

Median Overall PFS time for the ITT Population was 111 days. By cancer cohort, the median PFS times for the ITT Population were 167, 57, and 57 days for ASPS, CCS and TLA-RCC, respectively. Six-month, 1-year, and 2-year overall survival rates for all patients in the ITT population were 79.9%, 70.4%, and 47.7%, respectively. Overall 6-month, 1-year, and 2-year survival rates by cancer cohorts for the ITT population were 96.3% (6-month), 84.0% (1-year) and 69.7% (2-year) for ASPS, 40.9% (6-month), 40.9% (1-year), 27.3% (2-year) for CCS, 66.7% (6-month), 66.7% (1-year), 0.0% (2-year) for TLA-RCC and 100% (6-month), 50.0% (1 year), 50.0% (2-year) for Other. In general, ASPS patients had apparent higher survival rates than the other MiT tumor populations.

Safety Results:

Extent of Exposure: All 47 patients (SAF/ITT Population) received a mean cumulative dose over the whole study of 74909 mg (range: 120 to 541020 mg) and had a mean duration of exposure of 150 days (range: 13 to 899 days).

Adverse Events:

The following table summarizes the number of patients with treatment-emergent adverse events (TEAEs).

	All Patients (N=47)
At Least One TEAE	47 (100.0%)
At Least One TEAE Related to ARQ 197	43 (91.5%)
At Least One Severe (Grade 3 or Higher) TEAE	24 (51.1%)
At Least One Serious TEAE	14 (29.8%)
At Least One Serious TEAE Related to ARQ 197	3 (6.4%)
At Least One TEAE Leading to Permanent Discontinuation [n (%)]	1 (3.8%)
TEAE Leading to Death	2 (4.3%)

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Of the 47 patients who received ARQ 197, 43 (91.5%) had a TEAE that was considered related to ARQ 197. The most common (at least 5% of patients) drug-related TEAEs in all patients (n=47) were fatigue (23/47, 48.9%), nausea (20/47, 42.6%), vomiting (13/47, 27.7%), anemia (8/47, 17.0%), sinus bradycardia (8/47, 17.0%), diarrhea (7/47, 14.9%), leukopenia (6/47, 12.8%), neutropenia (6/47, 12.8%), headache (6/47, 12.8%), cough (5/47, 10.6%), lymphopenia (4/47, 8.5%), aspartate aminotransferase increased (4/47, 8.5%), alanine aminotransferase increased (4/47, 8.5%), anorexia (4/47, 8.5%), rash (4/47, 8.5%), thrombocytopenia (3/47, 6.4%), retching (3/47, 6.4%), , pyrexia (3/47, 6.4%), insomnia (3/47, 6.4%), and dyspnea (3/47, 6.4%). Three out of 47 (6.4%) patients had ARQ 197 treatment-related SAEs; all three patients were receiving 360 mg BID ARQ 197. Treatment-related SAEs included: febrile neutropenia (Grade 3 severe), thrombocytopenia (Grade 4 life threatening), and deep vein thrombosis (Grade 3 severe). Twenty-four of 47 (51.1%) patients had at least one $\geq$3TEAE, with anemia the most common severe TEAE reported.

Three out of 32 (9.4%) patients had dose reductions due to adverse experiences. One patient was reduced due to AEs (leukopenia, neutropenia) at Study Day 376 from 360 mg BID to 300 mg BID. A second patient was reduced due to AEs (neutropenia, leukopenia) at Study Day 29 from 360 mg BID to 240 mg BID, then due to AEs (lymphopenia, neutropenia, leukopenia) at Study Day 64 from 240 mg BID to 180 mg BID. A third patient was reduced due to AEs (neutropenia) at Study Day 120 from 360 mg BID to 240 mg BID.

Two out of 47 (4.3%) patients had study medication (1 receiving 120 mg BID and 1 receiving 360 mg BID ARQ 197) discontinued due to adverse events. The two patients were discontinued from study medication due to 5 possible or probable drug-related TEAEs (diarrhea, fatigue, headache, cough and thrombocytopenia). One of the 5 (20%) TEAEs that resulted in study drug discontinuation was a SAE: thrombocytopenia (life-threatening severity).

