2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug: ABT-263, navitoclax</td></tr>
<tr><td>Name of Active Ingredient: ABT-263</td></tr>
<tr><td colspan="3">Title of Study: A Phase 1/2a study evaluating the safety, pharmacokinetics, and efficacy of ABT-263 in subjects with small cell lung cancer or other non-hematological malignancies</td></tr>
<tr><td colspan="3">Coordinating Investigator: Charles Rudin, MD, John Hopkins University</td></tr>
<tr><td colspan="3">Study Sites: 7 sites in the Canada and the US (Phase 1) and 15 sites in Canada, the United Kingdom (UK), and US (Phase 2a)</td></tr>
<tr><td colspan="3">Publications: 1 article</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 19 April 2007
Last Subject Last Visit: 29 December 2010</td><td>Phase of Development: 1/2a</td></tr>
<tr><td colspan="3">Objectives:
The objectives of the Phase 1 study included:
Safety assessment
Dose-limiting toxicity (DLT) determination
Maximum tolerated dose (MTD) determination
Recommended Phase 2 dose (RPTD) and schedule determination
Pharmacokinetic profile evaluation
The objectives of the Phase 2a study included:
Safety assessment at the RPTD
Preliminary efficacy assessment</td></tr>
<tr><td colspan="3">Methodology: This was a Phase 1/2a, open-label, multicenter clinical study evaluating the safety, pharmacokinetics, and preliminary efficacy of the orally administered Bcl-2 family protein inhibitor, ABT-263, in subjects with small cell lung cancer (North America or UK) or other non-hematological malignancies (North America only). In the Phase 1 portion, ABT-263 was administered under 2 dosing schedules: an intermittent dosing schedule (21-day cycles with 14 consecutive days of dosing followed by a 7-day recovery) and a continuous dosing schedule (21- day cycles with 21 consecutive days of dosing). The Phase 2a portion evaluated ABT-263 at the RPTD and schedule that was determined in the Phase 1 portion.</td></tr>
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Number of Subjects (Planned and Analyzed): Phase 1: 50 subjects planned and 47 subjects dosed; Phase 2a: 40 subjects planned and 39 subjects dosed. All who dosed were included in the safety, pharmacokinetic, and efficacy analyses for both study portions.

Diagnosis and Main Criteria for Inclusion: Subjects were ≥ 18 years of age; had a histologically and/or cytologically documented diagnosis of SCLC or other nonhematologic malignancy; had received at least 1 prior chemotherapy treatment regimen and their disease was refractory or the subject had experienced progressive disease; had a life expectancy of at least 30 days; had an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2 for Phase 1 and ≤ 1 for Phase 2a; had clinically controlled neurologic symptoms for subjects with known brain metastases; and had no underlying signs or predisposing conditions of bleeding, thrombocytopenic associated bleeding, active peptic ulcer disease, or a significant history of cardiovascular disease.

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

Study Drug	Formulation	Manufacturer	Finishing Lot Numbers	Bulk Lot Numbers
ABT-263	Powder for oral solution (2.0 g/bottle base equivalent, (25 mg/mL when mixed)	Abbott	06-007778, 07-010790, 07-013855, 08-015447, 08-020153, 09-021546, 09-021826, 09-023452, 09-024194, 09-025026, 09-025745, 10-000139, 10-001017, 10-001412	06-005519, 06-005519, 07-010790, 07-013145, 08-016166, 08-016166, 08-016166, 09-021009, 09-021009, 09-021009, 09-021009, 09-021009, 08-016166, 09-021009

Duration of Treatment: Subjects on the intermittent dosing schedule administered ABT-263 in 21-day cycles with 14 consecutive days of ABT-263 administration followed by a 7 day recovery period. Subjects on the continuous dosing schedule administered ABT-263 in 21-day cycles with 21 consecutive days of ABT-263 administration. Prior to Cycle 1, subjects were administered ABT-263 at a lower dose (150 mg) for a 7- to 14-day lead-in period. Subjects on both dosing schedules administered ABT-263 until disease progression.

Criteria for Evaluation

Efficacy: Efficacy analyses were exploratory for both portions of the study. Efficacy endpoints were tumor response (objective response rate [ORR]), progression-free survival (PFS), time to tumor progression (TTP), overall survival (OS), duration of response, and ECOG performance stats. Tumor assessments were assessed using computed tomography or magnetic resonance imaging scans. Scans were assessed by the investigator according to Response Evaluation Criteria in Solid Tumors.

