2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-869	**Volume:**	
Name of Active Ingredient: linifanib	**Page:**	

Title of Study:

A Phase 2 Randomized, Placebo-Controlled, Double-Blind Study of ABT-869 in Combination With Paclitaxel Versus Paclitaxel Alone as First-line Treatment in Subjects With Locally Recurrent or Metastatic Breast Cancer

Coordinating Investigator:

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Study Sites: Four clinical sites in North America participated in the study.

Publications: There is 1 published abstract based on this study:

Rugo HS, Lopez-Hernandez J, Gómez-Villanueva A, Gupta N, Qian J, Qin Q, et al. ABT-869 in combination with paclitaxel (P) as first-line treatment in patients (Pts) with advanced breast cancer. [Abstract 5076]. Cancer Res. 2009;69(24)(suppl):790s.

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 08 July 2008 Last Subject Last Visit: 09 December 2009	

Objectives: The study objectives applied to the randomized portion of the study and were not addressed since the randomized portion was not conducted. The primary objective of the study was to assess if the addition of oral ABT-869 to paclitaxel can prolong progression-free survival (PFS) compared to paclitaxel alone in the first line treatment of subjects with metastatic breast cancer. The secondary objectives of the study were to evaluate overall survival and other efficacy endpoints, as well as the safety and tolerability of the combination. The tertiary objectives were to evaluate quality of life and performance status.

Methodology: This study was planned as a Phase 2, randomized, placebo-controlled, double-blind, multicenter study of the efficacy and tolerability of 0.20 mg/kg QD ABT-869 in combination with paclitaxel versus paclitaxel alone in subjects with documented locally recurrent or metastatic breast cancer in the first line metastatic therapy setting. The study also included an initial open-label, lead-in cohort to provide an initial assessment of coadministration of ABT-869 and paclitaxel.

Methodology (Continued):

In the open-label, lead-in cohort, 6 subjects were to be monitored for 2 cycles (8 weeks) to assess the PK interactions and the safety of the combination of 0.20 mg/kg QD ABT-869 and paclitaxel (90 mg/m^2). Per the protocol, a lower dose of ABT-869 (0.15 mg/kg QD) was explored in combination with paclitaxel based on the tolerability of the combination. The lead-in cohort was enrolled at sites in North America only.

Randomization into the blinded portion of the study was to begin after the lead-in cohort had completed 2 cycles of open-label therapy. Subjects were to be randomized in a 1:1 ratio to 1 of 2 treatment arms (paclitaxel + ABT-869 versus paclitaxel + ABT-869 matching placebo). Approximately 90 subjects were to be enrolled at approximately 50 sites. Based on a change in the ABT-869 development plan, only the lead-in portion was completed as planned and the randomized portion of the study was not initiated. For this reason, only the details of the study plan and results of the lead-in portion of the study are discussed in this report.

Study visits were conducted on Days 1, 8 and 15 of every 28-day cycle. When an investigator had determined that a subject should discontinue the study, a Final Visit was conducted.

Number of Subjects (Planned and Analyzed):

Six subjects were to be enrolled at each dose level in the lead-in portion. Five subjects were enrolled in the 0.20 mg/kg ABT-869 + paclitaxel treatment group and 5 subjects in the 0.15 mg/kg ABT-869 + paclitaxel treatment group for a total of 10 subjects. Ten subjects were included in the safety and efficacy analysis and 9 subjects were included in the pharmacokinetic analysis.

Diagnosis and Main Criteria for Inclusion:

Female subjects (≥ 18 years of age) diagnosed with adenocarcinoma of the breast who at enrollment had locally recurrent or metastatic disease that was not amenable to local treatment (surgical or radiation) with curative intent for which no prior chemotheapy had been received. At least 12 months must have passed since the subject received prior adjuvant or neoadjuvant cytotoxic chemotherapy.

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

Abbott supplied ABT-869 tablets in 2 strengths (2.5 mg and 10 mg) for oral administration. All subjects were to receive paclitaxel (90 mg/m^2) via IV infusion over 1 hour; paclitaxel was not supplied by Abbott.

