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-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)pyrrolidine-2,5-dione		

Title of Study:	A Randomized Controlled Phase 2 Trial of ARQ 197 in Patients with Unresectable Hepatocellular Carcinoma (HCC) Who Have Failed One Prior Systemic Therapy
Phase of Development:	2
Study Period:	First patient first visit date: 08 Oct 2009 Date of data cut-off for the CSR: 21 Oct 2011
Investigator(s):	Principal Investigator: Armando Santoro Dipartimento Oncologia Medica e Ematologia Istituto Clinico Humanitas IRCCS Viale Manzoni, 56 20089 Rozzano (Milano), Italy Please see Appendix 16.1.4 for the complete list of Investigators.
Study Center(s):	The following centers enrolled at least one patient: Belgium: 3 centers Canada: 2 centers Germany: 5 centers Italy: 8 centers United States: 2 centers
Publication (reference):	Rimassa L, Porta C, Borbath I, et al. Tivantinib (ARQ 197) versus placebo in patients with hepatocellular carcinoma (HCC) who failed one systemic therapy: Results of a randomized controlled phase II trial (RCT). *J. Clin.Oncol*. 2012;30:(suppl; abstr 4006).
Study Objectives/Hypothesis:	Primary Objective: • Evaluate the time to progression (TTP) among all patients treated with ARQ 197 compared to those treated with placebo Secondary Objectives • To evaluate the progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) among all patients treated with ARQ 197 compared to placebo • To evaluate the ORR in crossover population following radiographic disease progression on placebo • To further characterize the safety of ARQ 197 in patients with unresectable HCC • To further evaluate pharmacokinetics of ARQ 197

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	Exploratory Objectives • To evaluate the time to new lesion among all patients treated with ARQ 197 compared to placebo • To evaluate the association between hepatitis viral status and tumor markers of the MET signaling pathway, blood hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), soluble MET levels, other relevant signaling pathways such as PTEN, EGFR, VEGFR, KRAS, IGFR, pharmacogenomic markers (i.e. CYP2C19, UGT1A1), pharmacokinetics (PK), and key clinical endpoints including TTP, PFS, ORR, and OS. The key efficacy endpoints in subgroups of patients were also to be explored.
Study Design/Methodology:	This was a global, randomized, placebo-controlled, double-blinded Phase 2 study designed to compare treatment of ARQ 197 versus placebo in patients with unresectable HCC who had radiographic disease progression after systemic therapy or were unable to tolerate the therapy. Approximately 99 patients were to be enrolled from multiple study sites and randomly assigned with a 2:1 ratio to receive ARQ 197 (66 patients) or placebo (33 patients). The treatment assignment was to be stratified based on ECOG performance status (PS) and vascular invasion status. The treatments of ARQ 197 or placebo were to be continued until progression of disease, unacceptable toxicity, or another discontinuation criterion listed in this protocol was met. After radiographic disease progression was documented, treatment assignment was to be unblinded if the patient wished to enter the open-label crossover portion of the study. Patients who were assigned to the placebo arm and had documented radiographic disease progression were to receive ARQ 197 and were to be evaluated for ORR and DCR (crossover portion). Under the original protocol, a dose of 360 mg twice daily (BID) (3 x 120 mg ARQ 197/placebo capsules) ARQ 197 or placebo was to be administered by mouth (p.o.) BID without food (once in the morning and once in the evening about 12 hours apart, 1 hour prior or 2 hours after eating). In Amendment 1, it was amended to administer ARQ 197/placebo with meals. Under Amendment 2, a dose of 240 mg (2 capsules of 120 mg each) of ARQ 197/placebo was to be administered by mouth BID, once in the morning and once in the evening with meals, for a total daily dose of 480 mg. A treatment cycle was defined as 4 weeks for both treatment arms. Cycles were to be repeated every 4 weeks (28 days) based on toxicity and response. Treatment was to be continued until unacceptable toxicity, documented progression of disease, or another discontinuation criterion listed in the protocol was met.