Pharmacokinetic: Values for the pharmacokinetic parameters of ABT-263, including the C_{max}, the time to C_{max} (peak time, T_{max}), the terminal phase elimination rate constant (β), terminal elimination half-life ($t_{1/2}$), the area under the plasma concentration-time curvefrom time 0 to the time of the last measurable concentration (AUC_{0-t}) and from time 0 to infinite time (AUC_{0-inf}) for the doses on Cycle 1 Day –3, Cycle 1 Day 1, and Cycle 1 Day 14 in Phase 1, whenever applicable, were determined using noncompartmental methods. The percent of ABT-263 dose recovered in urine (%Ae) and renal clearance (CL_R) were determined if there was meaningful amount of ABT-263 recovered in urine.

Criteria for Evaluation (Continued)

Safety: Safety was evaluated based on assessments of adverse event monitoring, vital signs, physical examination, platelet counts, lymphocyte enumeration, electrocardiograms (ECGs), electrocardiograms, echocardiograms, and other laboratory assessments.

Statistical Methods

Efficacy: The distribution of PFS, TTP, and OS were estimated using Kaplan-Meier methodology. Median time to PFS, TTP, and OS and the corresponding 95% confidence intervals (CIs) were estimated.

Progression-free survival was defined as the number of days from the date the subject started study drug to the date the subject experienced an event of disease progression, or to the date of death if disease progression was not reached. Subjects with at least 2 post-Baseline CT or MRI scans were classified as a complete responder, partial responder, as having progressive disease, or as incomplete data for those without a Baseline or less than 1 post-Baseline scan. The ORR was defined as subjects with either a complete or partial response. Time to tumor progression for a given subject was defined as the number of days from the date the subject started study drug to the date of the subject's tumor progression. Time to tumor progression was collected up to 2 cycles (42 days) following the last available tumor evaluation. For OS, time to death for a given subject was defined as the number of days from the date the subject started study drug to the date of the subject's death. If a subject had not died, then the data were censored at the last study visit, the last contact date, or the date the subject was last known to be alive, whichever was last. The date of the last study visit was determined by selecting the last available date of the following study procedures for a subject. The duration of overall response for a given subject was defined as the number of days from the date the criteria are met for complete or partial response (whichever was recorded first) to the date that progressive disease was objectively documented. For the ECOG performance scale, descriptive statistics were summarized for each assessment. In addition, a mean change from baseline to each assessment was summarized.

Pharmacokinetic: Plasma concentrations of ABT-263 and pharmacokinetic parameter values were tabulated for each subject and each dose level, and summary statistics were computed for each sampling time and each parameter.

For subjects who participated in the Phase 1 14/21-day dosing portion of the study, an analysis was performed on pharmacokinetic variables for Cycle 1 Day –3 dose to simultaneously explore for demographic variables that explain some of the variability in pharmacokinetics and to address questions of dose proportionality and linear kinetics. An analysis was performed for dose-normalized C_{max}, T_{max}, and dose-normalized AUC_{0-t} andAUC_{0-inf}, provided that they were adequately determined from the data. The model used for the statistical analyses included dose level. This was done by classifying subjects by dose level or, if appropriate, using dose level as a continuous variable. Covariates such as age, body weight, body surface area, gender, and perhaps others that might have explained some of the variability in the population were included in the model initially. However, a covariate was dropped from the model if the regression coefficient was not significant at level 0.10. The natural logarithmic transformation was employed for C_{max} and AUC's unless the data clearly indicated that other transformation or the untransformed variable provided more nearly symmetric probability distributions and/or more nearly homogenous variances across dose levels. Within the framework of the model, tests that had good power for a trend with dose were performed on the effect of dose level.

Statistical Methods (Continued)

Pharmacokinetic (Continued):

For subjects who participated in the Phase 1 portion of the study, the effect of cycle on the Hour 0 concentrations on Day 14 was analyzed using a model that took into account intra- and inter-subject variability.

