CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	N020981 / 000
Drug Name:	HYCAMTIN (topotecan) oral capsules, 2.3 mg/m^2/day for 5 consecutive days repeated every 21 days
Indication(s):	Treatment of patients with relapsed small cell lung cancer
Applicant:	GlaxoSmithKline
Date(s):	Submission date: April 11, 2007 PDUFA due date: October 11, 2007 Review completion date: October 5, 2007
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Rajeshwari Sridhara, Ph.D., Team Leader Aloka Chakravarty, Ph.D., Division Director
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Keywords: small cell lung cancer, overall survival, un-stratified log-rank test

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1. EXECUTIVE SUMMARY

This is an original New Drug Application (NDA) submission for oral topotecan capsules seeking an indication for treatment of patients with relapsed small cell lung cancer (SCLC). This NDA is comprised of one Phase III trial, Study 478, as the primary basis for treatment efficacy evaluations.

1.1 Conclusions and Recommendations

Results from the NDA registration trial Study 478 indicate a survival benefit from addition of oral topotecan to best supportive care in patients with relapsed small cell lung cancer (SCLC). Median survival was 13.9 weeks (95% confidence interval [CI]: 11.1, 18.6 weeks) for patients under the best supportive care only, and was 25.9 weeks (95% CI: 18.3, 31.6 weeks) for patients treated with oral topotecan plus best supportive care. The unadjusted survival hazard ratio for best supportive care plus oral topotecan (BSC+OT) relative to best supportive care alone (BSC alone) was 0.64 (95% CI: 0.45, 0.90), and the un-stratified log-rank test for comparing survival curves between the two treatment groups was significant at a p-value of 0.0104. Issues related to the conduct of Study 478 such as study was closed earlier than planned, and some study sites may have failed to follow the stratification procedure, do not appear to alter the conclusion that adding oral topotecan to best supportive care appears to provide survival benefit to patients with relapsed SCLC.

1.2 Brief Overview of Clinical Studies

The sponsor conducted 3 efficacy studies in patients with relapsed SCLC. Study 478 is the primary efficacy study aiming to demonstrate treatment efficacy by comparing best supportive care plus oral topotecan (BSC+OT) to best supportive care alone (BSC alone) in terms of overall survival. Study 478 was an open-label trial with 141 patients randomized at 1:1 ratio to BSC+OT or BCS alone. Randomization for Study 478 was based on 4 stratification factors: time to progression since prior chemotherapy ($\leq$ 60 days or > 60 days), Eastern Co-operative Oncology Group (ECOG) performance status (0/1 or 2), gender (male or female), and liver metastases (absence or presence). Study 065 and Study 396 were conducted to provide supportive efficacy for oral topotecan by showing its comparability to the approved IV topotecan with respect to response rate and overall survival.

Study 478 was designed to address the European Committee for Human Medicinal Products request for a randomized study comparing topotecan with best supportive care using overall survival as the primary efficacy endpoint to support this indication. The sponsor used oral topotecan in Study 478, and conducted Study 065 and Study 396 to show the comparability between the two routes of drug administration.

IV topotecan for patients with relapsed SCLC was approved in June of 1998 based on a randomized Phase III study comparing IV topotecan with IV Cyclophosphamide, Adriamycin, and Vincristine. In Europe, neither IV nor oral topotecan have been approved for SCLC.

1.3 Statistical Issues and Findings

Statistical Issues associated with efficacy evaluations:

1) Study 478 was closed before the required target sample size was achieved. A total of 141 instead of targeted 220 patients were recruited. Survival analysis was performed with 130 deaths compared to originally planned 168 deaths, resulting a reduction in power from targeted 90% to 81% for testing the survival superiority hypothesis with addition of oral topotecan. Reason for closing the trial early, as claimed by the applicant, was due to poor recruitment in this trial and several centers withdrawing their participation (please refer to Appendix I for study accrual rate as provided by the applicant). To evaluate the impact of closing the study early, the reviewer compared the p-value of 0.0104 from un-stratified log-rank test to an alpha of 0.022 for the survival analysis with observed 130 deaths as an interim analysis. Since 0.0104 is less than 0.022, the survival comparison between oral topotecan and BSC alone remains statistical significant even with fewer events.
2) In the original protocol dated 07 Feb. 2000, duration of response to prior chemotherapy was listed as a randomization factor along with performance status, gender, and liver metastases. However, duration of response to prior chemotherapy was replaced by time to progression since prior chemotherapy in protocol amendment 03 dated 13 May 2004. According to applicant's response, number of days from discontinuation of first-line chemotherapy to relapse was asked when an investigator called in the randomization system per Procedures for Central Patient Registration and Randomization of the protocol, and the protocol was amended to reflect what was actually captured (please see Appendix II for the required information entered for randomization). To address the concern that duration of response may have been entered instead of time to progression in some patients, the reviewer calculated the survival hazard ratios adjusting for original protocol specified stratification factors or for the amended stratification factors, and results are similar (survival hazard ratio [95% CI] = 0.62 [0.43, 0.88] if adjusted for the factors as specified in original protocol; = 0.61 [0.43, 0.87] if adjusted for the factors as specified in amended protocol).

