2 SYNOPSIS

Name of Sponsor/Company: Cephalon, Inc. **Name of Finished Product:** Obatoclax **Name of Active Ingredient:** Obatoclax (CEP-41601)	**Individual study table referring to part of dossier in which the individual study or study table is presented** **Volume:** **Reference:**	(For National Authority Use Only)

Title of Study: A Phase 1 Followed by a Randomized, Phase 2 Study of Carboplatin and Etoposide with or without Obatoclax Administered Every 3 Weeks to Patients with Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Investigators and Study Centers: The study was conducted at a total of 59 study centers as follows: 26 in the United States of America, 8 in Hungry, 5 in India, 4 each in the Czech Republic, Poland, and Romania, 3 in Canada, 2 in Serbia and Montenegro, and 1 each in Bulgaria, Ireland, and the United Kingdom. A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 08 July 2008 to 17 November 2011 **Phase of Development:** Phase 1/Phase 2

Primary Objectives: The primary objective of Phase 1 was to determine the recommended Phase 2 dose of obatoclax, administered as either a 3-hour infusion on 3 consecutive days or as a 72-hour infusion (24-hour continuous infusion on 3 consecutive days), every 21 days, in combination with carboplatin and etoposide (CE). The primary objective of Phase 2 was to compare the overall response (OR) rate of 2 treatment groups, carboplatin, etoposide, and obatoclax (CEO) as a 3-hour infusion on 3 consecutive days and CE alone.

Secondary Objectives: The secondary objective of Phase 1 was to characterize the safety profile of obatoclax administered as a 3-hour infusion on 3 consecutive days and as a 72-hour infusion (24-hour continuous infusion on 3 consecutive days), in combination with CE.

The secondary objectives of Phase 2 were the following:

- compare the progression-free survival (PFS) of the 2 treatment groups
- compare the complete response (CR) rates of the 2 treatment groups
- compare the overall survival (OS) of the 2 treatment groups
- compare the safety profile of the 2 treatment groups
- compare changes in pulmonary function tests (PFTs) from baseline across the 2 treatment groups
- evaluate pharmacodynamic markers of the 2 treatment groups

Number of Patients (Planned and Analyzed): For Phase 1, 12 to 21 patients were planned to be enrolled in the 3-hour infusion groups, with an equal number in the 24-hour infusion groups; data from a total of 25 patients were analyzed for efficacy and safety. For Phase 2, 154 patients were planned to be enrolled; data from 155 patients were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Men and women, at least 18 years of age, were included in the study if all of the following main criteria were met (not all inclusive):

- pathological or cytological confirmation of small cell lung cancer (SCLC)
- extensive-stage (ES)-SCLC
- measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 with at least 1 lesion ≥2.0 cm using conventional technique or ≥1.0 cm with spiral computed tomography (CT) scan in a single dimension
- no previous chemotherapy
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1 (Phase 1); ECOG PS ≤2 (Phase 2)

- normal organ function, defined as: absolute neutrophil count (ANC) $\geq$1500/mm^3, platelets $\geq$100000/mm^3, total bilirubin $\leq$upper limit of normal (ULN); or total bilirubin $\leq$3.0 if liver metastases were present, and creatinine within normal institutional limits or calculated creatinine clearance $\geq$50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

Main Criteria for Exclusion: Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- other investigational or commercial agents or therapies administered with the intent to treat the patient's malignancy
- history of allergic reactions attributed to components of the obatoclax formulation (Polysorbate 20 and polyethylene glycol [PEG] 300)
- history of seizure disorders unrelated to SCLC brain metastases, or presence of symptomatic brain metastases
- uncontrolled, intercurrent illness, including, but not limited to, symptomatic neurological illness; active, uncontrolled systemic infection considered opportunistic, life-threatening, or clinically significant at the time of treatment; symptomatic congestive heart failure; unstable angina pectoris; clinically significant cardiac arrhythmia; significant pulmonary disease or hypoxia; or psychiatric illness/social situations that would limit compliance with study requirements

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: Obatoclax was supplied by the sponsor as a 30-mg lyophilized cake in a single-use vial (lot number: 716467). The diluent for CEP-41601 was also supplied by the sponsor as a 40 mL single-use vial (lot number: 716478) containing 96.2% PEG 300 (38.48 mL) and 3.8% Polysorbate 20 (1.52 mL). In Phase 1, CEP-41601 was administered as a 3-hour infusion on days 1 to 3 (dose groups: 15, 30, and 45 mg/day) and as a 24-hour infusion on days 1 to 3 (dose groups: 30, 45, and 60 mg/day). In Phase 2, CEP-41601 was administered as a 3-hour infusion on days 1 to 3 at a dose of 30 mg/day. A cycle of dosing was 21 days.

