2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Study Drug: ABT-751	**Volume:**	
Name of Active Ingredient: N-[2-[(4-hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide	**Page:**	
Title of Study: A Phase 1/2 Study Evaluating the Safety and Efficacy of ABT-751 in Combination with Docetaxel Versus Docetaxel Alone in Subjects with Advanced or Metastatic Non-small Cell Lung Cancer		
Rationale for Abbreviated Clinical Study Report: At the discretion of the sponsor, Study M05-782 was discontinued on 11 December 2007 due to an excess of mortality associated with the ABT-751 + docetaxel treatment arm. Although overall survival in the ABT-751 + docetaxel treatment group versus ABT-751 + placebo treatment group in the Phase 2 portion of the study was not statistically different, the study was discontinued in the interest of safety.		
Coordinating Investigator: Multicenter trial. Mary O'Brien, MD Royal Marsden Hospital Downs Road Sutton,Surrey SM2 5PT United Kingdom		
Study Sites: Approximately fifty multinational sites.		
Publications: Not applicable		
Studied Period: Date First Subject First Visit: 23 February 2007 Date Last Subject Last Visit: 06 February 2008	**Phase of Development:** 1/2	
Objectives: In the Phase 1 portion, objectives were to determine the maximum-tolerated dose (MTD) and recommended phase 2 dose (RPTD) of ABT-751 when administered with docetaxel. The objectives of the Phase 2 portion were primarily related to efficacy, such as PFS and TTP.		
Methodology: This was a Phase 1/2, multicenter study to evaluate ABT-751 in combination with docetaxel in subjects with advanced or metastatic non-small cell lung cancer (NSCLC). The Phase 1 portion of the study was a dose-escalation and open-label study to determine the maximum-tolerated dose (MTD) and recommended Phase 2 dose (RPTD) of ABT-751 in combination with docetaxel. The Phase 2 portion of the study was a double-blind, active-controlled, 1:1 randomized study to assess whether addition of ABT-751 at the RPTD to standard docetaxel can prolong progression-free survival (PFS) compared		

Methodology (Continued):

with docetaxel alone. The MTD, RPTD, safety profile, and pharmacokinetics were assessed in the Phase 1 portion of the study. The PFS, overall survival, 12-month survival rate, time to disease progression (TTP), PFS as determined by the investigator, disease control rate, response rate, and duration of response were to be assessed in the Phase 2 portion of the study.

All subjects were to receive standard docetaxel on Day 1 of each 21-day cycle, via intravenous (IV) infusion over 1 hour. Oral study drug (ABT-751 or placebo [in the Phase 2 portion only]) was to be administered orally once daily (QD) for 14 consecutive days followed by 7 days off drug.

Number of Subjects (Planned and Analyzed):

A maximum of 20 subjects were planned for enrollment in the Phase 1 portion. A total of 9 subjects, who were white and ranged in age from 43 to 66 years were enrolled in the study; 7 subjects received ABT-751 200 mg + docetaxel and 2 subjects received ABT-751 250 mg + docetaxel. The pharmacokinetic analysis included 6 subjects in the ABT-751 200 mg + docetaxel treatment group and 2 subjects in the ABT-751 250 mg + docetaxel treatment group.

Approximately 160 subjects were planned for enrollment in the Phase 2 portion. Forty subjects were randomized and 36 subjects received at least 1 dose of study drug in the ABT-751 200 mg + docetaxel treatment group and 39 subjects were randomized and 37 subjects received at least 1 dose of study drug in the placebo + docetaxel treatment group. Of these subjects, 18 (45%) females and 22 (55%) males were randomized to the ABT-751 + docetaxel treatment group and 15 (38.5%) females and 24 (61.5%) males were randomized to the placebo + docetaxel treatment group. With the exception of 3 subjects in the ABT-751 + docetaxel group, all subjects were white, and ranged in age from 47 to 84 in the ABT-751 + docetaxel treatment group and 41 to 77 in the placebo + docetaxel treatment group. In both treatment groups, the majority of subjects had received 1 prior antitumor regimen.