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	During the study, data on tumor measurement were to be collected at baseline and in 6-week intervals for the evaluation of TTP, PFS, ORR, and DCR. Survival data were to be collected for the evaluation of OS. The study was to continue until at least 78 total TTP events were reached. At the end of study, all remaining patients still on treatment were to have the option to be rolled over to an extension study to continue their treatment. Protocol Amendment 2 added clarification that after disease progression was documented, treatment assignment would be unblinded if the patient wished to enter the open-label crossover portion of the study. Protocol Amendment 3 further clarified that any patients who were discovered to be on placebo at the time the entire study was unblinded were to be offered the option to immediately crossover to ARQ 197 for at least two months prior to then being offered the option to roll over to the extension study to continue their treatment.
Duration of Treatment for Individual Patient:	Treatment was to be continued until unacceptable toxicity, documented progression of disease, or another discontinuation criterion listed in the protocol was met.
Number of Patients:	Planned: 99 Enrolled/Randomized: 107 Continuing in double-blind: 7 Discontinued double-blind: 100 Patients in placebo arm crossed over to ARQ 197: 23 Continuing in crossover: 5 Discontinued crossover: 18
Diagnosis and Main Criteria for Study Entry:	The study included patients with unresectable HCC who had radiographic disease progression after systemic therapy. Main inclusion criteria: • Written informed consent prior to initiation of any study-specific screening procedures • 18 years of age or older • Histologically or cytologically confirmed HCC • Archival, fresh core needle biopsy or fine needle aspiration (FNA) tumor samples

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- Received at least one cycle of prior systemic therapy (at least 3 weeks for continuously administered drugs) and experienced radiographic disease progression or was unable to tolerate therapy. If intolerance was manifested by a Grade 3 or 4 event of such nature that re-challenge was not acceptable, less than 3 weeks of continuous administration was to be allowed.
- Discontinued prior treatment for at least 4 weeks, or at least 2 weeks (14 days) if drug was administered continuously and orally (e.g. sorafenib or sunitinib), prior to the study randomization
- ECOG PS ≤ 1
- Local or loco-regional must have been completed ≥ 4 weeks prior to randomization
- Measurable disease as defined by a modified version of the revised RECIST version 1.1 (see CSR Section 6.6.1.1). Tumor lesions previously treated with local therapy should have demonstrated clear dimensional increase by radiographic assessment in order to be selected as target lesion(s) at baseline. (Radiological assessment needed to be redone within 7 days prior to randomization if the pre-study AFP level had increased by more than 30% since the last AFP level taken one to four months prior to randomization.)
- Adequate bone marrow, liver, and renal functions at the Pre-Study Visit.
- Women of childbearing potential must have had a negative pregnancy test performed within ten days prior to the start of study drug
- Male and female patients of child-bearing potential must have agreed to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last investigational drug dose received

Main exclusion criteria:

- More than 1 prior systemic regimen
- Child-Pugh B-C cirrhotic status
- Previous or concurrent cancer that was distinct from HCC in primary site or histology, EXCEPT cervical carcinoma *in situ*, treated basal cell carcinoma, and superficial bladder tumors (Ta, Tis, and T1). Any cancer curatively treated > 3 years prior to enrollment was permitted.
- History of congestive heart failure defined as Class II to IV per the New York

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Heart Association (NYHA) classification within 6 months prior to study entry; active coronary artery disease (CAD); clinically significant bradycardia or other uncontrolled, cardiac arrhythmia defined as ≥ Grade 3 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, or uncontrolled hypertension; myocardial infarction occurring within 6 months prior to study entry (myocardial infarction occurring > 6 months prior to study entry was permitted).

- Active clinically serious infections defined as ≥ Grade 3 according to NCI CTCAE, version 4.0
- Substance abuse, medical, psychological, or social conditions that may, in the opinion of the Investigator, have interfered with the patient's participation in the study or evaluation of the study results
- Any condition that was unstable or which could jeopardize the safety of the patient and his/her protocol compliance
- Known human immunodeficiency virus (HIV) infection
- Pregnancy or breast-feeding
- History of liver transplant

Investigational Product and Comparator Information:	Dosage Form: Capsule 120 mg ARQ 197 or matching placebo Route of Administration: oral Lot No.: ARQ 197 120 mg capsule, Lot # 8L132-P3; Placebo capsule, Lot #8M144-P1 Packaging Information: Drug was packaged as 90-count in 120 cc HDPE bottles. At the start of each cycle, patients were issued supplies of ARQ 197/placebo capsules adequate for one full cycle of therapy, at a dose of 360 mg BID (720 mg/day) or 240 mg BID (480 mg/day).