A corresponding analysis was also performed on pharmacokinetic variables of the dose on Cycle 1 Day 14 in both Phase 1 dosing schedules. The variables included dose-normalized C_{max}, T_{max}, and dose-normalized AUC_{0-t} (AUC_{0-8}). For the Phase 1 21/21-day dosing schedule, urine samples were not collected. For the Phase 1 14/21-day dosing schedule, the percent of dose recovered in urine as ABT-263 (%Ae) on Cycle 1 Day –3 were similarly analyzed provided that the variable was adequately determined from the data. A transformation for %Ae was used if it clearly provided more nearly symmetric probability distributions and/or more nearly homogenous variances across dose levels.

Safety: Safety summaries included all subjects participating in the study unless otherwise indicated. A safety analysis was performed for all subjects in the Phase 1 portion of the study once the MTD was reached and/or RPTD was determined, after the last enrolled subject completes one cycle of drug. A second safety analysis was performed for all subjects in both the Phase 1 and Phase 2a portion of the study upon completion of the study. The number and percentage of subjects reporting treatment-emergent adverse events were tabulated. Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

Summary/Conclusions

Efficacy Results: Patients with chemoresistant or chemosensitive SCLC have poor prognoses. Few effective therapies exist for those with this disease. In this Phase 1/2a study of the safety, pharmacokinetics, and preliminary efficacy of ABT-263 in subjects with SCLC or other non-hematological malignancies, efficacy endpoints were exploratory in nature. A total of 2 subjects had partial responses: 1 subject demonstrated a partial response on the 14/21-day dosing schedule in Phase 1 and another subject demonstrated a partial response in Phase 2a (21/21-day dosing schedule). These responses corresponded to ORRs of 2.1% and 2.6% in Phase 1 and Phase 2a, respectively. Response criteria were assessed by the investigator using RECIST criteria.

Key findings for other efficacy measures included:

- The median PFS was 43 days and 46 days in Phase 1 and Phase 2a, respectively.
- The median TTP was 43 days and 45 days in Phase 1 and Phase 2a, respectively.
- The median OS was 135 days and 96 days in Phase 1 and Phase 2a, respectively.
- In Phase 1, subjects performed slightly better on the 14/21-day dosing schedule versus the 21/21-day dosing schedule. Subjects on the 14/21-day schedule had a mean ECOG score of 0.7 at Baseline and a mean ECOG score of 1.1 at Final (mean change of 0.5). Subjects on the 21/21-day schedule had a mean ECOG score of 0.8 at Baseline and a mean ECOG score of 1.6 at Final (mean change of 0.8). In Phase 2a, subjects had a mean ECOG score of 0.6 at Baseline and a mean ECOG score of 1.3 at the Final Visit (mean change of 0.7).
- The mean best percentage change from Baseline in the sum of the longest diameter for all target lesions was an increase of 29.2% and an increase of 23.3% in Phase 1 and Phase 2a, respectively.

Pharmacokinetic Results: The average T_{max}, across various doses tested was ~5 to 8 h for the 14/21-day and 21/21 day dosing schedules in the Phase 1 portion of the study. The mean $t_{1/2}$ observed after a single dose of ABT-263 was ~15 h and mean CL/F was ~5 L/h. Renal excretion of ABT-263 was below the limit of detection.

Following a single dose of ABT-263, T_{max} values were comparable, AUC_{0-72}, and AUC_{0-inf} values exhibited dose-proportionality in the range of 10 mg to 475 mg dose. For C_{max} values, a trend of less than dose-proportional increase was observed over the entire dose range studied; however, within the dose range of 130 mg to 475 mg, the C_{max} values were essentially dose proportional.

Evaluation of ABT-263 dose-normalized trough concentrations over the first 4 cycles suggested that the pharmacokinetics of ABT-263 are essentially time independent. Dose-normalized ABT-263 trough plasma concentrations in Phase 1 and Phase 2a were comparable following oral administration of ABT-263.

