2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of 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 pemetrexed versus pemetrexed alone in subjects with advanced or metastatic non-small cell lung cancer

Rationale for Abbreviated Clinical Study Report:

The primary efficacy endpoint was not met.

Investigator: Multicenter trial

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Study Site(s):

Approximately 50 multinational sites.

Publications:

Not applicable

Studied Period (Years):	**Phase of Development:** 1/2
First Subject First Visit: 22 March 2006 Last Subject Last Visit: 05 January 2009	

Objective(s):

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 pemetrexed. The primary objective of the Phase 2 portion was progression-free survival (PFS).

Methodology:

This was a Phase 1/2 multicenter study to evaluate the safety and efficacy of ABT-751 in combination with pemetrexed in subjects with advanced or metastatic non-small cell lung cancer (NSCLC). The Phase 1 portion (conducted in the US only) was an open-label dose escalation study to determine the MTD and RPTD of ABT-751 when administered with pemetrexed. The Phase 2 portion of the study was double blind and active controlled, randomizing subjects in a 1:1 ratio to ABT-751 or placebo in combination with pemetrexed to assess if the addition of ABT-751 at the RPTD to standard pemetrexed treatment can prolong PFS compared to pemetrexed alone.

All subjects were to receive standard pemetrexed (500 mg/m^2) on Day 1 of each 21-day cycle, via intravenous (IV) infusion over 10 minutes; folic acid supplementation was started at least 5 days before the first dose of pemetrexed. Study drug (ABT-751 or placebo [in the Phase 2 portion only]) was 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, of which 3 subjects received ABT-751 200 mg + pemetrexed and 6 subjects received ABT-751 250 mg + pemetrexed were enrolled. The pharmacokinetic analysis included 3 subjects in the ABT-751 200 mg + pemetrexed treatment group and 6 subjects in the ABT-751 250 mg + pemetrexed treatment group.

Approximately 160 subjects were planned for enrollment in the Phase 2 portion of the study. A total of 165 subjects were randomized of which 3 were not dosed. Specifically, in ABT-751 200 mg + pemetrexed treatment group, 83 subjects were randomized and 81 subjects received at least 1 dose of study drug and, in the placebo + pemetrexed treatment group, 82 subjects were randomized and 81 subjects received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

The study population included male and female adult subjects (>= 18 years of age) 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. In addition, for the Phase 2 portion only, subjects must have experienced disease progression during or following the previous antitumor regimen and exhibited the presence of measurable disease according to response evaluation criteria in solid tumors (RECIST). All subjects were to have a life expectancy of >= 3 months. Female subjects were surgically sterile, postmenopausal for at least 1 year, or were not pregnant or breastfeeding. Female subjects who were neither surgically sterile nor postmenopausal and nonvasectomized males were to practice at least 1 of the acceptable methods of birth control specified in the clinical protocol.

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

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 pemetrexed (500 mg/m^2) on Day 1 of each 21-day cycle, via IV infusion over 10 minutes; folic acid supplementation was started at least 5 days before the first dose of pemetrexed. Dosing of ABT-751 or placebo was to occur with the start of the pemetrexed 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 evaluated.

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:

Subjects with controlled disease who had completed pemetrexed 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 pemetrexed were evaluated in the Phase 1 portion of the study.

Efficacy: In the Phase 2 portion, efficacy variables included PFS, overall survival, 12-month survival rate, time to disease progression, disease control rate, response rate, duration of response, quality of life, and performance status.

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 pemetrexed 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 pemetrexed. Parameters included, but were not limited to, observed maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), time to Cmax (T_{max}) and terminal phase elimination half-life ($t_{½}$).

Efficacy: The efficacy analyses including PFS, overall survival, 12-month survival rate, time to disease progression, 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.

Statistical Methods (Continued)

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 were compared between the 2 treatment groups using an analysis of covariance (ANCOVA) with baseline measurement the covariate.

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 was summarized for hematology and chemistry. 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 was determined. Subjects with vital sign parameters very low or very high criteria were also listed.

Summary/Conclusions

Pharmacokinetic Results:

Because the number of subjects for PK analysis was limited (N = 3 and 6 for 200 and 250 mg dose groups, respectively), only a limited PK analysis was performed. Values for C_{max}, AUC, T_{max} and $t_{½}$ of ABT-751 in the 200 mg and 250 mg groups were comparable to values observed in other ABT-751 studies. PK parameters of ABT-751 when coadministered with pemetrexed appeared to be similar to PK parameters of ABT-751 when administered alone.