Criteria for Evaluation:

Primary Efficacy:

- TTP, which was calculated as the time from randomization until disease progression per a modified version of the revised RECIST Version 1.1 criteria

Secondary Efficacy

- PFS calculated as the time from randomization until disease progression per revised RECIST Version 1.1 or death from any cause

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- OS calculated from the date of randomization until death from any cause
- ORR calculated as the number of patients with a confirmed complete or partial response divided by the total number of patients [ORR= (CR+PR)/# patients]
- DCR defined as the proportion of patients with best overall responses of CR, PR, and SD. DCR was to be used if there were not a sufficient number of patients with objective response to calculate ORR.

Exploratory Efficacy

- Time to new lesion calculated as the time from randomization until the first new lesion was detected per revised RECIST Version 1.1 criteria. See CSR Section 6.6.2.3 for further details on calculation of time to new lesion.
- TTP, PFS, ORR, and OS in subgroups of patients defined by biomarkers and markers of various signaling pathways

Pharmacokinetics/Pharmacodynamics:

Blood samples were to be collected on Day 1 of double-blind Cycle 1, 2, 3, and 4 to further evaluate the PK of ARQ 197 and any correlation with biomarkers (see below) and clinical endpoints.

One blood sample was to be collected from all patients on Day 1 of Cycle 1 only for detection of polymorphism of cytochrome P450 2C19 (CYP2C19) and UGT1A1. The goal was to explore the impact of CYP2C19 variants on primary and secondary endpoints as well as on pharmacokinetic parameters and possibly on biomarkers levels.

Tumor samples of archival, fresh core needle biopsy or fine needle aspiration (FNA) were to be collected at baseline for all patients. Archival samples or FNA samples were acceptable if core needle biopsy was not viable. Core needle biopsy samples collected within 30 days before the first day of treatment were considered fresh.

Optional tumor biopsies or FNA were to be performed at baseline and post-treatment (after Day 22 and preferably before Day 30 of Cycle 1) and at the end of treatment, if deemed safe for the patients and with their consent. Collected samples were to be evaluated for the expression of p-MET, total MET, and downstream markers of MET signaling including p-FAK, and p-ERK1/2, and markers of cell proliferation (Ki67) and apoptosis (TUNEL). Other biomarkers such as HER3, PI3K, HGF, PTEN, EGFR, VEGFR, KRAS, IGFR, and phospho-Akt could also have been evaluated.

Blood samples were also to be collected on Day 1 of every cycle for the analysis of dynamic changes in HGF, VEGF, and soluble MET and to correlate with data from PK studies and/or clinical outcome.

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Safety:

Drug safety was to be monitored and evaluated continuously throughout the study including the 30-day safety follow-up period. Safety variables included the reported AEs, changes in laboratory values, vital signs, ECOG PS, ECG, and PE.

Other-Assessment of anti-tumor activity:

Disease status and tumor response were assessed in 6-week intervals until progressive disease (PD), patient death, loss to follow-up, or as clinically indicated. Standard imaging studies were to be performed according to institutional procedures. Tumor response was evaluated using the revised guidelines for RECIST version 1.1.

The following definitions and criteria (from RECIST 1.1) were used for the baseline evaluations of existing disease and for the ongoing evaluation of tumor responses:

- Measurable disease: the presence of at least one measurable lesion
- Measurable lesions: lesions that could be accurately measured in at least one dimension 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 could not be accurately measured with calipers were to be recorded as non-measurable); and 20 mm by chest X-ray. Note that to be considered pathologically enlarged and measurable, a lymph node must have been ≥ 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 was to be measured and followed.
- Non-measurable lesions: all other lesions, including small lesions (LD < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable included: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that were not measurable by reproducible imaging techniques.

Statistical Methods:

The primary, secondary, and exploratory objectives in the Statistical Analysis Plan (SAP) are identical to the study objectives.