Pharmacodynamic Results: In the Phase 1 portion, changes in pro-GRP at Day 35 correlated to best tumor response in patients dosed ≥ 130 mg of ABT-263. With increasing ABT-263 dose and exposure, pro-GRP levels declined or stabilized, particularly in patients with SCLC and neuroendocrine tumors. In circulating tumor cells (CTCs), a direct correlation was observed between *BCL2* copy number and pro-GRP concentrations at Baseline. Additionally, evidence of tumor cell apoptosis, as measured by M30 concentrations, was observed at 6 hours after initial ABT-263 dose and sustained through 14 days of dosing. Statistically significant transient increases in M30 concentrations were observed at ABT-263 doses ≥ 130 mg. In the Phase 2a portion, optimized thresholds of biomarkers were identified and subjects with concentrations above these thresholds at Baseline and at Cycle 1 Day 14, had a better performance than those below the thresholds. When only focusing on NSE and CYFRA biomarkers, subjects with concentrations above the thresholds for both biomarkers performed statistically significantly worse than those who had concentrations below the optimized thresholds. Median PFS was 41 days versus 55 days and median OS was 61 days versus 242 days. An optimal threshold of 600 pg/mL of pro-GRP was identified that correlated with *BCL2* gene amplification. When looking at M30 concentrations and CTC levels, subjects with a high pro-GRP concentration correlated to higher M30 concentrations at 24 hours after dosing and lower increases in CTC levels at Day 14. The Phase 1 findings were confirmed: subjects with a high pro-GRP plasma concentration corresponded to higher *BCL2* amplification, increased tumor cell apoptosis concentrations, and a lower increase of CTCs. Furthermore, at sufficient doses, pro-GRP can be examined as a predictive marker for treatment with ABT-263.

Safety Results: During the dose-escalation portion of the study, ABT 263 was administered under an intermittent dosing schedule (14/21-day cycles) and a continuous dosing schedule (21/21 day cycles). In the intermittent schedule, doses ranged from 10 to 475 mg and in the continuous schedule, doses administered were 225 and 325 mg. Exposure to ABT 263 was similar between the 2 dosing schedules and a majority of subjects only dosed ABT-263 for 1 or 2 cycles. The RPTD and schedule was 325 mg under the continuous dosing schedule with a 150-mg 7- or up to 14-day lead in period prior to Cycle 1. Similar to the Phase 1 portion, a majority of subjects in Phase 2 only dosed ABT-263 for 1 or 2 cycles.

In both portions of the study, the most commonly reported adverse events were thrombocytopenia, decreased appetite, and gastrointestinal toxicities of diarrhea, nausea, and vomiting. Other more commonly reported adverse events were cough and fatigue in Phase 1 and constipation, dehydration, dyspnea, neutropenia, and SCLC stage unspecified (disease progression) in Phase 2a. The most commonly reported adverse events were mild or moderate except for thrombocytopenia and neutropenia, where for a majority of the subjects the events were severe. In the Phase 1 portion, a higher incidence of the most commonly reported adverse events was generally reported in subjects in the continuous dosing schedule compared to those in the intermittent dosing schedule. Furthermore, the frequency of adverse events typically associated with ABT-263 administration (thrombocytopenia, lymphopenia, and abnormal liver function) was greater in Phase 2 compared to Phase 1. Treatment-emergent adverse events that resulted in a fatal outcome occurred in 11 subjects in Phase 1 and 13 subjects in Phase 2. Almost all (21/24 subjects) died because of their underlying disease. In Phase 1, a higher frequency of subjects required a dosing modification for those on the intermittent dosing schedule compared to the continuous dosing schedule. However, ABT-263 appeared to be less tolerable in Phase 2 as a greater incidence of types of dosing modifications occurred than compared with the same dosing schedule in Phase 1.

Laboratory effects on platelets, lymphocytes, neutrophils, and liver function tests were consistent with the known effects of ABT-263 monotherapy clinical studies. For hematological analytes, dosing modifications associated with hematologic abnormalities were observed in 2 and 6 subjects in Phase 1 and Phase 2a, respectively. Subjects with more than 1 hematological cell line affected were minimal in Phase 1 (6 subjects) though more frequent in Phase 2 (17 subjects), and in a majority of these subjects, both lymphocytes and platelets were affected. In subjects with platelet abnormalities, bleeding or hemorrhage events were reported in 1 subject in Phase 1 and 5 subjects in Phase 2. In subjects with neutrophil or lymphocyte abnormalities, infections and infestations were reported in 2 and 6 subjects, respectively, in Phase 1 and in 4 and 6 subjects, respectively, in Phase 2. Dosing modifications associated with elevated liver enzymes were observed in 2 subjects in Phase 1 and in 4 subjects in Phase 2a.

Changes in urinalysis values, vital signs, ECGs, and echocardiograms were generally minimal and clinically unremarkable. Two subjects had dose modifications due to cardiac events of left ventricular dysfunction and left ventricular ejection fraction.

Conclusions: In conclusion, data suggest that ABT-263 can be safely administered under intermittent and continuous dosing schedules in subjects with SCLC.