Two out of 47 (4.3%) patients died during the study period, both patients with a TEAE of disease progression. Neither of the deaths was considered treatment-related by the investigator.

There were 64 laboratory-related TEAEs reported. Of these 64 events, 24 (37.5%) were categorized as Grade 3/4 intensity. There was no predominant event or pattern of laboratory-related events. Fifty-five events of myelosuppression-related adverse events (20 anemia, 12 neutropenia, 11 leukopenia, 7 lymphopenia, and 5 thrombocytopenia) were reported in 32 patients; 47/55 (85.5%) events were considered drug-related. Forty-two (89.4%) of the 47 patients had at least one abnormal physical examination finding following enrollment. A total of 34 (72.3%) of 47 patients had evidence of a physical examination abnormality prior to the start of study treatment and 40 (85.1%) of 47 patients had at least one abnormality during the treatment phase.

The mean changes from baseline in vital signs (blood pressure, heart rate, respiratory rate, temperature, weight) were small, with no apparent differences between dosing levels.

Twenty-seven (57.4%) out of 47 patients had Grade 0 (normal activity) and 20 (42.6%) out of 47 patients had Grade 1 (symptoms, but ambulatory) ECOG scores at baseline. At the End of Treatment Evaluation 18 (38.3%) patients had Grade 0, 17 (36.2%) patients had Grade 1, 3 (6.4%) patients had Grade 2 and 2 (4.3%) patients had Grade 3 (in bed more than 50% of time) ECOG scores consistent with the overall progression of disease. Seven patients did not have ECOG scores available at the end of study visit.

There were no clinically significant trends in ECG changes recorded during the study. However, 22 cardiac events (19 sinus bradycardia including 3 marked sinus bradycardia, 1 prolonged QT

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interval, 1 sinus arrhythmia, and 1 tachycardia) were reported in 13 patients. Two events occurred in the 120 mg BID ARQ 197 dosing level (1 sinus bradycardia, 1 tachycardia), one event in the 240 mg BID ARQ 197 dosing level (sinus bradycardia), and 19 events in the 360 mg BID ARQ 197 dosing level (17 sinus bradycardia, 1 prolonged QT, 1 sinus arrhythmia). Sixteen (72.7%) events were considered possibly/probably drug-related; all events resolved.

Pharmacokinetic/Biomarker Results: An exploratory analysis, which included PK profiling and noncompartmental methods for ARQ 197 Crystalline A formulation administered twice daily (BID) to patients with MiT tumors was performed. In addition, an assessment of the relationship between main phenotypes of CYP2D6 and CYP2C19 (i.e., ultra rapid, extensive, intermediate or poor metabolizers, as applicable) and the PK of ARQ 197 was described. A total of 2 dosing cohorts (120 mg BID and 360 mg BID) were included in the pharmacokinetic analysis. Major findings/conclusions are as follows:

Descriptive statistics of the major pharmacokinetic parameters of ARQ 197 after daily BID are presented by cohort below:

PK Parameter	Summary Statistic	Cohort 1 120 mg BID ARQ 197		Cohort 2 360 mg BID ARQ 197	
		Day 1	Day 22	Day 1	Day 22
$AUC_{0\text{-}inf}$ (ng·h/mL)	Mean±SD GeoMean (GeoCV%) N used	2574.5±1992.98 2145.3 (81.2%) 3	NA	15422.5 15422.5 1	NA
C_{max} (ng/mL)	Mean±SD GeoMean (GeoCV%) N used	788.2±615.53 615.7 (87.8%) 6	919.6±555.00 793.4(66.3%) 5	1251.0±606.70 1175.1(54.0%) 2	421.0 421.0 1
$t_{1/2}$ (h)	Median (Min, Max) N used	2.501(2.45,2.91) 3	3.548(3.17,3.64) 3	3.027 1	4.286 1
CL/F (L/h)	Mean±SD N used	64.46±34.670 3	NA	23.34 1	NA