Primary Efficacy Findings from, Study 478:

For the ITT population, median survival in the BSC alone group was 13.9 weeks compared with 25.9 weeks in the BSC + OT group. The difference between the groups in overall survival was statistically significant (p = 0.0104) based on the un-stratified log-rank test. The unadjusted

hazard ratio for BSC + OT relative to BSC alone was 0.64 (95% C.I. 0.45, 0.90). The hazard ratio adjusted for the stratification factors was 0.61 (95% C.I.: 0.43, 0.87).

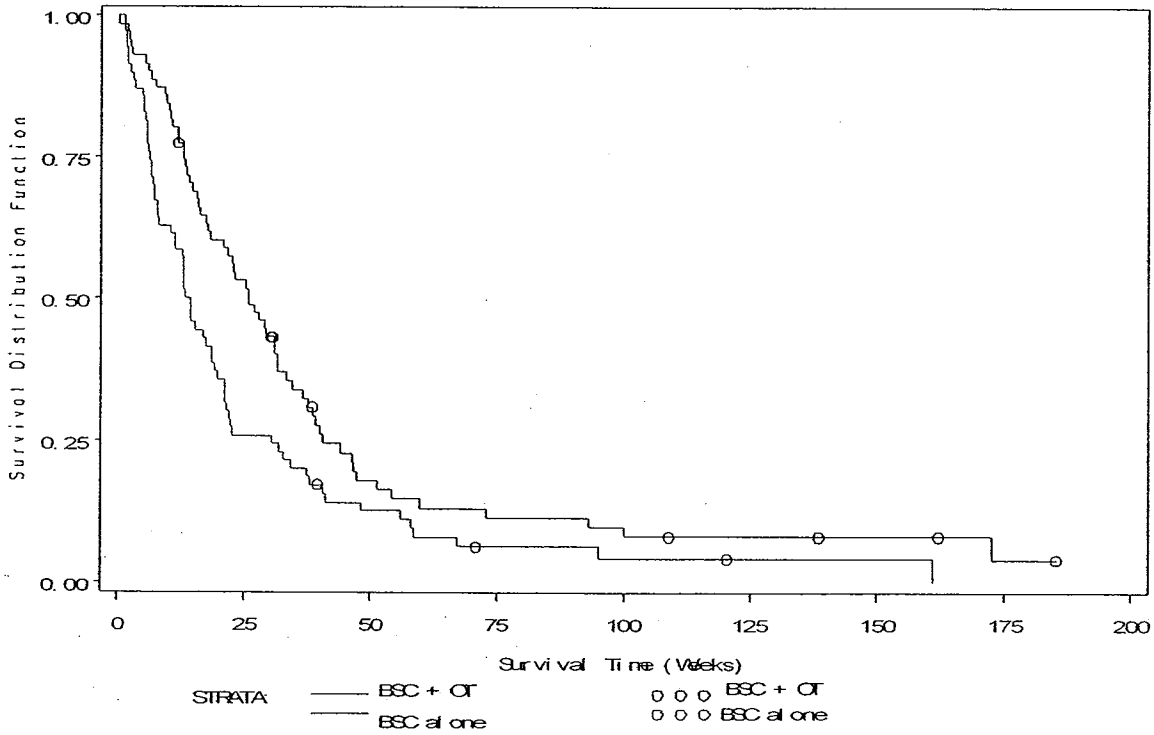
Table 1 Reviewer's Summary of Survival (Study 478, ITT Population)

