1. TITLE PAGE

CLINICAL STUDY REPORT: PROTOCOL TAC101-202

Study Title:	**A Phase 2, Double-Blind, Placebo-Controlled, Randomized, International, Multicenter Study of Oral TAC-101 as Second Line Treatment in Patients with Advanced Hepatocellular Carcinoma Who Received Sorafenib as First Line Therapy**
Product	**TAC-101**
Indication**:**	**Hepatocellular Carcinoma**
Report No.:	**TAC101-202**
IND No.:	**55,674**
Phase:	**2**
First patient enrolled:	**01 Aug 2008**
Last patient follow-up:	**10 May 2010**
Study terminated by Sponsor:	**06 May 2009**
Sponsor:	**Taiho Pharma USA, Inc.** **202 Carnegie Center, Suite 100** **Princeton, NJ 08540**
Sponsor Contact:	**Takashi Arima, PhD** **Taiho Pharma USA, Inc.** **Director, Clinical Research** **202 Carnegie Center, Suite 100** **Princeton, NJ 08540 USA** **Tel: +1 609-750-5300** **Fax: +1 609-750-7450**
Principal Investigator:	**Not applicable**
Final:	**22 Nov 2010**

This clinical study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines.

2. SYNOPSIS

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Title of Report: A Phase 2, Double-Blind, Placebo-Controlled, Randomized, International, Multicenter Study of Oral TAC-101 as Second Line Treatment in Patients with Advanced Hepatocellular Carcinoma Who Received Sorafenib as First Line Therapy

Report Number: TAC101-202

Phase: 2

Indication: Advanced hepatocellular carcinoma (HCC)

Investigators/Study Center(s): This study was conducted at 17 study centers globally.

Study Period: 01 Aug 2008 to 10 May 2010

Date of first enrollment: 01 Aug 2008

Date of last patient follow-up: 10 May 2010

Publications: None

Study Rationale: Liver cancer is the 5th most common cancer worldwide and the 3rd most common cause of cancer-related death in the world. The most important risk factors for hepatocellular carcinoma (HCC) are hepatitis B virus (HBV), hepatitis C virus (HCV), and dietary aflatoxins. Other well-established risk factors include alcoholic liver disease and hemochromatosis. Obesity, diabetes, steatosis, smoking, oral contraceptive use, and inadequate intake of selenium and antioxidants also have been implicated as risk factors. Doubling of liver cancer incidence rates in the United States of America (US/USA) and other developed countries over the past 30 years is partly attributed to chronic hepatitis C viral (HCV) infection. Although the prevalence of HCV infection is similar in the US and Japan, the incidence of HCC is 8 to 10 times higher in Japan. HCC is one of the leading causes of cancer deaths in Japan, where it ranks 3rd in males and 5th in females. In 2002, the death rate for HCC in Japan was 21 per 100,000 for males and 6.7 per 100,000 for females compared with 4.4 and 2.0 per 100,000 for males and females, respectively, in the US. The similar ratios of mortality/incidence rates worldwide reflect that the therapeutic modalities available today are poor. The development of TAC-101 would be one step toward improvement.

Currently marketed systemic chemotherapy agents, with the exception of sorafenib, provide marginal benefit. Despite the demonstrated survival benefit from sorafenib, it is still imperative to improve the effectiveness of systemic therapy in this patient population.

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Four-[3,5-bis(trimethylsilyl) benzamido] benzoic acid (TAC-101) is a synthetic retinoid that binds to retinoic acid receptors (RARs) and activates RAR transcriptional activity. TAC-101 has demonstrated antitumor activity in preclinical models. The possible mechanisms of action for TAC-101 include induction of apoptosis of HCC cells and inhibition of deoxyribonucleic acid (DNA) binding of activated protein 1 (AP-1). The compound has also been found to increase the RAR-response factors (RARβ or insulin-like growth factor binding protein-6 [IGFBP-6]) and inhibit the AP-1-related factor (the expression of vascular endothelial growth factor [VEGF] messenger ribonucleic acid [mRNA]).