NA = Not Applicable; SD = Standard Deviation

Major findings/conclusions are as follows:

- Based on the total (AUC_{last}, $AUC_{0\text{-}12}$) and peak (C_{max}) exposure ARQ 197 PK parameters, there was no apparent drug accumulation in plasma observed after 120 mg BID multiple oral dose administrations of ARQ 197 Crystalline A. The PK data were associated with a small sample size (≤ 6 patients) and high inter-patient variability.
- The PK data for patients receiving 360 mg BID were not conclusive due to a small sample size (≤ 2 patients) and, therefore, did not provide statistically or clinically reliable information.
- Due to a small sample size, the PK population in this study did not represent the variety of CYP2D6 and CYP2C19 phenotypes and, therefore, did not provide sufficient information for genotyping assessment.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Test Product: ARQ 197 (AQ 3227197)	**Volume:** **Page:**	
Name of Active Ingredient: (-)-*trans*-3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione		

Other Results:

Archival tumor tissue samples were obtained from twenty-four patients although 3 samples did not contain identifiable tumor cells. One patient had two archival samples, one from the primary kidney tumor and one from a liver metastasis. On study tumor biopsy samples were obtained from two patients. Of the 22 evaluable archival tumor samples 11 (50%) were strongly positive for c-Met, 6 (27%) were focally positive and 5 (23%) were weakly positive. No tumors were negative. Two antibodies were used to detect activated, phosphorylated c-Met, one specific for the docking site tyrosine (Y1349) phosphorylation, and one specific for the kinase domain (Y1234/5). Most tumors were negative or weakly positive for p-c-Met Y1349 (18/23, 78%) and p-c-Met Y1234/5 (13/23, 57%). Ten tumors scored focally positive for p-c-Met Y1234/5. One tumor (patient 29) was strongly positive for both p-c-Met markers. Activation of the c-Met signaling pathway leads to phosphorylation of Focal Adhesion Kinase (FAK). The pFAK antibody reacts with the phosphorylated tyrosine 861. Of the 10 tumors that were positive for p-c-Met Y1234/5, 9 were also positive for pFAK. The c-Met receptor is activated upon binding to the hepatocyte growth factor (HGF). A rabbit polyclonal antibody generated against the N-terminus of HGFα was used for the IHC. Twelve of the 22 evaluable archival tumor samples were positive for HGF. One (patient 25) was focally positive.

Of the available on-treatment tumor biopsies (post) for two patients, one patient's "pre" and "post" tumor samples were negative for p-c-Met. One patient's "pre" and "post" tumor samples were focally positive for all phospho-markers but there was no evidence of change with ARQ 197 treatment. Total c-Met staining was stronger in the post sample for the latter patient. There was no difference in staining of the cell proliferation marker, Ki67, for the same patient's "pre" and "post" tumor samples (28% and 31 % positive nuclei respectively). It was noted that the liver metastasis from one patient was positive for HGF and focally positive for p-c-Met and pFAK while the primary kidney tumor was negative for HGF and the phospho-markers.

The biomarker study demonstrated the feasibility of detecting tumor biomarkers from archival human tumors using IHC. Of the 22 evaluable archival tumor samples, 11 (50%) were strongly positive for c-Met, 6 (27%) were focally positive and 5 (23%) were weakly positive. Most tumors were negative or weakly staining for p-cMet. Ten tumors scored focally positive for pY1234/5 in some area of the tumor. One sample (patient 29) was strongly positive for both p-c-Met markers. Of the 10 tumors that were positive for p-c-Met Y1234/5, 9 were also positive for pFAK. Thirteen of the 22 evaluable archival tumors samples were positive for HGF. No change in tumor markers was observed in the two patients that had pre and post tumor samples.

