PROTOCOL SYNOPSIS	
Title of Study: **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**	
Protocol Number:	TAC101-202
Phase:	2
Indication:	Second line treatment for patients with advanced hepatocellular carcinoma (HCC) who received sorafenib as first line therapy
Rationale	• 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 and inhibition of deoxyribonucleic acid (DNA) binding of activated protein 1. The compound has also been found to inhibit vascular endothelial growth factor (VEGF) messenger ribonucleic acid (mRNA) production and VEGF expression. • In a recently completed Phase 2 study (Study 1528) in patients with HCC, TAC-101 did not produce responses while patients were on treatment (median duration of 42 days). However, a median survival time of 12.6 months (N = 27) was observed, which is considerably longer than that usually observed in this patient population. Thus, TAC-101 may have a stabilizing effect in HCC that could result in prolonged survival. • The clinical pharmacokinetics (PK) of TAC-101 were investigated in one Phase 1 and three Phase 1/2 studies. The area under the concentration-time curve (AUC) and maximum observed drug concentration (C_{max}) values increased with dose. No evidence of nonlinearity in apparent drug clearance (CL/F) was found across dose levels; drug clearance was unrelated to either patient body surface area or weight. There was no evidence of drug accumulation after 28 days dosing. • The TAC-101 dose regimen to be used in this study is 20 mg/day administered orally (PO) within 1 hour following a meal for 14 days followed by a 7-day recovery period. This dose regimen, which was determined (Study 1528) to be the maximum tolerated dose (MTD) of TAC-101 administered under fed conditions to HCC patients, was well tolerated by most patients in prior studies. • In a Phase 3, placebo-controlled study with the multikinase inhibitor sorafenib as first line treatment for patients with advanced HCC, median overall survival (OS) for the sorafenib group of patients in the intent-to-treat (ITT) population was 46.3 weeks (10.7 months), median time to tumor progression (TTP) was 24.0 weeks (5.5 months) by independent review, and median duration of treatment was 23 weeks (5.3 months). Sorafenib has recently become available as first line treatment for HCC in several countries and is expected to become the standard of care for the first-line treatment of advanced HCC. • Currently there is no second line therapy available for HCC. It is hypothesized that TAC-101 treatment can extend OS after discontinuation of sorafenib. This double-blind, placebo-controlled Phase 2 study is designed to assess the survival benefit of oral TAC-101 as second line treatment in patients with HCC who received sorafenib as first line therapy.
Study Objectives:	Primary • To investigate OS Secondary • To investigate antitumor activity (progression-free survival [PFS]) and time to tumor progression

	• 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 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 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
Study Design:	This Phase 2, randomized, double-blind, placebo-controlled international, multicenter study is designed to evaluate the efficacy and safety of TAC-101 as second line treatment in patients with advanced HCC following treatment with sorafenib as first-line therapy. After stratification by (1) Eastern Cooperative Oncology Group (ECOG) score (0 or 1 vs 2) and (2) presence/absence of vascular invasion and/or extrahepatic spread (yes vs no) patients will be randomized to either oral TAC-101 or placebo in a 1:1 ratio. Evaluations of safety and efficacy in both treatment arms will be based on a 21-day cycle. TAC-101 PK will be evaluated at selected time points on Day 1 of Cycle 1.
Study Duration:	Treatment with either TAC-101 or placebo will continue until the patient has clinical or tumor disease progression and, in the opinion of the Investigator, there is no clinical benefit to continue treatment or the patient meets 1 of the other criteria for treatment discontinuation. A comprehensive safety follow-up evaluation will be performed at least 30 days (+1 week) after discontinuation of study treatment. For patients who discontinue without tumor disease progression, patient survival status, use of intercurrent antitumor treatment, measurements of AFP and AFP-L3, and tumor imaging will be collected every 6 weeks (±1 week) until tumor disease progression. Following tumor disease progression for all patients, survival status and use of any intercurrent antitumor treatment will continue to be collected every 6 weeks (±1 week), and measurements of AFP and AFP-L3, and tumor imaging may be conducted optionally every 6 weeks (±1 week) until death or up to 2 years after the last patient is randomized. The primary analysis for this study will be conducted when 156 events (deaths) have been observed or after a minimum of 6 months from the date of randomization of the last patient, whichever is later. After the primary analysis is conducted, treatment code will be unblinded and survival follow-up may continue up to 2 years after the last patient is randomized. The sponsor will collect survival status on all consenting patients receiving study medication.
Study Population:	Male and female patients at least 18 years of age with advanced HCC who discontinued from first line treatment with sorafenib for any reason but have not received second line treatment for HCC, and have at least 1 tumor lesion which can be accurately measured according to Response Evaluation Criteria in Solid Tumors (RECIST).
Planned Sample Size:	220 total patients, 110/arm