Median survival (weeks)	BSC + OT	BSC alone
Median (95% CI)	25.9 (18.3, 31.6)	13.9 (11.1, 18.6)
Observed events	63 (88.7%)	67 (95.7%)
Hazard Ratio* (95% CI)	0.64 (0.45, 0.90)	
Log-rank p-value#	0.0104	

* Un-stratified hazard ratio for BSC+OT versus BSC alone

2-sided p-value from un-stratified log-rank test comparing survival between the two groups

Figure 1 Reviewer's Kaplan-Meier Curve for Survival (Study 478, ITT Population)



2. INTRODUCTION

2.1 Overview of Relapsed Small Cell Lung Cancer

Lung cancer is a global health problem, and is the leading cause of cancer death in the United States. Small cell lung cancer represents about 10-15% of worldwide cases of lung cancer. Of the 174,000 new cases of lung cancer diagnosed in 2005 in the US, approximately 13.8% of subjects were diagnosed with SCLC. The etiology of SCLC is strongly associated with tobacco use and is characterized by a very aggressive growth.

Untreated primary disease generally carries a 2 to 4 months median survival. While initial treatment with chemotherapy produces response rates in the 60-70% range, disease generally progresses within 11 to 13 weeks and median survival is within 28 to 30 weeks. In patients who experience a response to first-line chemotherapy, the expectation of a response to second-line chemotherapy is greater when the time to progression from the end of first line chemotherapy is longer than 90 days. Disease which recurs fewer than 90 days from the end of first-line therapy is classified as resistant disease. In clinical practice, patients with sensitive disease SCLC (disease which recurs later than 90 days from the end of first line therapy) will frequently receive chemotherapy in the second-line setting if the baseline laboratory values and performance status (PS) support this option. As the disease progresses, the patient's PS deteriorates and burden of cancer-related symptoms increase. Intravenous topotecan is the only approved therapy in the setting of relapsed (sensitive disease) SCLC.

2.1.1 Background

Topotecan is a semi synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I inhibitory activity. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I DNA complex and prevents relegation of these single strand breaks.

Intravenous (IV) topotecan was approved by the FDA on November 30 of 1998 for the treatment of patients with small cell lung cancer sensitive disease after failure of first-line chemotherapy. The US application for the IV topotecan in subjects with relapsed SCLC was based on randomized Phase III study comparing treatment with IV topotecan with IV Cyclophosphamide, Adriamycin and Vincristine (CAV). Two developments have occurred since the approval of IV tpotecan: (1) the Committee for Human Medicinal Products (CHMP) requested that a randomized study comparing topotecan with best supportive care (BSC) using overall survival as a primary endpoint be conducted to support the indication for relapsed SCLC, (2) sponsor's Study 065 showed that oral topotecan and IV topotecan demonstrated similar clinical activity in the relapsed SCLC setting. Thus, the sponsor's initiated randomized trials Study 478 comparing oral topotecan with best supportive care using overall survival as the primary efficacy endpoint, and Study 396 for showing the comparability of oral topotecan to IV topotecan, to support the indication of oral topotecan for treatment of patients with relapsed small cell lung cancer.

2.1.2 Clinical Studies

The sponsor conducted 3 efficacy studies in patients with relapsed SCLC:

1. Study 478 is the primary efficacy study aiming to demonstrate treatment efficacy by comparing oral topotecan plus best supportive care (BSC+OT) to best supportive care alone (BSC alone) in terms of overall survival. Study 478 was an open-label trial with 141 patients randomized at 1:1 ratio to receive BSC+OT or BCS alone. Randomization for Study 478 was planned to be based on 4 stratification factors: time to progression since prior chemotherapy (≤ 60 days or > 60 days), Eastern Co-operative Oncology Group (ECOG) performance status (0/1 or 2), gender (male or female), and liver metastases (presence or absence). This study was conducted at 40 centers in Bulgaria (3), Canada (1), Croatia (1), Hungary (9), Latvia (2), the Netherlands (1), Romania (4), Russia (1), Slovakia (2), the Ukraine (4), and the United Kingdom (13).

2. Study 065 and Study 396 were conducted to provide supportive efficacy for oral topotecan by showing its comparability to the approved IV topotecan with respect to response rate and overall survival. Both studies were multi-center randomized studies in patients with sensitive disease (> 90 days since prior chemotherapy) SCLC. Study 065 had 106 patients (oral topotecan: 52, IV topotecan: 54). Study 396 had 304 patients (oral topotecan: 153, IV topotecan: 151).

