2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT–869		
Name of Active Ingredient: linifanib		
Title of Study: An Open-Label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) versus Sorafenib in Subjects with Advanced Hepatocellular Carcinoma (HCC)		
Coordinating Investigator: Cailin Cainap, MD Senior Oncologist Institute of Oncology Cluj – Napoca 34-36 Republicii Street Cluj-Napoca, Romania 400015		
Study Sites: Approximately 207 investigators participated in the study at approximately 186 sites in 28 countries (Argentina, Australia, Austria, Belgium, Canada, Chile, China, Czech Republic, Germany, Greece, Denmark, Egypt, Spain, France, Hong Kong, Italy, Japan, South Korea, Mexico, Malaysia, Netherlands, Norway, New Zealand, Romania, Russia, Singapore, Taiwan, and the United States of America).		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 13 January 2010 Last Subject Last Visit: 30 July 2012	**Phase of Development:** 3	
Objectives: The primary objective of this study was to assess the overall survival of oral linifanib given as monotherapy once daily compared with sorafenib given twice daily per standard of care in subjects with advanced or metastatic HCC. The secondary objectives of this study were to assess time to progression and objective response rate in those subjects treated with linifanib compared with sorafenib. The tertiary objectives were to assess progression-free survival and quality of life.		
Methodology: This was a Phase 3, randomized, controlled, open-label, multinational, multicenter study to evaluate the efficacy and tolerability of linifanib (ABT-869) compared with sorafenib in subjects with advanced or metastatic HCC who had not received prior systemic therapy. Subjects were randomized in a 1:1 ratio to linifanib or sorafenib.		

Methodology (Continued):

Linifanib 17.5 mg was orally self-administered daily with at least 120 mL of water under fasting conditions in the evening. Fasting conditions were defined as no food or beverage consumption (except water and scheduled concomitant medications) for a minimum of 2 hours before dosing with linifanib and for a minimum of 2 hours after dosing with linifanib. There were no scheduled dosing breaks, but dose reductions or drug holidays due to study drug-related toxicities could occur based on the discretion of the investigator. Sorafenib 400 mg was orally self-administered twice daily per the dose recommendation on the label.

The screening procedures and baseline radiographic tumor assessments were to be performed within 21 days prior to the first dose of study drug (Study Day 1). If the screening visit was performed greater than 7 days prior to Study Day 1, the physical exam, laboratory tests, and a pregnancy test (for female subjects of childbearing potential) were to be repeated on Study Day 1. Vital sign and performance status assessments were to be performed on Study Day 1 for all subjects.

Study visits were to be conducted on Day 1 of the first 3 weeks and then on Day 1 of every 3 weeks thereafter (starting with Week 4). Subjects continued dosing with linifanib or sorafenib until they met the defined discontinuation criteria or until 31 May 2012. When an investigator determined that a subject should discontinue the study, a final visit was to be conducted.

Survival information (i.e., the date and cause of death) and posttreatment information were to be collected via interactive voice response system/interactive web response system at monthly intervals (or as requested by Sponsor to support data analysis) after the last study visit until the endpoint of death or until the subject became lost to follow-up or until 30 June 2012.

The safety of linifanib and sorafenib was assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, changes in laboratory and vital sign parameters, and electrocardiogram (ECG) results.

Number of Subjects (Planned and Analyzed):

Approximately 900 to 1,100 subjects were planned. A total of 1,035 subjects were randomized to either linifanib or sorafenib treatment and were included in the efficacy analyses. A total of 1,029 subjects received linifanib or sorafenib and were included in the safety analyses.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 18 years with unresectable or metastatic hepatocellular carcinoma (HCC), Eastern Cooperative Oncology Group score of 0 to 1, and acceptable hematology and chemistry values were eligible for enrollment.

Test and Reference Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Not applicable to an abbreviated clinical study report.

Duration of Treatment:

Therapy was to continue as a single agent until disease progression or toxicities prohibited further continuation.

Criteria for Evaluation:

Safety: Adverse events, laboratory assessments, vital signs, multiple gated acquisition scan, echocardiogram, and physical examinations.