In a Phase 2 study in patients with HCC in the US (Study 1528), response was evaluable by World Health Organisation (WHO) criteria in 21 of 28 patients; no patient had a complete response (CR) or partial response (PR), but 12 of 21 evaluable patients had disease stabilization. Two patients (9.5%) had late PR on restaging computed tomography (CT) scans after discontinuing TAC-101. Median survival for the 27 patients in the intent-to-treat population treated with 20 mg was 12.6 months and for the 21 evaluable patients; median survival was 19.2 months. That was considerably longer than usual for patients with advanced HCC, many of whom had received prior chemotherapy as well as surgical or other ablative procedures. Thus, while TAC-101 did not induce tumor regression, it appears to have a stabilizing effect, prolonging survival over what was expected historically.

Aside from best supportive care, there is no second line therapy available for HCC. It was hypothesized that TAC-101 treatment could extend Overall Survival (OS) after discontinuation of sorafenib.

Objectives:

Primary:

- To investigate Overall Survival (OS)

Secondary:

- To investigate antitumor activity (Progression Free Survival [PFS] and Time to Tumor Progression [TTP])
- To assess the adverse event (AE) profile and tolerability of TAC-101 as second line treatment

Optional /Exploratory:

- To evaluate the biological effects on alpha-fetoprotein (AFP) and AFP-L3
- To evaluate TAC-101 pharmacokinetics (PK) and relationship between selected efficacy and safety parameters in patients who received TAC-101 treatment
- To investigate antitumor activity after treatment discontinuation
- To evaluate the biological effects on selected RAR-related factors and a growth factor
- To investigate the relationship between tumor gene expression (mRNA expression) of co-activators, co-repressors and efficacy parameters
- To store residual complimentary deoxyribonucleic acids (cDNAs) after reverse transcription polymerase chain reaction (RT-PCR) analysis for co-factors for possible future investigation of mRNA expression of genes related to efficacy or resistance of TAC-101
- To purify and store DNA of whole blood for possible future investigation of genetic variations that may be associated with efficacy and drug-related toxicity
- To store plasma for possible future investigation of expression of biomolecules that may be associated with efficacy and drug-related toxicity.

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Study Design: This study, conducted at multiple sites globally, was a randomized, double-blind (DB), placebo-controlled, Phase 2, efficacy and safety study of TAC-101 as second-line treatment of patients with advanced HCC who failed first-line therapy with sorafenib. Patients were stratified by (1) Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2) and (2) presence/absence of vascular invasion and/or extrahepatic spread (yes vs no). After stratification, patients were randomized in a 1:1 ratio to receive either TAC-101 or placebo. Patients took 2 10-mg tablets/day administered orally on the first 14 days of each 21-day treatment cycle; the last 7 days were a recovery period.

Treatment with study medication was to continue until the patient had disease progression and/or, in the opinion of the Investigator, there was no clinical benefit to continued treatment, or the patient met 1 of the other criteria for treatment discontinuation. Imaging assessments were conducted every 6 weeks during study treatment from Day 1 (±1 week), regardless of a dose delay. If the patient discontinued study treatment for reasons other than disease progression, imaging assessments were collected every 6 weeks until disease progression. In addition, imaging assessments could be collected optionally every 6 weeks following disease progression until death or up to 2 years after the last patient was randomized. The determination of antitumor efficacy was based on objective tumor assessments made according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria of unidimensional evaluation.

As of 05 May 2009, enrollment of patients in this study was terminated by the Sponsor based on safety concerns in the TAC-101 Phase 2 study program. Only 52 of 220 planned patients had been enrolled at this time. On 06 May 2009 all sites were notified to discontinue all patients from treatment. The Sponsor followed all patients treated with TAC-101 for survival as outlined in the study protocol until May 2010. The last patient follow-up visit was 10 May 2010.