Combination Drugs and Active Control: Carboplatin and etoposide were obtained as commercial drug products (locally sourced); they were prepared and administered according to the current product labeling. Carboplatin was administered intravenously (iv) on day 1 at an area under the plasma concentration versus time curve (AUC) of 5. Etoposide was administered at a dose of 100 mg/m^2 iv on days 1 to 3. All combination regimens were administered using a 21-day treatment cycle.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: In both phases of the study, the treatment period consisted of a 21-day cycle. Patients were expected to complete 6 cycles of combination chemotherapy with either CEO or CE. Patients enrolled in 1 of the CEO groups in Phase 1/Phase 2, who were without disease progression and completed all 6 cycles of combination therapy, were eligible to receive obatoclax alone as maintenance therapy. Obatoclax maintenance therapy was administered every 21 days at the same dose and schedule as during combination therapy, until disease progression.

General Design and Methodology: This was a multicenter, open-label, 2-part study (Phase 1/2) of obatoclax conducted in patients with ES-SCLC.

Phase 1 was designed to determine the maximum tolerated dose (MTD) of obatoclax when given together with CE, in separate obatoclax dose escalation cohorts. Dose groups for the 3-hour (on 3 consecutive days) obatoclax infusion schedule were 15, 30, and 45 mg/day. Dose groups for the 24-hour obatoclax infusion schedule were 30 mg/day (90 mg total over 3 days), 45 mg/day (135 mg total over 3 days), and 60 mg/day (180 mg total over 3 days). Dose-limiting toxicities (DLTs) in cycle 1 were evaluated for the purposes of obatoclax dose escalation. Cycle length for both groups was 21 days. Treatment was administered on an outpatient basis, with sponsor-notified exceptions.

In Phase 2, patients were randomized on a 1:1 basis to either CEO or CE. The obatoclax 3-hour infusion schedule (on 3 consecutive days) at a dose of 30 mg/day was selected to be administered in Phase 2 in combination with carboplatin (AUC 5) (day 1 only) and etoposide 100 mg/m^2 (days 1, 2, and 3), and compared with the CE. All combination regimens were administered using a 21-day treatment cycle.

In both phases of this study, patients received up to 6 cycles of combination chemotherapy, unless there was evidence of disease progression, an intolerance to therapy, withdrawal of consent for any reason, or death. Patients who responded to treatment or had stable disease (SD), but experienced DLTs, were allowed to continue on therapy at a reduced dose once the DLTs resolved to below grade 2. Patients who had a response (complete response[CR] or partial response [PR]) to the first 6 cycles of combination chemotherapy received prophylactic cranial irradiation (PCI) if no brain metastases were noted after completion of study drug treatment. Prophylactic cranial irradiation started after patients had recovered from the reversible toxicities of the 6 combination treatment cycles, but no later than 6 weeks after the start of the last cycle of combination chemotherapy.

Patients enrolled in 1 of the CEO groups in Phase 1 or Phase 2, who were without disease progression and completed all 6 cycles of combination therapy, were eligible to receive obatoclax alone as maintenance therapy (or, if appropriate, after completion of PCI). Obatoclax maintenance therapy was administered every 21 days at the same dose and schedule as during combination therapy, until disease progression. The initiation of obatoclax maintenance therapy was timed such that patients receiving this treatment continued to have tumor evaluations every 6 weeks. Patients enrolled in the CE group in Phase 2 were not eligible to receive obatoclax maintenance therapy; no crossovers were permitted.

Primary Efficacy Measures and Endpoint: The primary efficacy variable, the OR rate, was defined as subjects with a best response of CR or PR and was based on RECIST version 1.0 criteria, as determined by the study center investigators. Tumor evaluations were conducted every 6 weeks to assess response to the therapy.

Secondary Efficacy Measures and Endpoints: The secondary efficacy variables and endpoints included rates of PFS, CR rates, and rates of OS of the 2 treatment groups.

Safety Variables: In this study, safety was assessed by the evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, body weight, electrocardiogram (ECG) findings, PFT findings, physical examination and neurological findings, ECOG PS, CT or brain magnetic resonance imaging (MRI) results, chest X-rays, and concomitant medication usage. For each safety parameter, all findings (whether normal or abnormal) were recorded in the case report form (CRF), and the investigator judged the clinical significance of any abnormalities.

Pharmacodynamics: On days 1, 3, and 8 in cycle 1 only (Phases 1 and 2), samples were drawn for analysis of pharmacodynamic markers of apoptosis (histone-oligonucleosomal deoxyribonucleic acid [DNA] complexes and M65 and M30 assays).

Statistical Considerations: Phase 1 OR and CR rates were analyzed separately, both by infusion duration and by each separate dose cohort. No statistical hypothesis testing was performed.