Efficacy Results:

For the primary efficacy variable of PFS, Kaplan-Meier estimates of median progression-free survival were 71 days in the ABT-751 + pemetrexed treatment group and 58 days in the placebo + pemetrexed treatment group. No statistically significant differences between the 2 treatment groups were observed when assessed using the stratified log-rank test ($P = 0.819$) or the stratified Cox proportional hazards regression analysis (hazard ratio: 0.973, 95% CI: 0.648, 1.462, $P = 0.896$). For overall survival, a secondary efficacy variable, Kaplan-Meier estimates of median overall survival were 247 days in the ABT-751 + pemetrexed treatment group and 205 days in the placebo + pemetrexed treatment group. No statistically significant differences between the 2 treatment groups were observed when assessed using the stratified log-rank test ($P = 0.410$) or the stratified Cox proportional hazards regression analysis (hazard ratio: 0.837, 95% CI: 0.552, 1.269, $P = 0.402$). These results indicate that a significant therapeutic advantage was not achieved by administering ABT-751 in combination with pemetrexed for treatment of Stage III/IV NSCLC.

Safety Results:

Nine subjects were enrolled in the Phase 1 portion of the study; 3 subjects received ABT-751 200 mg + pemetrexed and 6 subjects received ABT-751 250 mg + pemetrexed. None of the subjects in the 200 mg cohort experienced a DLT. The 250 mg cohort was started with 3 subjects and was expanded to a total of 6 subjects based on 1 subject who experienced a DLT of grade 3 peripheral neuropathy. The 200 mg dose was selected based on the above findings and experience with this dose administered as a single agent in 4 previous Phase 2 studies (M02-416, M02-446, M02-447, and M02-448) in which this dose was determined to be the MTD. Of the 3 subjects in the expanded 250 mg cohort, 1 subject experienced a DLT of grade 5 intestinal infarction. As a result of 2 subjects experiencing DLTs, it was concluded that the MTD had been exceeded. This conclusion was further supported by a review of the incidence of grade 3 or 4 neutropenia in the 200 mg group (0 of 3 subjects, 0%) group compared with the 250 mg group (3 of 6 subjects, 50%).

In the Phase 2 portion, the median number of cycles was 3.0 for the ABT-751 + pemetrexed treatment group (range: 1 to 20) and the placebo + pemetrexed treatment group (range: 1 to 19). The median duration of study drug exposure was 36.0 (range: 4 to 281) days in the ABT-751 + pemetrexed treatment group and 42.0 (range: 4 to 258) days in the placebo + pemetrexed treatment group.

Seventy-nine (97.5%) subjects in each treatment group experienced at least 1 treatment-emergent adverse event. The most common adverse events (occurring in ≥ 25% of subjects) were primarily blood and lymphatic, and gastrointestinal events. The most common adverse events either had a similar incidence between groups or had a higher incidence in the ABT-751 + pemetrexed treatment group versus placebo + pemetrexed treatment group: fatigue (45.7% versus 40.7%), anemia (39.5% versus 25.9%), nausea (37.0% versus 35.8%), anorexia (37.0% versus 18.5%), constipation (35.8 % versus 9.9%), diarrhea (28.4% versus 17.3%), and neutropenia (25.9% versus 14.8%). Of the common events, constipation and anorexia occurred in a statistically significantly greater proportion of subjects in the ABT-751 + pemetrexed treatment group compared with the placebo + pemetrexed treatment group ($P < 0.001$ and $P = 0.024$, respectively).

Three of the most common treatment-emergent events were also the most common study drug-related (ABT-751 versus placebo) adverse events (occurring in ≥ 25% of subjects in either treatment group): constipation (27.2% versus 6.2%), nausea (21.0% versus 25.9%), and fatigue (28.4% versus 21.0%).