Evaluation Parameters:

- Tumor assessments based on RECIST criteria
- Adverse events (AEs), physical examinations, electrocardiogram (ECG), and vital signs
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests
- Child-Pugh score of cirrhosis severity
- Alpha-fetoprotein (AFP and AFP-L3) levels
- PK measurements

Study Population and Main Criteria for Inclusion: The study enrolled male and female patients ≥18 years of age with a diagnosis of advanced unresectable histologically confirmed HCC who had discontinued from first-line treatment with sorafenib monotherapy for any reason (ie, disease progression, intolerance) at least 14 days prior to randomization but had not received any second-line treatment for HCC. Patients had a Child-Pugh score <8 and an ECOG performance status grade of 0, 1 or 2, and met minimum laboratory test result requirements.

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Number of Patients Planned, Enrolled and Analyzed:		**Number Patients Planned/Enrolled/Number Patients Analyzed (N/N)**		
		Placebo	**TAC-101**	**Total**
	Efficacy	110/26/26	110/26/26	220/52/52
	PK	Not applicable	110/26/4	110/26/4
	Safety	110/26/26	110/26/26	220/52/52

Dose and Mode of Administration, Batch Number of Investigational Product: All patients randomized to the TAC-101 group initially received TAC-101 20 mg/day (2 x 10-mg tablets) administered orally with approximately 240 mL (8 oz) water within 1 hour following a morning meal. Treatment was given in 21-day cycles with treatment on Days 1-14 and a recovery period on Days 15-21. One dose reduction to 10 mg/day (1 x 10 mg tablet) was permitted.

The TAC-101 10-mg tablet batch numbers were S07G79, S07G81.

Dose and Mode of Administration, Batch Number of Comparative Product:

Patients randomized to the placebo group received placebo 2 x 10-mg tablets/day administered orally with approximately 240 mL (8 oz) water within 1 hour following a morning meal. Treatment was given in 21-day cycles with treatment on Days 1-14 and a recovery period on Days 15-21.

Placebo tablets batch numbers were S07E84P, S07E85P

Duration of Treatment: The study treatment cycle was defined as the following:

- Treatment days were Days 1 to 14
- Treatment recovery days were Days 15 to 21

The study drug was only to be given on Days 1 to 14 of each cycle. Within a cycle, days on which study drug was held due to toxicity counted as treatment days. Hence, dosing in any cycle was not to be extended past Day 14, regardless of the number of days drug was withheld. The recovery period could be extended an additional 21 days at the discretion of the Investigator to allow patients to recover from AEs or treatment-related toxicities. Treatment continued on 21-day cycles until the patient met any of the study treatment discontinuation criteria.

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Statistical Methods: The safety population consisted of all randomized patients who received at least one dose of double-blind medication (ie, TAC-101 or placebo) and was summarized by the treatment received. This population was the primary population for safety evaluation and was also used to summarize the efficacy endpoints and to list the PK parameters after the study was terminated by the Sponsor.

PK: Pharmacokinetic data from all patients on active treatment in the PK population was presented for TAC-101 and its 2 metabolites, TAC-101-M-1 and TAC-101-M-2. Plasma concentration data and maximum observed plasma concentration (C_{max}) were listed for all patients on active treatment providing samples. The relationship between exposure to study drug (as reflected by plasma concentration over time on Day 1) and the occurrence of any thromboembolic event (TE) was presented graphically by individual patients who either had or had not experienced a TE during the study. There were no other analyses of the PK data.

Efficacy: The study was stopped after only 52 of the required 220 patients (26 of 110 patients in each treatment group) were randomized. Therefore there was no longer adequate power for any meaningful tests of the efficacy data and no statistical tests were carried out. Efficacy data were listed and presented with descriptive statistics only.

Safety: Safety data (AEs, TEs, Child-Pugh class and scores, vital signs, ECOG performance status, ECG, and clinical laboratory results) were summarized descriptively and/or listed.

Results

Demographics:

In the placebo group, 22 patients (86.4%) were male and 4 (15.4%) were female; mean age was 68.2 years (range: 54 – 82 years). The majority (76.9%) were neither Hispanic nor Latino with 92.3% White and 7.7% Black. The majority had an ECOG performance status of 0 or 1 (92.3%) and presence of vascular invasion or extrahepatic spread (65.4%).