Study 478 is a randomized controlled trial with overall survival as the primary endpoint, and will be the primary basis for the efficacy evaluations of oral topotecan.

2.1.3 Major Statistical Issues

1) Study 478 was closed before the required target sample size was achieved. A total of 141 instead of targeted 220 patients were recruited. Survival analysis was performed with 130 deaths compared to originally planned 168 deaths, resulting a reduction in power from targeted 90% to 81% for testing the survival superiority hypothesis with addition of oral topotecan. Reason for closing the trial early, as claimed by the applicant, was due to poor recruitment in this trial and several centers withdrawing their participation (please refer to Appendix I for study accrual rate as provided by the applicant). To evaluate the impact of closing the study early, the reviewer compared the p-value of 0.0104 from un-stratified log-rank test to an alpha of 0.022 for the survival analysis with observed 130 deaths as an interim analysis. Since 0.0104 is less than 0.022, the survival comparison between oral topotecan and BSC alone remains statistical significant even with fewer events.

2) In the original protocol dated 07 Feb. 2000, duration of response to prior chemotherapy was listed as a randomization factor along with performance status, gender, and liver metastases. However, duration of response to prior chemotherapy was replaced by time to progression since prior chemotherapy in protocol amendment 03 dated 13 May 2004. According to applicant's response, number of days from discontinuation of first-line chemotherapy to

relapse was asked when an investigator called in the randomization system per Procedures for Central Patient Registration and Randomization of the protocol, and the protocol was amended to reflect what was actually captured (please see Appendix II for the required information entered for randomization). To address the concern that duration of response may have been entered instead of time to progression in some patients, the reviewer calculated the survival hazard ratios adjusting for original protocol specified stratification factors or for the amended stratification factors, and results are similar (survival hazard ratio [95% CI] = 0.62 [0.43, 0.88] if adjusted for the factors as specified in original protocol; = 0.61 [0.43, 0.87] if adjusted for the factors as specified in amended protocol).

2.2 Data Sources

Data used for this review are located on network with path \\CDSESUB1\EVSPROD\NDA020981\0000\m5\datasets and \\CDSESUB1\EVSPROD\NDA020981\0014\m5\datasets. Data submission occurred on April 11 and August 24 of 2007.

Reviewer's Comment:
Data submission on August 24 of 2007 includes the revised DEM dataset, which replaces the original dataset with the correct non-missing value for duration of response to prior chemotherapy variable "DURWKS".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Data from the Phase III pivotal study 478 will be the primary basis of efficacy evaluation. Study 478 will be further described below in terms of study design and efficacy endpoints, analysis populations, and analysis methods. Reviewer's evaluation will focus on comparative assessments of efficacy results for using best supportive care plus oral topotecan (BSC+OT) versus best supportive care alone (BSC alone) as the treatment of patients with relapsed SCLC.

3.1.1 Study 478

3.1.1.1 Study Design and Efficacy Endpoints

Study 478 was an open-label, multi-center study to evaluate the survival benefit to patients with resistant SCLC of receiving treatment with oral topotecan in addition to palliative active symptom control. Enrolled patients were randomized at 1:1 ratio to receive either BSC alone or BSC plus oral topotecan 2.3 mg/m^2/day administrated for 5 consecutive days repeated every 21 days. The treatment randomization was stratified based on time to progression from end of prior

chemotherapy (≤ 60 days or > 60 days), performance status (0/1 or 2), gender (male or female), and liver metastases (present or absent).

The primary study objective was to compare the overall survival between patients with resistant SCLC who received active symptom control or best supportive care alone (BSC alone) and those who received best supportive care plus oral topotecan (BSC + OT). Secondary objectives were to compare the effect of the two treatment strategies on disease symptom control and quality of life, to estimate the response rate and time to progression for patients randomized to receive topotecan in combination with active symptom control and to evaluate the qualitative and quantitative toxicities of oral topotecan.

Study efficacy endpoints were:

- Primary: Overall survival, defined as the time from randomization to death
- Secondary:
    a. Response rate, defined as the percentage of all patients responding to treatment.
    b. Time to progression, defined as the time from between randomization and the first radiologically or clinically documented evidence of progression.
    c. Patient symptom assessment according to self-reported GSK Patient Symptom Assessment, EQ-5D Health Status Questionnaire, and the visual analogue assessment.