Duration of Treatment:

Subjects were to continue to dose ABT-869 and paclitaxel until criteria for discontinuation, which included disease progression, were met.

Criteria for Evaluation

Efficacy: tumor assessments, target lesion measurement, performance status, FACT-B (version 4) quality of life.

Pharmacokinetic: ABT-869 and metabolites, and paclitaxel plasma concentrations.

Safety: adverse events, laboratory assessments, vital signs, physical examination, and MUGA scan.

Statistical Methods

Efficacy:

Efficacy analyses included the objective response rate (complete response and partial response), best response (complete response, partial response, stable disease, progressive disease, and incomplete data), and best percent change in the sum of longest diameters for target lesions identified at Baseline.

Pharmacokinetic:

For the lead-in cohort, values for the pharmacokinetic parameters of ABT-869 and metabolite(s), including the maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), the minimum observed plasma concentration (C_{min}) and the area under the plasma concentration curve for the 24-hour dosing interval (AUC_{24}) were determined using non-compartmental methods. Values for the pharmacokinetic parameters of paclitaxel, including C_{max}, T_{max}, the terminal phase elimination rate constant (β) and the area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}) were determined.

Safety:

Safety summaries included all subjects participating in the lead-in portion. Data were presented by treatment group and overall.

The number and percentage of subjects having treatment-emergent adverse events (i.e., those that began on or after the day of the first dose of study drug and within 30 days after the last dose of study drug) were tabulated by the Medical Dictionary for Regulatory Activities version 12.1 (MedDRA® version 12.1) system organ class and preferred term. The tabulations were also provided with further breakdowns by NCI CTCAE toxicity grade and relationship to study drug. Serious adverse events, events leading to discontinuation of treatment, and events leading to death, were summarized. All summaries were done by dose, with an adverse event attributed to the initially received treatment.

Laboratory and vital signs data were summarized. The baseline value (i.e., last measurement before the beginning of study drug administration) was included in the statistical analysis and changes from baseline were summarized. Where applicable, blood chemistry and hematology determinations were categorized according to NCI CTCAE grades, and shifts from baseline NCI CTCAE grades to maximum and final postbaseline grades for each treatment group were assessed. Urine protein, vital signs, and left ventricular ejection fraction (LVEF), per MUGA scan, values were evaluated for possible clinical significance using criteria developed at Abbott.

Summary/Conclusions

Efficacy Results:

Because the randomized portion was not conducted, only limited efficacy analyses were performed on data collected during the lead-in portion. Based on investigator assessment of radiographic data, no subjects experienced a complete response and 4 subjects, 2 from each treatment group, experienced a confirmed partial response. Of the 7 subjects for whom complete data were available for assessment of best tumor response, no subjects had a complete response, 4 subjects had a partial response, 2 subjects had stable disease, and 1 subject had progressive disease. Partial responses in all 4 subjects were observed following dose reduction of ABT-869; for 2 of the subjects this included the initial partial response. Reduced ABT-869 doses ranged from 2.5 mg to 7.5 mg. One subject also had partial responses at a reduced dose of paclitaxel (65 mg/m^2).

Of the 7 subjects included in the analysis of best percentage change from baseline in the sum of the longest diameter of all target lesions, 6 subjects had decreases, including the 4 confirmed partial responders whose changes ranged from –34.10% to –90.0%. The remaining subject had an increase from baseline of 17% in the sum of the largest diameter of target lesions.

Based on an informal review of ECOG performance status scores, scores either remained constant (4 subjects), increased by 1 point (5 subjects), or increased by 2 points (1 subject) during the study. Throughout the study, none of the ECOG scores were higher than 2. At the final assessment all ECOG scores were either 0 or 1. Therefore, while no improvements from baseline were observed, any worsening was modest and all subjects remained ambulatory.

Pharmacokinetic Results:

The PK interaction between ABT-869 and paclitaxel is inconclusive in the current study due to limited data from this study and based on all the available non-clinical and clinical data.