Statistical Methods

Efficacy:

Time to death for a given subject was defined as the number of days from the day the subject was randomized to the date of the subject's death. All events of death were included, regardless of whether the event occurred while the subject was still taking study drug. If a subject had not died, the data were censored at the date when the subject was last known to be alive.

Time to progression was defined as the number of days from the date of randomization to the date of earliest disease progression, per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. All disease progression was included regardless of whether the event occurred while the subject was still taking study drug. If the subject did not experience disease progression, the data were censored at the date of last radiographic tumor assessment. If the subject did not experience disease progression and did not have any post-baseline radiographic tumor assessments, the subject was censored at the date of randomization. If a disease progression event occurred at the time when a subject missed 2 or more scheduled consecutive radiographic tumor assessments, this subject was censored at the last radiographic tumor assessment prior to the missing tumor assessments.

The objective response rate was defined as the proportion of subjects with a confirmed complete or partial response, per RECIST Version 1.1.

Safety:

Analyses of adverse events included only "treatment-emergent" events with onset on or after the day of the first dose of study drug. Analyses did not include those that occurred greater than 30 days after the last dose of study drug. Treatment-emergent adverse events were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for number and percent of subjects experiencing an adverse event at a given National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) toxicity grade, relationship to study drug, adverse events that resulted in study drug discontinuation, and serious adverse events were provided.

Changes from baseline for blood chemistry, hematology parameters, urinalysis, and vital sign parameters were summarized for each scheduled postbaseline visit and for the final visit. The baseline measurements on the day of or prior to the first dose of study drug were used as the baseline measurements. The Final Visit was defined as the last postbaseline measurement collected within 30 days of the last dose of study drug. The postbaseline visit included those visits occurring within 30 days of the last dose of study drug. Blood chemistry and hematology variables were categorized according to NCI CTCAE grades, and shifts from baseline grades to maximum and final post-baseline grades were assessed. The maximum grade and final post-baseline grade occurred within 30 days of the last dose of study drug.

Detailed data listings were provided for subjects experiencing potentially clinically significant (PCS) vital sign values according to the AbbVie-defined criteria for PCS (very low and very high) values. All collected measurements were included in these listings, regardless of the number of days after the last dose of study drug.

Summary/Conclusions

Efficacy Results:

Median overall survival, when estimated death dates were censored, was 299 days (95% confidence interval [CI] 255 – 342) for subjects in the sorafenib group and 276 days (95% CI 247 – 309) for subjects in the linifanib group. The stratified hazard ratio (linifanib over sorafenib) was 1.039 (95% CI 0.892 – 1.210). Overall survival was not statistically significantly different between the treatment groups. When a data cutoff of 667 deaths was used, the upper limit of the 95.1% CI hazard ratio was 1.221, which is greater than the non-inferiority margin of 1.0491. Therefore, non-inferiority was not met.

Median time to disease progression, when censoring disease progression events missing 2 or more consecutive CT scans, was 123 days (95% CI 85 – 127) for subjects in the sorafenib group and 165 days (95% CI 129 – 169) for subjects in the linifanib group. The stratified hazard ratio (linifanib over sorafenib) was 0.759 (95% CI 0.643 – 0.895). Subjects in the linifanib group had a statistically significantly longer time to progression than those in the sorafenib group ($P = 0.001$).

The confirmed objective response rate (complete response or partial response) was statistically significantly greater for the linifanib group (52 [10.1%] subjects) compared with the sorafenib group (32 [6.1%] subjects) ($P = 0.018$).

Pharmacokinetic Results:

The PK of linifanib was evaluated in 12 Chinese and 6 Japanese subjects with advanced HCC. Linifanib PK appeared to be similar between the 2 groups.

Safety Results:

Overall, a statistically significantly greater proportion of subjects receiving linifanib than subjects receiving sorafenib experienced adverse events that were grade ≥ 3, serious, or led to reduction, interruption, or discontinuation of study drug. The incidence of deaths was similar between treatment groups.