Safety Results (Continued):

As was observed with the analysis of all adverse events, study drug-related events of constipation occurred in a statistically significantly greater proportion of subjects in the ABT-751 + pemetrexed treatment group compared with the placebo + pemetrexed treatment group ($P < 0.001$). In addition, a statistically significantly greater proportion of subjects in the ABT-751 + pemetrexed treatment group (14.8%) compared with the placebo + pemetrexed treatment group (3.7%) experienced pemetrexed-related constipation ($P = 0.027$)

Fifty (61.7%) subjects in each treatment group experienced at least 1 grade 3 or 4 adverse event. Of the common study drug-related events (all grades) that occurred in a statistically significantly greater proportion of subjects in the ABT-751 + pemetrexed treatment group, grade 3 constipation occurred in 3 subjects in the ABT-751 + pemetrexed treatment group, and grade 3 anorexia occurred in 5 subjects in the ABT-751 + pemetrexed treatment group and 2 subjects in the in the placebo + pemetrexed treatment group. There were no grade 4 events of constipation or anorexia. Common study drug-related grade 3 or 4 adverse events (occurring in ≥ 5% of subjects) occurred in similar proportion of subjects in the ABT-751 + pemetrexed treatment group versus the placebo + pemetrexed treatment group: neutropenia (11.1% versus 7.4%) and anemia (3.7% versus 6.2%).

Forty-five (55.6%) subjects in the ABT-751 + pemetrexed treatment group and 33 (40.7%) subjects in placebo + pemetrexed treatment group discontinued study drug due to an adverse event. NSCLC (7 subjects, ABT-751 and 10 subjects, placebo) was the most common adverse event leading to discontinuation in each treatment group. With the exception of fatigue (4 subjects) and nausea, vomiting, disease progression, pneumonia (3 subjects each) which led to discontinuation in the ABT-751 + pemetrexed treatment group and fatigue and pulmonary embolism that each led to discontinuation of 3 subjects in the placebo + pemetrexed treatment group, the remaining adverse events led to discontinuation of no more than 2 subjects per treatment group. The overall proportion of subjects discontinuing due to gastrointestinal adverse events (13.6% versus 2.5%) was statistically significantly greater in the ABT-751 + pemetrexed treatment group compared with the placebo + pemetrexed treatment group ($P = 0.018$). There were no statistically significant differences between the 2 treatment groups for individual gastrointestinal events leading to discontinuation (nausea, vomiting, constipation, diarrhea, and ileus) or for any other adverse events resulting in discontinuation.

Thirty-nine (48.1%) subjects in the ABT-751 + pemetrexed treatment group and 40 (49.4%) subjects in the placebo + pemetrexed treatment group experienced at least 1 treatment-emergent serious adverse event. Individual serious adverse events typically occurred in 1 or 2 subjects in a given treatment group. Those events occurring in more than 2 subjects per treatment group included NSCLC (8 subjects), pneumonia (5 subjects), and atrial fibrillation (3 subjects) in the ABT-751 + pemetrexed treatment group. Events occurring in more than 2 subjects in the placebo + pemetrexed treatment group were NSCLC in 9 subjects, pneumonia in 4 subjects, and anemia, thrombocytopenia, dehydration, dyspnea, hemoptysis, and pulmonary embolism that were each reported in 3 subjects.

With the exception of 1 death in the placebo + pemetrexed treatment group that occurred on treatment, all deaths occurred after subjects had stopped receiving study drug. Eleven (13.6%) subjects in the ABT-751 + pemetrexed treatment group and 15 (18.5%) subjects in the placebo + pemetrexed treatment group died within 30 days following the last dose of study drug. The majority of deaths were attributed to underlying disease (i.e., NSCLC) or disease progression. Of the events of with outcome of death not attributed to underlying disease, febrile neutropenia in the ABT-751 + pemetrexed treatment group and infection in the placebo + pemetrexed treatment group were the only events considered related to study drug.

Safety Results (Continued):

Analysis of hematology parameters for mean change from baseline revealed some statistically significant differences between the 2 treatment groups. Mean decreases from baseline to the final visit were statistically significantly greater in the ABT-751 + pemetrexed treatment group compared with the placebo + pemetrexed treatment group for hematocrit (-0.041 versus -0.026, $P = 0.035$), RBCs (–0.51 versus –0.30, $P = 0.008$), WBCs (–2.17 versus –0.26, $P = 0.010$), lymphocytes (–0.303 versus –0.115, $P = 0.026$), and neutrophil count (–1.549 versus 0.018, $P = 0.024$). For some of these parameters statistically significant differences were also observed at time points before the final visit. While statistically significant differences were observed between the ABT-751 + pemetrexed treatment group and the placebo + pemetrexed treatment group for these and other hematology parameters, the change from baseline for each hematology variable over time within each treatment group and the differences between the 2 treatment groups were not considered clinically meaningful.