Patients' data were analyzed based on the following treatment grouping:

- ARQ 197 240 mg BID
- ARQ 197 360 mg BID
- ARQ 197 both dosage groups combined
- Placebo
- The efficacy and safety results are also summarized for the crossover period

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On 24 Sep 2010, all sites were notified to reduce the dose of ARQ 197 for all patients to 240 mg BID (per protocol Amendment 2 dated 06 Oct 2010). Patients who were randomized prior to the notification letter on 24 Sep 2010 were assigned to the treatment group of ARQ 197 360 mg BID. Patients who were randomized on or after the date of the notification letter were assigned to the treatment group of ARQ 197 240 mg BID. The ARQ 197 group was for all patients who received 240 mg BID or 360 mg BID at randomization. The patient data during the crossover period were analyzed separately. The following subgroups were defined and used for efficacy analyses:

- MET High patients: MET High was defined as MET staining intensity of Grade ≥ 2+ and expressed in ≥ 50 % tumor cells by IHC
- MET Low patients
- HBV positive patients
- HCV positive patients (excluding HBV positive patients)
- HBV negative and HCV negative patients
- Patients who received prior systemic cancer therapy for ≤ 60 days
- Patients who received prior systemic cancer therapy for > 60 days

Analysis Sets-Four analysis populations were defined for this study as follows:

- Intention-to-Treat (ITT) population: all randomized patients
- Per-Protocol (PP) population: patients who completed at least 75% of one cycle of treatment (based on days on treatment regardless of dosage taken) with ARQ 197 or placebo and who had at least one post-baseline tumor evaluation.
- Safety population (SAF): patients who received any amount of ARQ 197 or placebo
- Other Efficacy population: In addition to ITT and PP populations, the patient population switched to ARQ 197 treatment from placebo treatment was to be considered for ORR analyses.

For the ITT population, all analyses were performed according to the treatment group to which the patients were randomized.

For the PP and SAF populations, all analyses were performed according to the treatment the patients received.

All demographic and baseline characteristics were to be listed and summarized descriptively for the ITT population. For HCC, listings and summary statistics were to be tabulated for diagnosis for the ITT population including tumor staging at initial diagnosis, time since initial diagnosis, tumor staging at study entry, time since most recent relapse/progression, presence/absence of target and non-target lesions at baseline, type of biopsy/procedure, time since the most recent biopsy/procedure, and histological grade.

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Prior cancer history and additional cancer type were to be listed.

Medical history, surgical history, and ongoing conditions, including cancer-related conditions and symptoms were to be listed for the ITT population.

For tumor markers, summary statistics for AFP were to be presented at each visit for the ITT population. Descriptive statistics were to be presented for each of the biomarker parameters by visit for the ITT population. Descriptive statistics for CYP2C19 and UGT1A1 were to be presented for the ITT population.

- Investigator reported overall lesion response (Source 1)
- Central radiology reported overall lesion response (Source 2)

The categorization by RECIST 1.1 was based on Source 2 for the final primary analyses. The same analyses were repeated on Source 1 as sensitivity analyses. Discrepancies between reported local and central responses were identified and discordance was summarized.

Efficacy:

The following between treatment comparisons were conducted on all efficacy endpoints.

- ARQ 197 vs. placebo
- ARQ 197 240 mg BID vs. placebo
- ARQ 197 360 mg BID vs. placebo

Time to Progression (TTP) was calculated as the time from randomization until disease progression per a modified version of the revised RECIST Version 1.1 criteria. Patients who died or discontinued from the study without disease progression were to be censored at the time of their last tumor assessment before death or discontinuation. Patients who did not have documented radiographic progression at the time the TTP analyses was performed were to be censored at the time of their last tumor assessment.

Progression-Free Survival (PFS) was calculated as the time from randomization until disease progression per RECIST or death from any cause. Patients who were alive and did not have documented radiographic progression at the time the PFS analyses were performed were to be censored at the date of their last tumor assessment. Patients who discontinued from the study due to reasons other than disease progression or death were to be censored (i.e., considered not to have died or progressed) in the PFS analyses at the date of their last tumor assessment.

Overall Survival (OS) was calculated from the date of randomization until death from any cause. Any patient without a date of death in the database at the time the survival analyses was performed was to be censored at the time of their last study contact in the analyses.

Time to new lesion was calculated as the time from randomization until the first new lesion was detected per a modified version of the revised RECIST Version 1.1 criteria. For patients who had disease progression and with a new lesion, the date of the new lesion was the assessment date at which the first new lesion was detected. For patients who died or discontinued from the study without disease progression

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or patients discontinued from the study due to disease progression, but without a new lesion detected, the date of new lesion was to be censored at the time of their last tumor assessment before death or discontinuation. The date of last tumor assessment was the date the last tumor assessment (CR, PR, SD, or PD) was made and was used for patients who did not have a new lesion detected. If no baseline or post-baseline assessments was available, this was considered as the date of randomization.