Safety Results:

Ten female subjects were enrolled with mean (SD) and median (range) durations of ABT-869 exposure of 145.7 (128.08) days and 77.5 (35 to 412) days, respectively. In the 0.20 mg/kg ABT-869 + paclitaxel treatment group (N = 5), 2 subjects had the dose of ABT-869 reduced and 2 additional subjects discontinued ABT-869 for events that in the investigators opinion were possibly related to ABT-869. The events leading to dose reduction were skin reaction (description: hand-foot skin reaction) reported for 1 subject (reduced from 10 mg to 7.5 mg ABT-869) and fatigue reported for the other subject (reduced from 10 mg to 7.5 mg to 5.0 mg ABT-869). The events resulting in discontinuation were headache at a dose of 12.5 mg ABT-869 reported for 1 subject and pulmonary embolism at a dose of 15.0 mg ABT-869 reported for the other subject; the latter subject also discontinued due to noncardiac chest pain and anxiety that were considered by the investigator to be not related to ABT-869. The investigator also attributed the event of pulmonary embolism to disease progression. Per protocol-specified criteria, based on these events, the 0.15 mg/kg ABT-869 + paclitaxel treatment group was initiated.

Summary/Conclusions (Continued)

Safety Results (Continued):

All 10 subjects experienced at least 1 treatment-emergent adverse event. The most frequently reported adverse events in the 2 treatment groups combined were fatigue, neutropenia, diarrhea, hypertension, alopecia, nausea, vomiting, glossodynia (pain localized to tongue), and dysphonia. The frequently reported events each occurred in at least 2 subjects per treatment group and incidence was considered similar between the 2 groups. The events of fatigue, diarrhea, and hypertension have also been observed as frequently reported events in other ABT-869 clinical studies. Neutropenia, nausea, vomiting, diarrhea, and alopecia are adverse events known to be associated with paclitaxel treatment. These events may also reflect complications or manifestations of underlying advanced breast cancer.

All 10 subjects experienced at least 1 severe (grade 3 or 4) adverse event. The majority of grade 3 or 4 adverse events occurred in no more than 1 or 2 subjects overall. All of the severe (grade 3 or 4) events were grade 3 in severity with the exception of events of neutropenia and pulmonary embolism for which 1 subject each experienced at least 1 grade 4 event. The most frequently reported grade 3 or 4 adverse events (reported by 3 or more subjects) in the 2 treatment groups combined were neutropenia (5 subjects), hypertension (4 subjects), and fatigue (3 subjects). These frequently reported grade 3 or 4 events were also among the frequently reported adverse events regardless of severity. With regard to the other frequently reported adverse events of any severity, grade 3 events of glossodynia, diarrhea, and vomiting were reported by 1 subject each; no grade 3 events of nausea, alopecia, or dysphonia were reported. The incidence of severe events was considered similar between the 2 groups.

During the study and through 30 days following the last dose of ABT-869, no adverse events were reported with the outcome of death (grade 5 events).

Three subjects experienced a total of 6 serious adverse events. Two subjects experienced more than 1 serious adverse event. A serious adverse event of pulmonary embolism that was considered possibly related to both ABT-869 and paclitaxel was reported for 1 subject who had a history of pulmonary embolism. All other serious adverse events were considered not related or probably not related to ABT-869 or paclitaxel.

Maximum shifts from grade 0 to 2 at baseline to grade 3 or 4 postbaseline for the 5 hematology parameters included in the analysis (hemoglobin, platelet count, white blood cell count, neutrophils, and lymphocytes) were infrequent with no more than 1 subject per treatment group experiencing a shift for a given parameter; 5 total subjects experienced at least 1 shift during the study before the final assessment. No grade 3 or 4 values were observed at the final assessment. One subject experienced a shift to grade 4 for white blood cell count postbaseline, all other shifts for white blood cell count, neutrophils, and lymphocytes were grade 3. While hematologic adverse events were associated with grade 3 or 4 values for 4 subjects, only 1 subject had an event (neutropenia) that was considered possibly related to ABT-869 with all remaining events considered not related or probably not related to ABT-869. None of the events associated with grade 3 or 4 hematology values were serious or resulted in dose reduction, dose interruption, or discontinuation of ABT-869. An analysis of aPTT (sec) or prothrombin time (INR) values was also performed and revealed that no grade 3 values were reported during the study; grade 4 criteria are not defined for these parameters.