Diagnosis and Main Criteria for Inclusion: The study population included male and female adult (≥ 18 years of age) subjects with pathologicially (histologically or cytologically) documented NSCLC that was locally advanced (Stage III) not amenable to curative surgery or radiotherapy or metastatic (Stage IV). Subjects may have received only 1 prior antitumor treatment regimen in the advanced (Stage III or Stage IV) setting and could have also received 1 additional antitumor regimen in the neoadjuvant or adjuvant setting. Subjects experienced disease progression during or following the previous antitumor regimen and had a life expectancy of ≥ 3 months. Female subjects were postmenopausal, surgically sterile and were not pregnant or breast-feeding; female subjects not meeting these criteria and nonvasectomized males practiced at least one of the acceptable methods of birth control specified in the protocol.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration:

ABT-751 or placebo (Phase 2 only) was administered orally once daily (QD) for 14 consecutive days followed by 7 days off drug. In the Phase 1 and Phase 2 portions, subjects received standard docetaxel (75 mg/m^2) on Day 1 of each 21-day cycle, via IV infusion over 1 hour. Dosing of ABT-751 or placebo was to occur with the start of the docetaxel infusion on Day 1 of each cycle.

In the Phase 1 portion, the initial dose of ABT-751 was 200 mg QD. A dose of ABT-751 250 mg was also explored.

Test Product/Reference Therapy, Dose/Strength/Concentration, and Mode of Administration (Continued):

In the Phase 2 portion, subjects were randomized 1:1 to receive ABT-751 or placebo in a double-blind design. The RPTD (ABT 751 200 mg), defined from the results of the Phase 1 portion and data from previous studies in which this dose was determined to be the MTD, was administered to subjects during the Phase 2 portion.

Duration of Treatment: Prior to study termination, subjects with controlled disease who had completed docetaxel therapy were permitted to stay on oral study drug as long as other antitumor treatment had not been initiated.

Criteria for Evaluation

Pharmacokinetic: Plasma pharmacokinetic parameters of ABT-751, ABT-751 glucuronide, ABT-751 sulfate, and docetaxel were evaluated in the Phase 1 portion of the study.

Efficacy: In the Phase 2 portion, PFS, overall survival, 12-month survival, TTP, response rate, duration of response, disease control rate, quality of life, and performance status were evaluated.

Safety: Adverse events, laboratory assessments, and vital signs were assessed in the Phase 1 and Phase 2 portions of the study.

Statistical Methods

Pharmacokinetic: The measured plasma concentrations of ABT-751, ABT-751 glucuronide, ABT-751 sulfate, and docetaxel were tabulated for each subject by day, and summary statistics were computed for each sampling time. Noncompartmental methods were used to determine plasma pharmacokinetic parameters of ABT-751, ABT-751 glucuronide, ABT-751 sulfate, and docetaxel. Parameters included, but were not limited to, observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), Time to C_{max} (T_{max}) and terminal phase elimination half-life ($t_{1/2}$).

Efficacy: The efficacy analyses including PFS, overall survival, 12-month survival rate, TTP, response rate, disease control rate, quality of life, and performance status were to be performed on all subjects randomized in the phase 2 portion of the study. For the Phase 1 portion of the study, descriptive statistics were presented for disease control rate and response rate on all subjects enrolled.

Safety: Safety analyses included all subjects who received at least 1 dose of ABT-751 or placebo (study drug). Adverse events were summarized using the Medical Dictionary for Regulatory Activities (MedDRA; version 11.0). Treatment-emergent adverse events were defined as those events that began after the first dose of study drug and within 30 days after the last dose of study drug. The number and proportion of subjects who experienced treatment-emergent adverse events were summarized by MedDRA primary system organ class and preferred term. A subject with more than 1 adverse event reported for the same preferred term was counted only once for that term. Statistical comparisons between Phase 2 treatment groups were performed using Fisher's exact test.

Mean change from baseline was determined for hematology, chemistry, urinalysis, and vital sign parameters at each visit. For the Phase 2 portion, mean changes from baseline between the 2 treatment groups were compared using an analysis of covariance (ANCOVA) with baseline measurement as a second factor.

Statistical Methods (Continued)

Safety (Continued):

The individual subject changes from baseline to subsequent study visits for hematology and chemistry parameters were evaluated with shift tables using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The number of subjects whose baseline laboratory values shifted from grade 0 to 2 to a maximum or final grade of 3 or 4 is summarized for hematology and chemistry were determined. Subjects with laboratory values meeting grade 3 or 4 criteria for hematology variables and chemistry variables were also listed. The final value for each subject was the last postbaseline value that occurred within 14 days after the last dose of study drug.

Urinalysis parameters were assessed for individual subjects using the upper and lower limits of the reference range.