Conclusions:

ARQ 197 demonstrated a favorable safety profile among the 47 patients with microphthalmia transcription (MiT) tumor who were treated in this multi-center, single arm, two-stage phase II study with continuous ARQ 197 therapy at doses of 120 to 360 mg BID. Twenty-six patients were enrolled under the original protocol at 120 mg BID initial dose. When Amendment 1 was developed, a maximum tolerated dose (MTD) had recently been reached in a phase I study and the newly recommended dose for future studies of ARQ 197 was 360 mg BID. Twenty-one additional patients were enrolled under Amendment 1. A total of 47 patients were enrolled in the study.

The ITT population was considered the primary analysis population for this study. One patient (tumor type CCS) included in both the ITT (1/47 [2.1%]) and EVAL (1/38 [2.6%]) Populations had a partial

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response (PR) to treatment. This patient response met the Simon 2-Stage Optimal design criteria for proceeding from Stage 1 (26 patients enrolled) to Stage 2 (21 patients enrolled).

By Cancer type in the ITT Population, 28 out of 47 (59.6%) patients had SD, (22/27 patients [81.5%] in the ASPS cohort, 3/11 patients [27.3%] in the CCS cohort and 3/6 patients [50%] in the TLA-RCC cohort. Sixteen out of 47 patients (34.0%) had PD (4/27 patients [14.8%] in the ASPS cohort, 6/11 patients [54.5%] in the CCS cohort, 3/6 patients [50%] in the TLA-RCC cohort, and 3/3 (100%) in the Other cohort).

Median Overall PFS time for the ITT Population was 111 days. By cancer cohort, the median PFS times for the ITT Population were 167, 57, and 57 days for ASPS, CCS and TLA-RCC, respectively. Six-month, 1-year, and 2-year overall survival rates for all patients in the ITT population were 79.9%, 70.4%, and 47.7%, respectively. Overall 6-month, 1-year, and 2-year survival rates by cancer cohorts for the ITT population were 96.3% (6-month), 84.0% (1-year) and 69.7% (2-year) for ASPS, 40.9% (6-month), 40.9% (1-year), 27.3% (2-year) for CCS, 66.7% (6-month), 66.7% (1-year), 0.0% (2-year) for TLA-RCC and 100% (6-month), 50.0% (1 year), 50.0% (2-year) for Other. In general, ASPS patients had apparent higher survival rates than the other MiT tumor populations.

The most common (in ≥10% patients) TEAE were: fatigue 31/47 patients (66.0%), nausea 24/47 patients (51.1%), vomiting 18/47 patients (38.3%), anemia 12/47 patients (25.5%), cough 12/47 patients (25.5%), pain in extremity 12/47 patients (25.5%), sinus bradycardia 10/47 patients (21.3%), diarrhea 10/47 patients (21.3%), pyrexia 10/47 patients (21.3%), headache 10/47 patients (21.3%), upper respiratory tract infection 8/47 patients (17.0%), anorexia 8/47 patients (17.0%), neutropenia 7/47 patients (14.9%), dyspnea 7/47 patients (14.9%), back pain 7/47 patients (14.9%), leukopenia 6/47 patients (12.8%), alanine aminotransferase increased 6/47 patients (12.8%), chest pain 5/47 patients (10.6%), edema peripheral 5/47 patients (10.6%), arthralgia 5/47 patients (10.6%), dizziness 5/47 patients (10.6%), hemoptysis 5/47 patients (10.6%), and rash 5/47 patients (10.6%).

The most common drug-related TEAEs in all patients (n=47) were nausea (20/47, 42.6%), vomiting (13/47, 27.7%), anemia (8/47, 17.0%), and sinus bradycardia (8/47, 17%). Three out of 47 (6.4%) patients had ARQ 197 treatment-related SAEs.

Treatment with ARQ 197 was tolerable at doses of 120 mg to 360 mg BID in patients with MiT tumors. ARQ 197 showed some preliminary efficacy at both 120 and 360 mg BID doses, particularly in patients with ASPS. However, based on these data, the sponsor will not immediately proceed to a full phase II program for this indication.

Date of the Report: 12 March 2012