At least 1 adverse event was experienced by 511 (98.5%) subjects in the sorafenib group and 508 (99.6%) subjects in the linifanib group. The adverse events reported in this study are similar to those seen in other studies of linifanib and with other agents in the vascular endothelial growth factor (VEGF)/platelet-derived growth factor (PDGF) tyrosine kinase receptor inhibitor class, including left ventricular dysfunction, hypothyroidism, malaise, edema peripheral, blood thyroid stimulating hormone increased, proteinuria, dyspnea, oropharyngeal pain, palmar plantar erythrodysesthesia syndrome, hypertension, and skin ulcer. With the exception of dyspnea and palmar plantar erythrodysesthesia syndrome, a statistically significantly ($P \leq 0.05$) greater proportion of subjects in the linifanib group experienced these adverse events compared with the sorafenib group.

Summary/Conclusions (Continued)

Safety Results (Continued):

Clinically meaningful changes in laboratory values were reflective of agents in the anti-VEGF class (increased urine protein:creatinine ratio; proteinuria). For both treatment groups, percentage increases in laboratory values of > 10% from mean baseline to mean final assessment were observed for lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and total bilirubin, and decreases of > 10% were observed for albumin. For the linifanib group only, an increase of > 10% was observed for blood urea nitrogen (BUN). For the sorafenib group only, a decrease of > 10% was observed for inorganic phosphate. Mean increases in systolic and diastolic blood pressure values were observed, and PCS very high systolic and diastolic blood pressure values were experienced by approximately half of subjects in each group. However, a statistically significantly greater proportion of subjects in the linifanib group than the sorafenib group experienced adverse events of hypertension.

Conclusions:

Median overall survival, when estimated death dates were censored, was 299 days (95% CI 255 – 342) for subjects in the sorafenib group and 276 days (95% CI 247 – 309) for subjects in the linifanib group. The stratified hazard ratio (linifanib over sorafenib) was 1.039 (95% CI 0.892 – 1.210). Overall survival was not statistically significantly different between the treatment groups. When a data cutoff of 667 deaths was used, the upper limit of the 95.1% CI hazard ratio was 1.221, which is greater than the non–inferiority margin of 1.0491. Therefore, non–inferiority was not met.

Median time to disease progression, when censoring disease progression events missing 2 or more consecutive CT scans, was 123 days (95% CI 85 – 127) for subjects in the sorafenib group and 165 days (95% CI 129 – 169) for subjects in the linifanib group. The stratified hazard ratio (linifanib over sorafenib) was 0.759 (95% CI 0.643 – 0.895). Subjects in the linifanib group had a statistically significantly longer time to progression than those in the sorafenib group ($P = 0.001$).

The confirmed objective response rate (complete response or partial response) was statistically significantly greater for the linifanib group (52 [10.1%] subjects) compared with the sorafenib group (32 [6.1%] subjects) ($P = 0.018$).

The PK of linifanib appeared to be similar between Chinese and Japanese subjects with advanced HCC.

A statistically significantly greater proportion of subjects receiving linifanib than subjects receiving sorafenib experienced adverse events that were grade ≥ 3, serious, or led to reduction, interruption, or discontinuation of study drug.

With the exception of dyspnea and palmar-plantar erythrodysesthesia syndrome, effects known to be related to VEGF inhibition were significantly higher in subjects receiving linifanib than in those receiving sorafenib.

More events of hepatic failure, hepatotoxicity, hyperbilirubinemia, and hepatic encephalopathy were reported in the linifanib group than the sorafenib group. No significant differences were noticeable in ALT, AST, or AP between the 2 treatment groups.

Summary/Conclusions (Continued)

Conclusions (Continued):

The total number of adverse events relating to hepatobiliary disorders and cases of hepatic encephalopathy were reported more frequently in the linifanib group than the sorafenib group ($P < 0.001$). Baseline characteristics such as Child-Pugh score, liver function tests, and exposure and known risks for hepatic injury such as a history of hepatitis, alcohol ingestion, and cirrhosis were similar in both groups. The reason for this difference is still unclear.

Serious adverse events of hypoglycemia (generally reported in patients with diabetes mellitus) and mucosally-associated events (e.g., peri-rectal inflammation and mucositis) were proportionally higher in the linifanib group than the sorafenib group.