The mean change from baseline to final visit was determined for each vital sign parameter. For the Phase 2 portion, mean changes from baseline between the 2 treatment groups were compared using ANCOVA with baseline measurement as a second factor. The number of subjects with vital sign parameters meeting very low or very high criteria were determined. Subjects with vital sign parameters very low or very high criteria were also listed.

Summary/Conclusions

Pharmacokinetic Results: Values of C_{max}, AUC, T_{max}, and $t_{1/2}$ of ABT-751 in the 200-mg group were comparable to values observed in other ABT-751 studies. Pharmacokinetic parameters of ABT-751 in the 200 mg-group (co-administered with docetaxel) appeared to be similar to PK parameters of ABT-751 when administered alone. Due to the limited number of subjects and the small dose range, assessment of dose proportionality and PK linearity of ABT-751 was not performed in this study.

Efficacy Results: The premature discontinuation of the study confounded the interpretation of the efficacy results, which were time based and included parameters such as PFS and TTP. Therefore, efficacy data are not discussed in the report. Based on the analysis of overall survival in all randomized subjects in the Phase 2 portion, 19 (47.5%; N = 40) subjects in the ABT-751 + docetaxel treatment group and 21 (53.8%; N = 39) subjects in the placebo + docetaxel treatment group died at any point during the data collection period.

Safety Results: At the discretion of the sponsor, Study M05-782 was discontinued on 11 December 2007 due to an excess of mortality associated with the ABT-751 + docetaxel treatment arm. Although overall survival in the ABT-751 + docetaxel treatment group versus the placebo + docetaxel treatment group in the Phase 2 portion of the study was not statistically different, the study was discontinued in the interest of safety. The conclusions based on the Phase 2 data that were available at the time the decision was made to discontinue the study were consistent with the conclusions based on the final data; more deaths associated with infection occurred in the ABT-751 + docetaxel treatment group compared with the placebo + docetaxel treatment group. Specifically, in the analysis of final data, 4 deaths in the ABT-751 + docetaxel treatment group and 2 deaths in the placebo + docetaxel treatment group were associated with infection. The premature discontinuation of the study confounded the safety evaluation because treatment was stopped early for some subjects and the safety observation period was reduced. However, a full analysis of safety was conducted.

Summary/Conclusions (Continued)

Safety Results (Continued):

In the Phase 2 portion, blood, lymphatic, and gastrointestinal events were among the most common adverse events. The most common adverse events either had a similar incidence between the groups or had a higher incidence in the ABT-751 + docetaxel treatment group versus the placebo + docetaxel treatment group: fatigue (50% vs. 45.9%), neutropenia (47.2% vs. 45.9%), constipation (44.4% vs. 27%), diarrhea (33.3% vs. 32.4%), alopecia (30.6% vs. 18.9%), nausea (30.6% vs. 27%), stomatitis (27.8% vs. 8.1%), and anemia (25% vs. 21.6%). Of these events, stomatitis occurred in a statistically significant greater proportion of subjects in the ABT-751 + docetaxel treatment group compared with the placebo + docetaxel treatment group ($P = 0.045$). Neutropenia- and infection-associated events were among the common severe (grade 3 or higher) and serious adverse events. Specifically, neutropenia, neutropenic sepsis, febrile neutropenia, and pneumonia in the ABT-751 + docetaxel treatment group and febrile neutropenia, neutropenia, and pneumonia in the placebo + docetaxel treatment group were among the most common events in both categories. Serious adverse events associated with infection (events coded to the infections and infestations MedDRA system organ class) occurred in 12 (33.3%) subjects in the ABT-751 + docetaxel treatment group and 9 (24.3%) subjects in the placebo + docetaxel treatment group. There were no statistically significant differences observed when comparing the 2 treatment groups for individual severe or serious adverse events.

Conclusions: During the Phase 2 portion of Study M05-782 (ABT-751 or placebo in combination with docetaxel in Stage III/IV NSCLC), an apparent excess in the number of deaths was observed during an interim evaluation of safety data in subjects receiving ABT-751 + docetaxel compared with subjects receiving placebo + docetaxel. As a result of this finding, the study was discontinued in the interest of subject safety. However, there were no statistically significant differences observed in the incidence of events resulting in death between the ABT-751 + docetaxel treatment group and the placebo + docetaxel treatment group. In addition, there was no statistically significant difference observed in overall survival when comparing the 2 treatment groups. Results of the final analysis were consistent with the interim evaluation of safety. No further studies using the combination of ABT-751 + docetaxel are planned, and combining ABT-751 with another microtubule inhibitor is not recommended.