Treatment Regimen:	Patients randomized to TAC-101 will receive TAC-101 20 mg (administered as 2 × 10-mg formulated tablets) PO daily with approximately 240 mL (8 oz) of water under fed conditions (no later than 1 hour after a meal) for 14 days followed by a 7-day recovery period. This cycle will be repeated every 21 days. Patients randomized to placebo will receive 2 placebo tablets (identical in appearance to the TAC-101 tablets) administered PO daily with approximately 240 mL (8 oz) of water under fed conditions (no later than 1 hour after a meal) in a regimen identical to that for TAC-101. All patients may be treated with palliative treatment as clinically indicated, excluding any systemic chemotherapy, biologic therapy, immunotherapy, radiotherapy, local therapy/surgery, and any experimental therapy for the treatment of HCC.
Safety Endpoints:	• AEs, and AEs of special interest (thromboembolic events [TEs]) • Clinical laboratory tests (serum chemistry, hematology, urinalysis, coagulation, and lipid metabolism) • Physical examinations including vital signs assessment; ECOG performance score • Concomitant medications • Electrocardiogram (ECG) • Tolerability (discontinuations, treatment delays, dose reductions) Standard safety monitoring and grading using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v. 3.0) will be performed.
Efficacy Endpoints:	Primary • Overall survival Secondary • Progression-free survival and time to tumor progression Optional/Exploratory • Changes in plasma levels of AFP and AFP-L3 • Antitumor activity based on imaging assessments • Changes in selected RAR-related factors and a growth factor • Tumor gene expression
PK Endpoints:	Maximum Plasma Concentration (C_{max}) and Area Under the Plasma Concentration-Time Curve ($AUC_{0\text{-}inf}$)
Statistical Methods:	Analysis Populations • Full Analysis Set (FAS) population – all randomized patients who receive at least 1 dose of TAC-101 or placebo, with study treatment assignment designated according to randomization, regardless of whether patients receive a different treatment from that to which they were randomized. • Safety population – all randomized patients who received any dose of study drug analyzed by the treatment received. • PK population – patients in the TAC-101 arm who consented to have PK assessment and provide PK blood samples. Primary Endpoint Efficacy Evaluation: The superiority test (1-sided) of TAC-101 versus placebo for the primary OS analysis will be based on the stratified log-rank test. In addition, the hazard ratio will be estimated based on Cox's proportional hazard model. Sensitivity analysis for the superiority of TAC-101 will be performed using the unstratified log-rank test. Additionally, graphical displays of time to event parameters will be produced. Cox's regression approach will be used to assess the influence of other baseline characteristics and prior and follow-up treatment effects on survival.

	Secondary Endpoints Efficacy Evaluation: PFS and TTP will be analyzed using the same methods as for OS. Additionally, graphical displays of time to event parameters will be produced (eg, for PFS and TTP). Descriptive statistics will be used to summarize optional/exploratory endpoints, including antitumor activity after treatment discontinuation, and change in AFP and AFP-L3 levels. Safety Evaluation: The general safety and tolerability of TAC-101 compared to placebo will be summarized based on AEs, AEs of special interest (TEs), routine clinical laboratory evaluations (serum chemistry, hematology, urinalysis, coagulation parameters, and lipid metabolism), physical examination, and ECOG performance status. PK Evaluation: Pooled data of plasma concentrations of TAC-101 and its metabolites will be subjected to population PK analysis to estimate individual drug exposure. The relationship between TAC-101 PK parameters (individually estimated C_{max} and $AUC_{0\text{-}inf}$) and selected efficacy/safety parameters will be explored.
Sample Size:	Sample size considerations are based on the OS endpoint. The median OS in the placebo group is hypothesized to be 4.4 months. This is based on the 10.7-month median OS and 5.3-month median duration of treatment observed in the Phase 3 study of sorafenib versus placebo in first-line patients and allowing a 1-month transition period between therapies. The median OS for first-line patients in the TAC-101 open-label, single-arm Phase 2 study (1528) was 12.6 months. Assuming a median OS for second-line patients in the TAC-101 arm of 6.6 months and a target hazard ratio (TAC-101:placebo) of 0.667, equivalent to a 50% improvement in OS, the study will have 80% power to test the superiority of TAC-101 versus placebo using a stratified log-rank test with one-sided probability of 0.05 when the target number of events (ie, deaths) is 156. Assuming a 14-month uniform accrual, a minimum 6 month follow-up period, and a loss to follow-up (withdrawal of consent) rate of 10%, a total of 220 patients will be enrolled to achieve the specified number of events in the scheduled follow-up time.
Interim Analysis:	There will be no interim analysis to test for early demonstration of a potential superior survival advantage for TAC-101. As such, no alpha spending has been taken into consideration for sample size calculation and the final analysis will be performed at the 5% significance level. A safety review will be conducted by a Data Monitoring Committee (DMC) after 50 patients have been treated for 2 cycles and will include a comparison of the serious adverse event (SAE) profile including TEs for TAC-101 versus placebo. In addition, incremental and cumulative safety data will be reviewed by the DMC at quarterly intervals until study completion.