In Phase 2, the overall disease response rate of CEO versus CE was tested using RECIST criteria. Statistical hypothesis testing of response data, using Fisher's Exact test, was conducted to compare the OR rate (CR+PR) and the clinical benefit rate (CR+PR+SD) in the CEO group with that of the CE group in a 1-sided test of superiority at an alpha level of 0.05. The 2-sided 90% exact confidence interval (CI) was calculated for the response rate in each treatment group. A secondary analysis (response-evaluable analysis) evaluated the OR rate and the clinical benefit (rate of confirmed CR, PR, and SD) in the efficacy-evaluable (EE) population. Time-to-event data, including duration of response (DOR), PFS, and OS, were summarized using Kaplan-Meier methodology; the 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% CIs; the percentage of censored observations was also tabulated. Time-to-event variables (DOR, PFS, and OS) were compared between the 2 treatment groups using logrank test at 1-sided alpha level of 0.05, and hazard ratios (HRs) were calculated using cox proportional hazard model. Medians of DOR, PFS, and OS and their 95% CIs were calculated using Kaplan-Meier methodology. In addition, the proportion of patients who were progression free at 6 months and who were alive at 12 months was summarized. Progression free survival was defined as the duration in days from the date of randomization until the date of progressive disease (or relapse) or death (due to any cause). Overall survival was defined as the duration in days from the date of randomization until the date of death. The DOR was also tabulated to more fully describe the durability of responses. A sensitivity analysis was performed on data from any patient who initiated new cancer therapy (eg, a new chemotherapy regimen or radiation therapy other than PCI) without prior disease progression documented on the investigator's opinion page or without the investigator's statement that the patient had clinical progression. A 2^{nd} sensitivity analysis was performed

on data from any patient who had disease progression on a tumor assessment that occurred immediately after 1 or more missing tumor assessments.

Adverse events were summarized by phase and treatment group for the following: treatment-emergent adverse events by system organ class (SOC), preferred term (PT), and common terminology criteria for adverse events (CTCAE) grade; the most common adverse events that occurred in each phase; treatment-related adverse events; serious adverse events; adverse events of grade 3 severity or above; and adverse events leading to withdrawal from the study.

The actual value and change from baseline for each on-study evaluation and last value on study were summarized by treatment group for each clinical laboratory parameter (including hematology and clinical chemistry). A subset listing was presented for all grade 3 or higher laboratory values. Shift tables were produced for selected laboratory parameters; the number of patients with each baseline National Cancer Institute (NCI) CTCAE grade and changes to the worst NCI CTCAE grade were summarized. The nadirs for white blood cell (WBC), ANC, platelets, and hemoglobin during cycle 1 were calculated for each patient and summarized in tabular form.

The actual value and change from baseline for each on-study evaluation and last value during the study were summarized for vital signs and PFTs. Eastern Cooperative Oncology Group PS and shifts from baseline were tabulated. Clinically significant abnormal vital signs, defined as a temperature at or below 96ºF (32ºC) or above 104ºF (40ºC); pulse below 40 beats per minute (bpm) or above 150 bpm; respiration rate below 10 breaths/minute or above 30 breaths/minute; systolic blood pressure (SBP) above 200 mmHg or below 80 mm Hg; diastolic blood pressure (DBP) above 110 mmHg or below 50 mm Hg, were listed on a per-patient basis.

Summary of Results

Patient Disposition and Demography: In Phase 1, 25 patients received at least 1 dose of study treatment. The majority of patients were men (56%) and white (92%); the median age was 66 years. At screening, 64% of patients had an ECOG PS of 1 (restricted activity). In Phase 2, 155 patients received at least 1 dose of study treatment. The majority of patients were men (53% and 59%, in the CEO and CE groups, respectively), and white (94% and 93%, respectively) with median ages of 62 years and 63 years, respectively. At screening, patients in both the CEO and CE groups (57% and 63%, respectively) had a baseline ECOG PS of 1.

Efficacy Results: In Phase 1, the overall disease response rate (CR or PR) was higher for patients treated with the 3-hour infusion schedule (81%) compared with patients treated with the 24-hour infusion schedule (44%). Results across all patients for the analysis of clinical benefit (CR/PR/SD) also favored the 3-hour infusion schedule, with a clinical benefit rate of 94%, compared with 67% for the 24-hour infusion schedule. Median OS of patients was 12.4 months (CI: 8.1, 16.5) for the 3-hour infusion schedule, compared with 9.3 months for the 24-hour infusion schedule (CI: 2.6, 12.9).