Best Overall Response was determined once all the data for the patient was known and was defined as the best response across all time points (for example, a patient who had SD at first assessment, PR at second assessment, and PD on last assessment had a best overall response of PR).

Disease Control Rate (DCR) was defined as the proportion of patients with the best overall responses of CR, PR, and SD.

The primary efficacy analysis was the comparison of TTP between the ARQ 197 vs. placebo groups based on the ITT population. The Kaplan-Meier product-limit method was used to estimate the distribution of TTP in each group. The median TTP for each treatment group was based on the Kaplan-Meier estimate and the 95% confidence intervals (CIs) for each treatment group, calculated using the method of Brookmeyer and Crowley (1982). The corresponding Kaplan- Meier curves were also presented. The hazard ratio (HR) and its 95% CI of ARQ 197 compared to placebo group were estimated using the unadjusted Cox regression model with the treatment group as the only covariate.

Hypothesis testing for a potential superiority claim with regard to TTP was performed with a two-sided significance level of α=0.10.

The primary efficacy variable of TTP was also analyzed based on the ITT population to estimate the overall HR of ARQ 197 compared to placebo, ARQ 197 360 mg BID compared to placebo, and ARQ 197 240 mg BID compared to placebo separately with their 95% CIs using the Cox proportional hazard regression model adjusted for HBV positive at baseline (Yes vs. No) with and without the following baseline prognostic factors:

- Baseline ECOG PS status (0 versus 1)
- Baseline vascular invasion status (Yes vs. No)
- Distant metastasis at baseline (Yes vs. No)

Analyses of Secondary Efficacy Variables (PFS, OS, ORR, and DCR) were performed on the ITT population. PFS was analyzed using the same approach as the TTP except that the Cox regression analysis was not to be performed.

OS was analyzed using the same approach as the TTP including the Cox regression analysis.

For ORR, patients with the best OR of 'Not all Evaluated' were to be treated as non-responders in the calculation. The objective response rate of CR+PR along with the Clopper-Pearson 95% CIs were summarized for each treatment group.

The treatment groups were also compared using the logistic regression adjusted by the covariates of

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baseline prognostic factors. The model adjusted odds ratio of ARQ 197, ARQ 197 240 mg BID, and ARQ 197 360 mg BID compared to placebo in ORR and its 95% CI were presented.

If there were not a sufficient number of patients with objective response, the above analyses were to be performed on DCR instead. In addition, the percent and its Clopper-Pearson 95% CI of patients in each RECIST response category (CR, PR, SD, and PD), as well as DCR, were to be estimated.

Time to New Lesion was analyzed for the ITT population using the same approach as the TTP except that the Cox regression analysis was not performed.

The analyses of TTP and PFS, as well as the analyses of OS, were also performed for all subgroups of the ITT population. The Kaplan-Meier product-limit method was used to estimate the distributions of these time-to-event variables in each treatment group. The treatment groups were to be compared using the log-rank test. The HR and its 95% CI between treatment groups were to be estimated using the unadjusted Cox regression model with treatment group as the only covariate.

Sensitivity Analyses:

All primary, secondary, and exploratory analyses except subgroup analysis were to be repeated for Investigator-reported overall lesion response and per-protocol population as sensitivity analyses.

Pharmacokinetics/Pharmacodynamics:

The PK data were listed. Population PD and PK analysis were conducted separately and were not part of the SAP for this study. See the final population PK Report.[1]

Safety:

The safety evaluation was performed on all patients in the SAF population. The safety evaluation during the crossover period was to be analyzed separately for the crossover population.

Adverse Events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

AEs were summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE was to be counted only once in the AE category.

Separate AE summaries were to be presented by primary SOC, PT, and maximum CTC Grade. A patient with multiple CTC Grades for an AE was to be summarized under the maximum CTC Grade recorded for the event.

[1] Pharsight Technical Report: Population Pharmacokinetics and Neutropenia Exposure-Response Relationship for Tivantinib in Patients with Hepatocellular Carcinoma.

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The following AE summaries were to be produced by primary SOC, PT, and treatment group:

- All TEAEs
- Severe TEAEs (Grade 3 or higher)
- TEAEs related to treatment (ARQ 197, placebo)
- SAEs
- SAEs related to treatment (ARQ 197, placebo)
- TEAEs leading to treatment discontinuation
- TEAEs resulting in death
- TEAEs by primary SOC, PT, and maximum CTC grade.