In the TAC-101 group, 23 patients (88.5%) were male and 3 (11.5%) were female; mean age was 71.1 years (range: 57 – 82 years). The majority (84.6%) were neither Hispanic nor Latino with 88.5% White, 7.7% 'Other', and 3.8% Asian. The majority had an ECOG performance status of 0 or 1 (96.2%) and presence of vascular invasion or extrahepatic spread (65.4%).

PK Results: PK results were not summarized.

Efficacy Results: Efficacy results were not analyzed statistically.

Primary Endpoint: Based on results of 52 patients, mean OS was 8.35 ± 5.4 months (range: 1.0 -17.0 months) for the 26 patients in the placebo group and 8.23 ± 5.4 months (range: 1.0 – 21.0 months) for 26 patients in the TAC-101 group.

Secondary Endpoints: Mean PFS was 4.82 ± 3.6 months (range: 1.0 - 13.0 months) for 22 patients in the placebo group and 4.95 ± 4.9 months (range: 2.0 – 20.0 months) for 21 patients in the TAC-101 group. Mean time to tumor disease progression was 4.09 ± 3.1 months (range: 1.0 - 12.0 months) for 22 patients in the placebo group and 4.14 ± 4.4 months (range: 2.0 – 20.0 months) for 21 patients in the TAC-101 group. The best overall response by RECIST criteria while on placebo treatment was partial response for 1 patient (3.8%), stable disease for 10 patients (38.5%), and disease progression for 3 patients (11.5%). The best overall response while on TAC-101 treatment was stable disease for 7 patients (26.9%) and disease progression for 2 patients (7.7%).

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Safety Results:

In the placebo group, 25 patients (95.2%) reported 121 AEs, including 11 patients (42.3%) with at least 1 serious adverse event (SAE). No patients in the placebo group experienced a thromboembolic event (TE). Fourteen patients (53.8%) had 31 AEs of Grade 3 or higher; 6 patients (23.1%) had an AE that resulted in death (4 deaths, 15.4% of patients, were related to tumor progression; 1 death [3.8% of patients] was related to liver disease; and, 1 death [3.8% of patients] was related to other reason [cardiac arrest]); 9 patients (34.6%) had at least 1 AE considered related to double-blind (DB) study medication. As the most extreme action taken for an AE, 6 patients (23.1%) had DB medication discontinued and 1 patient (3.8%) had dose interrupted/delayed. The most commonly (>2 patients, >7.7%) reported AEs were fatigue (26.0%), diarrhoea, oedema peripheral (each 19.2%), abdominal pain, ascites, vomiting, hyperbilirubinaemia, pruritus (each 15.4%), general physical health deteriorations, performance status decreased, bronchitis, arthralgia, cough, and dyspnoea (each 11.5%). Eleven patients (42.2%) experienced a total of 15 treatment emergent SAEs. SAEs in the placebo group were gastrointestinal haemorrhage, fatigue (2 patients each), cardiac arrest, left ventricular failure, oesphageal varices haemorrhage, disease progression, general physical health deterioration, cytolytic hepatitis, hepatic failure, hyperbilirubinaemia, weight decreased, hepatic encephalopathy, and dyspnoea (1 patient each). The 2 SAEs of fatigue and 1 of weight loss were considered related to DB study medication. AEs resulting in death were cardiac arrest, disease progression, general physical health deterioration, hepatic failure, hyperbilirubinaemia, and hepatic encephalopathy; all of these AEs were considered not related to DB study medication. The 8 AEs that resulted in discontinuation of study medication were abdominal pain, ascites, oesphageal varices haemorrhage, performance status decreased, hyperbilirubinaemia, hepatic encephalopathy (1 patient each, 3.8%), and general physical health deterioration (2 patients, 7.7%). Nine patients (34.6%) had 14 AEs considered by the Investigator as related to DB study medication (fatigue [5 patients, 19.2%, 7 AEs], hypothyroidism, diarrhoea, vomiting weight decreased, hyperkalaemia, dry skin, palmar erythema [1 patient each, 3.8%, 1 AE]). Two patients (7.7%) each had a related AE of Grade 3 or 4 (2 fatigue). Nineteen of 26 patients were reported to have died by the last contact visit. All of these deaths were reported to have occurred within 22 to 349 days following the last dose of DB study medication, including 3 deaths ≤30 after the last dose.