1.0 FLOW CHARTS

TABLE 1.A STUDY SCHEDULE

Assessment	Screening/ Baseline	Cycle 1 Day		Additional Cycles Day		End of Treatment (EOT)	Safety Follow-up	Survival Follow-up
	Day -14 to -1	1 (±2 d)	15 (±2 d)	1 (±2 d)	15 (±2 d)	As soon as possible following last dose	30 days (+1 week) after last dose	Every 6 weeks (±1 week)
Sign ICF	X							
Eligibility Criteria, CLIP Score	X							
Randomization	X[a]							
Medical History	X							
Child-Pugh Classification	X[b]			X[b]				
PE, Vital Signs, Weight	X	X		X		X	X	
Height	X							
ECOG PS	X	X		X		X	X	
ECG	X	X		X		X	X	
Chest X-ray	X							
Tumor Imaging	X[c]			X[c]		X		X[d]
Hematology, Chemistry	X[e]	X	X	X	X	X	X	
Coagulation	X[e]	X	X	X	X	X	X	
Urinalysis	X[e]	X		X				
Serum or Urine Pregnancy Test	X[f]							
Hepatitis tests for HBV and HCV	X[g]							
Plasma AFP and AFP-L3 Levels	X[e]	X		X		X		X[d]
RAR-Related Factors/Growth Factor	X			X[h]				
Tissue Assessment for Co-factors Regulating RAR Transcriptional Activity	X[i]							
Blood Sampling for DNA Banking	X							
Blood Sampling for Plasma Banking	X		X		X[o]			
PK Blood Samples		X[j]						

(continued)

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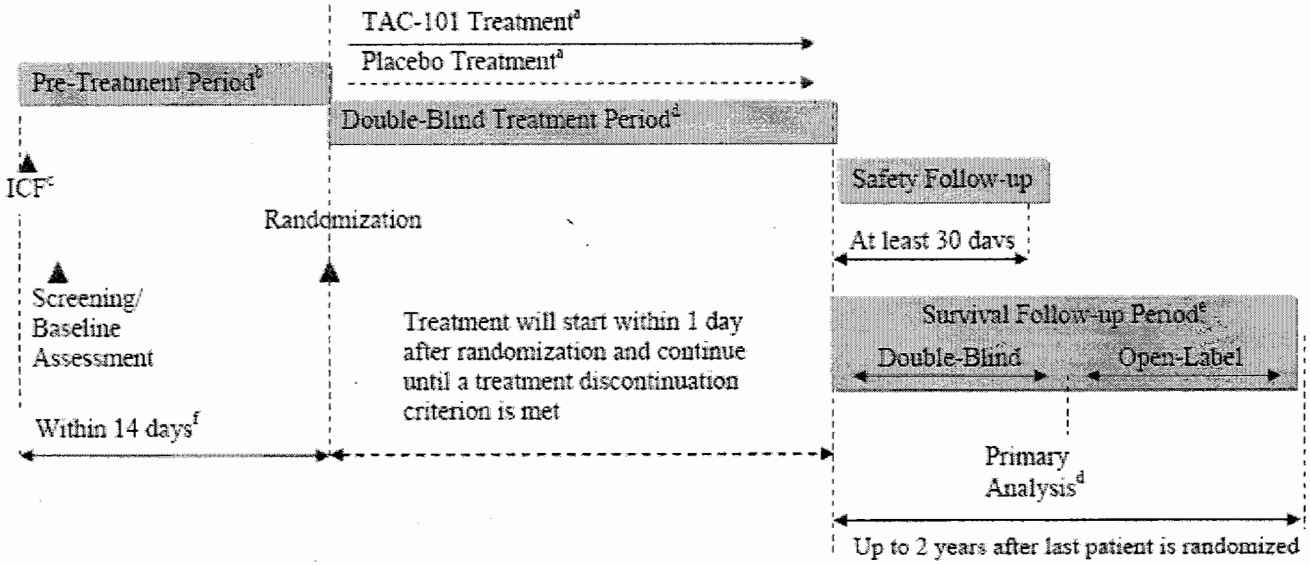
Assessment	Screening/ Baseline	Cycle 1 Day		Additional Cycles Day		End of Treatment (EOT)	Safety Follow-up	Survival Follow-up
	Day -14 to -1	1 (±2 d)	15 (±2 d)	1 (±2 d)	15 (±2 d)	As soon as possible following last dose	30 days (+1 week) after last dose	Every 6 weeks (±1 week)
Survival Status								X[k]
Concomitant Medications and Therapies	X	→	→	→	→	→	X	X[k,l]
Adverse Event Evaluation	X	→	→	→	→	→	X[m]	
Dispense Study Drug [n]		X		X				