Liver Toxicity:

Patients with elevated post-baseline ALT, AST, or total bilirubin were to be identified. Number and percentage of these patients were to be tabulated by treatment groups.

Clinical Laboratory Assessments:

Summary statistics for baseline, post baseline measurements, and change from baseline at every post baseline visit were to be presented for hematology, serum chemistry, liver function tests, and electrolytes, by treatment groups. For the crossover ARQ 197 group only, summary statistics were to be summarized by post baseline visits; no change from baseline was to be calculated.

Vital Signs:

Summary statistics for baseline, each post baseline measurements, and change from baseline for each post baseline measurement were to be presented for every vital sign parameter by treatment groups. For the crossover ARQ 197 group only, summary statistics were to be summarized by post baseline visits; no change from baseline was to be calculated.

ECOG PS:

Number and percent of patients with each ECOG value were to be presented for baseline and each post baseline measurement by treatment groups. In addition, the shift table comparing post baseline to baseline was to be presented by treatment groups.

Electrocardiograms:

All ECG measurements were to be presented in the data listings. The number and percentage of patients having newly occurring notable ECG abnormalities were to be summarized by treatment groups.

Physical Examination:

Data from physical examinations (PEs) were to be presented in the data listings. All clinically significant changes from baseline were to be reported as AEs.

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Summary:

All 107 enrolled patients received at least one dose of ARQ 197 or placebo; therefore the ITT and SAF populations were identical. Ninety-two patients comprised the PP population.

Efficacy Results:

Treatment with ARQ 197 met the primary endpoint of Study ARQ 197-215 with a statistically significant 56% improvement in TTP (HR = 0.64, log-rank p = 0.04) compared to placebo. Median (CI) TTP values for ARQ 197 and placebo were 6.9 (6.1, 12.0) and 6.0 (5.9, 6.7) weeks, respectively.

The analysis of TTP was repeated for the comparison of TTP for the treatment groups of ARQ 197 360 mg BID vs. placebo and ARQ 197 240 mg BID vs. placebo on the ITT population. Trends toward improvements in TTP for both the ARQ 197 360 mg BID vs. placebo (HR = 0.63, log-rank p = 0.08) and ARQ 197 240 mg BID vs. placebo (HR = 0.65, log-rank p = 0.10) groups were observed.

Important benefit was observed in MET High patients who experienced a 133% improvement in TTP (HR = 0.43, log-rank p = 0.03). Median (CI) TTP values for MET High patients in the ARQ 197 and placebo groups were 11.7 (6.0, 36.9) and 6.1 (5.9, 7.0) weeks, respectively.

The ARQ 197 total group also showed 49% improvement in PFS compared to placebo (HR = 0.67, log-rank p = .06). Median (95% CI) PFS values for ARQ 197 and placebo were 6.7 (6.0, 11.7) and 6.0 (5.9, 6.7) weeks, respectively.

The ARQ 197 total group compared to placebo analysis in MET High patients demonstrated a 122% improvement in PFS (HR = 0.45, log-rank p = 0.02). Median (CI) PFS values for MET High patients in the ARQ 197 total and placebo groups were 9.6 (6.0, 20.1) and 6.0 (5.9, 6.1) weeks, respectively. No apparent differences in OS between the ARQ 197 total group or each of the ARQ 197 dose groups compared to the placebo group were noted.

Important OS benefits were observed for the ARQ 197 total group compared to placebo in MET High patients. The HR=0.47 represents 113% improvement (log-rank p = 0.06). Median (95 % CI) OS values for MET High patients in the ARQ 197 total and placebo groups were 7.5 (3.9, 14.6) and 3.8 (2.1, 7.8) months, respectively. Updated OS survival is available in the addendum.

Safety Results:

Among 107 patients with unresectable HCC who were treated in this placebo-controlled Phase 2 study, 71 received ARQ 197 and 36 received placebo during the double-blind period. ARQ 197 demonstrated a manageable safety profile at the dose level of 240 mg BID given continuously.

The median exposure duration of therapy was 57.0 days (range: 8 to 379 days) in patients treated with ARQ 197 with a median cumulative dose of 27600 mg. Of the 107 patients evaluable for safety for the double-blind period, 100 (93.5%) patients experienced at least one TEAE including 69 (97.2%) of

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-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)pyrrolidine-2,5-dione		

ARQ 197 and 31 (86.1%) of placebo-treated patients.