The largest number of maximum shifts from grade 0 to 2 at baseline to grade 3 or 4 in both treatment groups occurred for lymphocytes, leukocytes, and neutrophils. More subjects in the ABT-751 + pemetrexed treatment group compared with the placebo + pemetrexed treatment group experienced maximum shifts for these variables: lymphocytes (22 versus 19), leukocytes (17 versus 8), and neutrophils (13 versus 8). The difference between the 2 groups for maximum shifts in leukocytes was statistically significant (17 out of 54 for ABT-751 versus 8 out of 56 for placebo, $P = 0.041$). For these parameters, shifts to the final visit were markedly reduced and, while more subjects experienced shifts in the ABT-751 + pemetrexed treatment group, no statistically significant differences were observed when comparing the ABT-751 + pemetrexed treatment group with the placebo + pemetrexed treatment group: lymphocytes (10 versus 7), leukocytes (6 versus 3), and neutrophils (3 versus 0). Although no formal statistical testing was performed, a similar trend was observed when looking at individual subjects with at least 1 grade 3 or 4 hematology values: leukocytes (20 versus 11), lymphocytes (22 versus 19), neutrophils (16 versus 15), hemoglobin (4 versus 6), and platelets (4 versus 4). When comparing the ABT-751 + pemetrexed treatment group with the placebo + pemetrexed treatment group for incidence of study-drug related adverse events associated with these grade 3 or 4 hematology values, the 2 groups appeared to be similar: anemia (3 versus 4), leukopenia (4 versus 3), thrombocytopenia (2 versus 3), neutropenia (6 versus 6), febrile neutropenia (0 versus 1), and decreased lymphocyte count (1 versus 1). None of the grade 3 or 4 lymphocyte values were associated with events of lymphopenia.

In the analysis of chemistry parameters for mean changes from baseline to final visit, a statistically significant difference in mean change from baseline to the final visit for sodium was observed when comparing the ABT-751 + pemetrexed treatment group (–1.2) with the placebo + pemetrexed treatment group (0.4, $P = 0.016$). Statistically significant differences between treatment groups were observed at 1 or more visits before the final visit for other chemistry parameters. The mean changes from baseline for each chemistry variable and any differences between the 2 treatment groups were not considered clinically meaningful. Shifts from grade 0 to 2 at baseline to grade 3 or 4 maximum or final shifts were not observed for the majority of chemistry parameters assessed. At the final visit, the number of shifts decreased for most chemistry parameters, none had increased, and no more than 2 subjects per treatment group experienced a final shift for a given chemistry parameter. None of the changes in clinically chemistry parameters were considered clinically meaningful. In addition, there were no clinically meaningful changes in urinalysis or vital signs.

Safety Results (Continued):

While statistically significant differences between Phase 2 treatment groups were observed, these differences were not considered clinically meaningful based on review of severe events (grade 3 or 4), serious adverse events, events leading to discontinuation, deaths, and individually clinically significant laboratory findings. The most common adverse events (fatigue, anemia, nausea, anorexia, constipation, diarrhea, and neutropenia) and laboratory findings in the present study were consistent with previous ABT-751 monotherapy and combination studies.

Conclusions:

As there was not a significant therapeutic advantage in efficacy observed by administering ABT-751 in combination with pemetrexed for treatment of Stage III/IV NSCLC, further exploration of ABT-751 in adult NSCLC is not warranted. However, observed differences between the Phase 2 treatment groups in the safety analyses were not considered clinically meaningful. The most common adverse events (fatigue, anemia, nausea, anorexia, constipation, diarrhea, and neutropenia) and laboratory findings in the present study were consistent with previous ABT-751 monotherapy and combination studies. Furthermore, analysis of safety data for the present study did not reveal the same safety concern of increased mortality that was observed in an ABT-751 and docetaxel combination study in NSCLC patients (M05-782). Overall, the results of the safety analysis indicate a consistent safety and tolerability profile for ABT-751 that is appropriate for a cancer patient population.