In Phase 2, the primary endpoint of the best OR rate in the EE population suggests a very modest benefit for the CEO group compared with the CE group (62% versus 53%, respectively). The clinical benefit rate was higher for patients in the CEO group, compared with those in the CE group (81% versus 68%, respectively); near statistical significance was achieved only in patients with the response of CR/PR/SD who received the CEO treatment (1-sided p=0.0539). In the subgroup of patients who could be assessed for confirmation of response (ie, who had a cycle 4 response assessment) or who discontinued before cycle 4 because of an adverse event, disease progression, or death, the overall disease response rate was higher in the CEO group, compared with the CE group (68% versus 55%)(1-sided p=0.0759). For this subgroup, the clinical benefit rate was significantly higher in the CEO group, compared with the CE group (87% versus 71%, respectively; 1-sided p=0.0113).

Evaluation of the secondary endpoints for Phase 2 included PFS, CR, OS, and DOR. Median PFS in the intent-to-treat (ITT) population and EE population (included PS 0-2 patients) was 5.8 months for the CEO group, compared with 5.2 months for the CE group, HR=0.821, p=0.114. In the ITT/EE population, median OS was 10.5 months (CI: 8.9, 13.8) for the CEO group, compared with 9.7 months (CI: 7.3, 11.2) for the CE group, HR=0.823, p=0.121. Sixty-three patients in the CEO group were alive at 6 months, compared with 56 patients in the CE group, which marked the end of 6 cycles of treatment and PCI. By 9 months, the groups were the same, with 47 patients alive in the CEO group, compared with 44 patients in the CE group. There did not appear to be a difference in OS if patients, when progressed, received

posttreatment chemotherapy; however, more patients in the CEO group received subsequent treatment, compared with those in the CE group.

Duration of disease response was not statistically different in the EE population between the CEO and CE treatment groups (4.6 months versus 4.5 months, respectively).

Safety Results: In Phase 1, dose-limiting neuro-psychiatric events (somnolence, euphoric mood, and mental status changes) were observed in 2 of 6 patients on the 45-mg/day, 3-hour infusion schedule. These dose-limiting toxicities (DLTs) led to the selection of the 30-mg/day dose for evaluation in Phase 2, with the 3-hour infusion schedule.

The most commonly reported adverse events during Phase 2, events of grade 3 or 4 severity, were hematologic toxicities. The incidence of these events was not higher in the CEO group, indicating no additional contribution of obatoclax to the known and labeled hematologic toxicity profile of CE. Evaluation of nadir values for WBC, ANC, platelet count, and hemoglobin showed no differences between the treatment groups and the incidence of laboratory reports of grade 3 or 4 neutropenia, thrombocytopenia, and anemia also were similar. Patients who received obatoclax (Phase 1 or 2) experienced neuro-psychiatric adverse events, primarily somnolence, euphoric mood, and dizziness; the majority of the events were transient and mild in severity. Withdrawal for these events was not common and decreased over time with the number of on-treatment cycles. The highest incidence was reported during cycle 1 treatment, indicating that these events do not appear to result from cumulative toxicity.

Fourteen deaths occurred within 30 days of the last dose of study treatment, 4 (5%) patients in the CEO group and 10 (14%) patients in the CE group. The majority of deaths (10 of 14) were associated with respiratory failure, or other pulmonary conditions (edema, hemorrhage, or embolism), or with infection, and were considered unrelated to study treatment. Four deaths, including 1 (1%) in the CEO group and 3 (4%) in the CE group, were considered treatment-related. The overall incidence and types of serious adverse events reported in the 2 treatment groups were similar and consistent with cytotoxic chemotherapies. The most commonly reported serious adverse events in the CEO and CE groups were anemia (9% and 8%, respectively), febrile neutropenia (4% and 5%, respectively), neutropenia (4% in both treatment groups), thrombocytopenia and pneumonia (3% each in both treatment groups), and hyponatremia (4% , CEO group only). The overall discontinuation rate because of adverse events was similar in the CEO (21%) and CE groups (22%), as were the types of events leading to discontinuation.

Review of clinical laboratory data, vital signs measurements, PFTs, ECGs, and ECOG PS did not show any clinically meaningful differences between the CEO or CE group for changes over the course of treatment.

Pharmacodynamic Results: The analysis was not initiated; no data are available for the defined pharmacodynamic markers.

Conclusions: Obatoclax at a dose of 30 mg/day, administered as a 3-hour infusion on days 1, 2, and 3 of a 21-day cycle, can be administered in combination with carboplatin and etoposide in chemotherapy-naive patients with ES-SCLC. However, no improvement in OR rate, OS or PFS was demonstrated in Phase 2 of this study. Additionally, side effects such as euphoria, somnolence, agitation, and other neuropsychiatric-related events, appeared to be uniquely limited to treatment with CEO. Thus, based on efficacy that did not achieve statistical significance and safety issues, CEO does not appear to be a combination that would benefit the ES-SCLC population as a first-line treatment.