The most common TEAEs (≥ 10% of all patients) were asthenia (24.3%), fatigue (23.4%), decreased appetite (22.4%), diarrhea (19.6%), edema peripheral (19.6%), neutropenia (18.7%), ascites (16.8%), anemia (15.9%), abdominal pain (15.0%), cough (13.1%), pyrexia (12.1%), and nausea (11.2%). Fifty-three of 107 (49.5%) patients had at least one severe (≥ Grade 3) TEAE including 37 (52.1%) of ARQ 197 and 16 (44.4%) of placebo recipients. The most common severe TEAEs (≥5% of all patients) reported were neutropenia (9.3%), anemia (8.4%), disease progression (7.5%), and fatigue (5.6%). The frequency of severe TEAEs appeared to be lower with ARQ 197 240 mg BID than ARQ 197 360 mg BID (48.5% vs. 55.3%, respectively). Moreover, the incidence of severe (≥ Grade 3) neutropenia was reduced to 6.1% in the 240 mg BID group compared to 21.1% in the ARQ 197 360 mg BID group.

Overall, 47 of 107 (43.9%) patients had TEAEs that were Grade 1 (mild) or Grade 2 (moderate) in severity. The distribution of AEs by NCI CTCAE grade was similar between the ARQ 197 and placebo treatment groups. TEAEs experienced by patients in the ARQ 197 240 mg BID group compared to the ARQ 197 360 mg BID group were Grade 1 or 2 in 51.5% vs. 39.5% of patients.

Fifty-six (52.3%) patients had at least one TEAE that was considered related to study drugs including 44 (62.0%) of ARQ 197 and 12 (33.3%) of placebo recipients. Drug-related TEAEs that occurred in ≥ 5% of all patients included neutropenia (17.8%), anemia (11.2%), fatigue (11.2%), asthenia (9.3%), decreased appetite (8.4%), diarrhea (7.5%), and thrombocytopenia (5.6%). Drug-related TEAEs related to myelosuppression and cardiac disorders were notably more frequent in the ARQ 197 treatment groups.

Twenty-three (21.5%) patients experienced fatal TEAEs including: 13 (18.3%) patients in the ARQ 197 group and 10 (27.8%) patients in the placebo group. Overall, the most common TEAE leading to death was disease progression in 8 (7.5%) patients.

Thirty-eight (35.5%) patients experienced at least one TEAE that was considered serious including 24 (33.8%) patients in the ARQ 197 total group and 14 (38.9%) patients in the placebo group. The most common (≥ 5%) SAE reported was disease progression in 8 (7.5%) patients. Thirteen (12.1%) patients had a least one treatment-related SAE including: 12 (16.9%) in the ARQ 197 group and 1 (2.8%) patient in the placebo group. Twenty-one (19.6%) patients had study medications discontinued secondary to a TEAE during the double-blind period including: 6 out of 33 (18.2%) patients in the ARQ 197 240 mg BID group, 7 out of 38 (18.4%) patients in the ARQ 197 360 mg BID group and 8 out of 36 (22.2%) patients in the placebo group. The most common TEAE leading to discontinuation from study medications was disease progression in the placebo group (11.1%) and the ARQ 197 240 mg BID group (6.1%). The most common TEAE leading to discontinuation in the ARQ 197 360 mg BID group was neutropenic sepsis (4.2%). ARQ 197 dose was reduced due to TEAEs in 17 patients in the ARQ 197 groups during the double blinded period and in 6 patients in the placebo group during the crossover period. Neutropenia and bradycardia were the most common reasons for dose reductions.

A total of 29 ARQ 197-treated patients experienced myelosuppression events categorized under blood and

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lymphatic system disorders including 18 neutropenia, 15 anemia, 7 thrombocytopenia, 5 leukopenia, 3 pancytopenia, 2 febrile neutropenia, and 1 lymphopenia). The incidence of neutropenia in the ARQ 197 360 mg BID group (28.9% [11 patients]) was improved to 21.2% (7 patients) for the 240 mg BID group. Improvements at the lower dose were also seen for thrombocytopenia (10.5% [4 patients] vs. 9.1% [3 patients]), leukopenia (7.9% [3 patients] vs. 6.1% [2 patients]), pancytopenia (7.9% [3 patients] vs. 0% [0 patients]), and febrile neutropenia (5.3% [2 patients] vs. 0% [0 patients]).