In the TAC 101 group, 26 patients (100.0%) reported 158 AEs; 12 patients (46.2%) had at least 1 SAE and 6 patients (23.1%) had 7 TEs (all TEs were considered SAEs and related to study medication). Sixteen patients (61.5%) had 27 AEs of Grade 3 or higher; 2 patients (7.7%) had an AE that resulted in death (1 related to tumor liver disease, 1 related to another reason [pneumonia]; none of the AEs resulting in death were considered related to DB study medication); and, 15 patients (57.7%) had at least 1 AE considered related to DB study medication. As the most extreme action taken for an AE, 11 patients (42.3%) had DB medication discontinued and 3 patients (11.5%) had the dose interrupted/delayed. The most commonly (>2 patients, >7.7%) reported AEs were asthenia (26.9%), fatigue, oedema peripheral (each 23.1%), anorexia, arthralgia (each 19.2%), abdominal pain, diarrhoea, musculoskeletal pain, deep vein thrombosis, hypertension (each 15.4%), dizziness, dyspnoea, epistaxis, palmar-plantar erythrodysaesthesia syndrome, and rash (each 11.5%). The 7 TEs were 4, 15.4%, deep vein thrombosis, 2, 7.7%, arterial thrombosis, and 1, 3.8%, pulmonary embolism (PE). The 13 AEs resulting in discontinuation of DB study medication were deep vein thrombosis, 4 patients (15.4%); atrial thrombosis, blood bilirubin increased 2 patients each (7.7%); performance status decreased, hepatic failure, pneumonia, pulmonary embolism, and thrombophlebitis superficial 1 patient each (3.8%). The most common (>2 patients, >7.7%) AEs considered by the Investigator as related to DB study medication were asthenia, fatigue (each 23.1%); anorexia, arthralgia, musculoskeletal pain (each 15.4%), palmar-plantar erythrodysaesthesia syndrome, deep vein thrombosis (each 11.5%). Nine patients (34.6%) had 10 related AEs of Grade 3 or 4 (2 each atrial thrombosis and deep vein thrombosis; 1 each asthenia, fatigue, musculoskeletal pain, osteoarthritis, pulmonary embolism, and hypertension). In the TAC 101 group, 12 patients (46.2%) experienced a total of 14 treatment emergent SAEs including 2 patients with SAEs with an outcome of death. SAEs in the TAC 101 group were deep vein thrombosis (4 patients), atrial thrombosis, dyspnoea (2 patients each), abdominal pain, oedema due to hepatic disease, hepatic failure, pneumonia, epilepsy, and pulmonary embolism (1 patient each). Twenty of 26 patients were reported to have died by the last contact visit. All of these deaths were reported to have occurred within 2 to 325 days following the last dose of DB study medication, including 2 deaths ≤30 after the last dose.

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Clinical laboratory tests other than coagulation parameters, physical examination, vital signs, ECOG, and ECG findings did not indicate any further increased risk with TAC-101 treatment of patients with advanced HCC who had previously failed sorafenib therapy.

Conclusions:

There is an increased risk for the occurrence of a thromboembolic event in patients with advanced HCC treated with TAC-101 after sorafenib treatment as 1st line therapy. This study was terminated early due to the unexpected higher occurrence of thromboembolic events than that observed in the previous Phase 2 Study 1528. The higher thromboembolic event rate is caused by an activation of the coagulation system indicated by the increase of D-dimer after TAC-101.

Because only 52 of 220 planned patients were randomized and dosed with DB study medication in this study, no statistical analyses were performed and no conclusions can be drawn as to the differences in efficacy between TAC-101 and placebo in patients with advanced HCC who had previously failed sorafenib therapy.

Too few patients were evaluable to assess the pharmacokinetics of TAC-101 and its metabolites in this study.

Date of the Report: 22 Nov 2010