Summary/Conclusions (Continued)

Safety Results (Continued):

Shifts from grade 0 to 2 at baseline to grade 3 or 4 maximum value for chemistry parameters at any time during the study or at the final assessment were infrequent with 1 subject in each treatment group experiencing a shift for at least 1 parameter. One subject in the 0.20 mg/kg ABT-869 + paclitaxel treatment group had grade 3 values for multiple chemistry parameters (low sodium, potassium, magnesium, and glucose, and high glucose) with adverse events associated with the low electrolyte values. One subject in the 0.15 mg/kg ABT-869 + paclitaxel treatment group had grade 3 low calcium values at postbaseline. With the exception of a grade 3 low sodium value observed at the final assessment, no chemistry values met grade 3 or 4 criteria at the final assessment. Four subjects who had low or normal TSH values at baseline had at least 1 value that was above the ULN (5.5 mIU/L) postbaseline of which 2 subjects had associated adverse events (hypothyroidism and thyroid stimulating hormone increased) for which supplementation with levothyroxine was initiated. Both events resolved at or before the final assessment; levothyroxine treatment was ongoing in 1 of the 2 subjects.

Two subjects in the 0.20 mg/kg ABT-869 + paclitaxel treatment group who had normal urine protein dipstick results at baseline had a 2+ urine protein value during the study. The high value was associated with an event of proteinuria for 1 of the 2 subjects with high values. This event was considered possibly related to ABT-869 and not related to paclitaxel with no action indicated for the event. Neither subject had a medical history of renal dysfunction.

A review of shifts for vital signs parameters from baseline normal to postbaseline high and/or low values indicated that no shifts from normal values to low systolic or diastolic blood pressure, low or high heart rate, or high body temperature occurred. The only very low values occurred for body temperature (3 of 10 subjects) and very high values occurred for systolic (7 of 10 subjects) and diastolic (3 of 10) blood pressure. No adverse events were associated with the low body temperature values. Of the 8 total subjects with at least 1 assessment of very high systolic blood pressure, very high diastolic blood pressure, or both, associated events of hypertension were reported for 5 subjects. One subject also had events of palpitations and tachycardia. Four of the 5 subjects with associated events of hypertension had pre-existing hypertension and were receiving anti-hypertensive treatment at baseline. All subjects with associated events initiated anti-hypertensive treatment or had modification of baseline anti-hypertensive treatment, as applicable, during the study, which allowed treatment with ABT-869 to continue uninterrupted in most cases. One event of hypertension resulted in interruption of ABT-869. None of the events of hypertension were serious, grade 4, or resulted in discontinuation or dose reduction of ABT-869. Cardiac function was further assessed by review of percent changes in LVEF from baseline; 2 subjects had a decrease in LVEF from baseline of 10% or higher and 1 subject had an increase in LVEF from baseline of 10% or higher. No adverse events were associated with the LVEF changes.

Conclusions:

The safety profile observed in this study, which is consistent with previous ABT-869 studies and paclitaxel product labeling, is appropriate for a population of subjects with locally recurrent or advanced breast cancer. The combination of 0.15 mg/kg or 0.20 mg/kg ABT-869 QD and paclitaxel (90 mg/m^2 on Days 1, 8, and 15 of each 28 day cycle) resulted in encouraging clinical activity and supports further evaluation in this patient population. Overall, the safety results combined with the potential for clinical activity support further evaluation of ABT-869 in a larger number of subjects with locally recurrent or advanced breast cancer. For future studies, the recommended weight-based dose of ABT-869 in combination with standard doses of paclitaxel is no higher than 0.15 mg/kg QD.