A total of 12 ARQ 197-treated patients experienced cardiac events (5 bradycardia, 4 sinus bradycardia, 2 arrhythmia, 1 extrasystoles, 1 atrial fibrillation, and 1 myocardial ischemia). The incidence of any of these cardiac events was ≤ 7% in either treatment group.

In summary, adverse events were reported at similar rates in ARQ 197 and placebo groups except for higher incidences of hematologic events in the ARQ 197 group. Decreased incidences of hematologic events were observed after ARQ 197 was dose reduced from 360 mg BID to 240 mg BID. ARQ 197 demonstrated a manageable safety profile at the dose of 240 mg BID.

Pharmacokinetic/Pharmacodynamic Results:

Sparse blood sampling was performed for population pharmacokinetic data analysis. The full population pharmacokinetic results for this study are reported separately from this study in a comprehensive population pharmacokinetic report.[1] ARQ 197 PK was adequately characterized by a two-compartment model with zero- and first-order absorption processes and first-order elimination. Subjects with HCC and hepatic impairment showed a 3-fold increase in ARQ 197 exposures relative to other cancer subjects. At 240 mg, the median (95% CI) predicted total exposure is 23500 ng.hr/mL (10780 – 37420 ng.hr/mL). However, within HCC patients, Child Pugh status did not further influence ARQ 197 exposure. Additionally, there was no discernible effect of CYP 2C19 phenotype on ARQ 197 exposures. Median exposure was slightly higher in subjects receiving CYP 2C19 inhibitors but this was not statistically significant. Incidence of neutropenia correlated with predicted ARQ 197 steady-state exposure (AUCss). Thus, higher ARQ 197 exposure (AUCss) in HCC patients predicted higher incidence of Grade 3 or worse neutropenia. Median ARQ 197 exposure (AUCss) associated with Grade 3 or worse neutropenia in this analysis was 39880 ng.hr/mL, while this value was 18620 ng.hr/mL for patients not showing toxicity. For HCC patients, the predicted incidence of Grade 3 or worse neutropenia was 13.6% (95% PI: 7.7 – 22.3%) following 240 mg BID and 5.4% (2.6 – 10.5%) following 120 mg BID, administered as tablets with food.

Other Results:

Not Applicable

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Conclusions:

Treatment with ARQ 197 met the primary endpoint of Study ARQ 197-215 with a statistically significant 56% improvement in TTP (HR = 0.64, log-rank p = 0.04) compared to placebo. Median (CI) TTP values for ARQ 197 and placebo were 6.9 (6.1, 12.0) and 6.0 (5.9, 6.7) weeks, respectively.

Clinically meaningful benefit was observed in MET High patients who experienced a 133% improvement in TTP (HR = 0.43, log-rank p = 0.03). Median (CI) TTP values for MET High patients in the ARQ 197 and placebo groups were 11.7 (6.0, 36.9) and 6.1 (5.9, 7.0) weeks, respectively.

The ARQ 197 total group also showed 49% improvement in PFS compared to placebo (HR = 0.67, log-rank p = .06).

The ARQ 197 total group compared to placebo analysis in MET High patients demonstrated a 122% improvement in PFS (HR = 0.45, log-rank p = 0.02). Median (CI) PFS values for MET High patients in the ARQ 197 and placebo groups were 9.6 (6.0, 20.1) and 6.0 (5.9, 6.1) weeks, respectively. No apparent differences in OS between the ARQ 197 total group or each of the ARQ 197 dose groups compared to the placebo group were noted.

Clinically meaningful OS benefits were observed for the ARQ 197 total group compared to placebo in MET High patients. The HR=0.47 represents 113% Improvement (log-rank p = 0.06). Updated OS data are available in the Clinical Study Report ARQ 197-215Addendum (Tables 2.1-2.3).

Adverse events were reported at similar rates in the ARQ 197 and placebo arms except for higher incidences of hematologic events in the ARQ 197 arm. Decreased incidences of hematologic events were observed after ARQ 197 dose reduced from 360 mg BID to 240 mg BID. ARQ 197 demonstrated a manageable safety profile at the dose of 240 mg BID.

Date of the Report: 20 December 2012