EOT = End of Treatment; PE = physical examination; ECOG = Eastern Cooperative Oncology Group; PS = Performance Status; d = Study Day.

[a] Randomization will be conducted on Day -1 or Day 1.
[b] Obtain within 72 hours prior to study medication administration on Day 1, Cycle 1. Obtain prior to dosing on Day 1 (-2 days) of all subsequent cycles.
[c] Tumor imaging will be done at Screening/Baseline any time within 4 weeks prior to the first dose of study treatment on Day 1, Cycle 1, and every 6 weeks (±1 week) during treatment, regardless of a dose delay.
[d] If patient discontinues study treatment without tumor disease progression, collect AFP and AFP-L3 data every 6 weeks (±1 week) until tumor disease progression (PD). Following PD, collect AFP and AFP-L3 data optionally every 6 weeks (±1 week) until death or up to 2 years after the last patient is randomized.
[e] Hematology, serum chemistry, urinalysis, coagulation, and AFP and AFP-L3 tests on Day 1 Cycle 1 may be omitted if baseline evaluations were collected within 72 hours prior to study medication administration on Day 1 Cycle 1. Obtain prior to dosing on Day 1 (-2 days) of each cycle.
[f] Obtain negative pregnancy test within 2 days prior to Day 1 Cycle 1 and prior to randomization.
[g] The test need not be repeated if there is previous positive documentation of HBV or HCV.
[h] RAR-related Factors will be assessed every 6 weeks (±1 wk) during the treatment period.
[i] Initial assessment to be done on tissue removed prior to study, if available; tests need not be completed prior to study entry.
[j] PK blood samples will be drawn at 4 hours (±1 hr), 8 hours (±1 hr), and 24 hours (±1 hr) after the first dose of study drug on Day 1, Cycle 1. The 24-hour sample must be collected prior to dosing on Day 2.
[k] Collect every 6 weeks (±1 week) until death or up to 2 years after the last patient is randomized.
[l] Collect concomitant antitumor therapies only.
[m] All AEs occurring within 30 days from the last dose of study medication will be collected.
[n] Patients will receive study medication for 14 days followed by a 7-day recovery period. This cycle will be repeated every 21 days.
[o] Obtain plasma sample on Day 15 (± 2 days) of Cycle 2 only.

FIGURE 1.A TAC101-202 STUDY DESIGN SCHEMA



[a] Patients will receive study medication for 14 days followed by a 7-day recovery period. This cycle will be repeated every 21 days.

[b] Patients last dose of sorafenib must be prior to Day -14. Patients must have discontinued from sorafenib at least 14 days prior to randomization.

[c] Signing of the ICF must occur during the pretreatment period and prior to performing any study procedures.

[d] The primary analysis will be conducted when 156 events (deaths) have been observed or at a minimum of 6 months after last patient randomized, whichever is later. At that time treatment code will be unblinded.

[e] For patients who discontinue without tumor disease progression, patient survival status, use of intercurrent antitumor treatment, measurements of AFP and AFP-L3, and tumor imaging will be collected every 6 weeks (±1 week) until tumor disease progression. Following tumor disease progression for all patients, survival status and use of any intercurrent antitumor treatment will continue to be collected every 6 weeks (±1 week), and measurements of AFP and AFP-L3, and tumor imaging may be conducted optionally every 6 weeks (±1 week) until death or up to 2 years after the last patient is randomized.

[f] Baseline tumor imaging may be done any time within 4 weeks prior to the first dose of study treatment on Day 1, Cycle 1.