Survival was monitored on all patients. However, radiological assessment of tumor response was assessed only in the oral topotecan plus BSC arm and only required after three courses of treatment to confirm a clinically indicated response or a disease progression.

3.1.1.2 Sample Size Considerations

Sample size calculations as described in the final protocol:
"

The primary aim of the study is to answer the question, whether the addition of oral topotecan to active symptom control leads to prolonged overall survival.

Ho: overall survival with BSC only = overall survival with BSC + topotecan
H1: overall survival with BSC only ≠ overall survival with BSC + topotecan

According to this hypothesis, tests concerning the primary end point will be performed as two-sided tests.

Using reported results from Spiro [12], the estimated median survival with Active Symptom Control alone is expected to be 12 weeks. Estimated median survival with Active Symptom Control and oral topotecan therapy is anticipated to be 20 weeks. To demonstrate the survival superiority with the addition of oral topotecan in this fixed sample study design, 110 patients per treatment arm (total: n=220) would have to be recruited. The assumptions used for this calculation are as follows:

• A 5% risk of erroneously claiming superiority of the experimental arm in the presence of no true underlying difference (type I error)

• A 90% chance of successfully declaring superiority in the presence of a true underlying difference (power, 1 - type II error).

• The two-sided testing procedure will be the nonparametric log-rank test. It is assumed that all patients are followed for a fixed length of time, and that the hazard ratio is constant over time

• Minimum follow-up time for all patients: 30 weeks or until death.

"

The trial was closed before the required target sample size was achieved. The reason for closing the trial early, as claimed by the applicant, was due to poor recruitment in this trial and several centers withdrawing their participation. Study 478 recruited a total of 141 patients with 130 deaths observed, which reduced the power of the study from targeted 90% to 81% for testing the pre-specified survival superiority hypothesis with addition of oral topotecan.

Reviewer's Comments:

1. Spiro [12] = Spiro SG, Souham RL, Geddes DM, et al. Duration of chemotherapy in Small Cell Lung Cancer: A Cancer Research Campaign trial. *British Journal of Cancer.* 1989; 59(4): 578- 583.
2. Two European agencies MPA and NAM met with the applicant in October of 2003, and agreed to the applicant's proposal to the final survival analysis conducted at 125 events for an approximately 80% power.

3.1.1.3 Analysis Populations

Three analysis populations were used for efficacy analyses:

1. The intent-to-treat (ITT) population consists of all randomized patients and was the primary efficacy analysis population.
2. The modified ITT population comprises of all patients with at least one post-randomization evaluation in the BSC alone arm and all treated patients in the best supportive care plus oral topotecan (BSC+OT) arm. The modified ITT population was the analysis population for safety and quality of life outcomes.
3. The modified per-protocol population excludes patients who had a documented protocol violation or patients in the BSC arm who received subsequent chemotherapy. The modified per-protocol was used only to conduct survival analysis to be compared to survival results from the ITT population.

3.1.1.4 Analysis Methods

The primary efficacy endpoint is the overall survival, defined as the time from randomization to death. Survival distributions for treatment groups were estimated using the Kaplan-Meier Product Limit and displayed graphically. The treatments were compared using an un-stratified

log-rank test. Primary survival analysis was based on the ITT population. A separate survival analysis using the modified per-protocol population was conducted as a sensitivity analysis.

Secondary efficacy evaluations were based on response rate, time to progression, and symptom data on self-reported GSK Patient Symptom Assessment, Visual Analog Scale and the EuroQol (EQ-5D) instruments. The response rate for the BSC + OT group was summarized along with binomial two-sided 95% confidence interval for all randomized patients. Time to progression was summarized for all patients in the BSC + OT group by Kaplan-Meier estimates. The effect of treatment regimen on quality of life was assessed using summary statistics and Generalized Estimating Equation (GEE) or mixed models in the modified ITT population.

Reviewer's Comments:

1. Analyses on response rate and time to progression were descriptive for the fact that these parameters were available from only patients in the BSC+OT arm.
2. Analyses on symptom data will be viewed as descriptive (rather than confirmatory) for the reasons: 1) the analyses were conducted using only a subset of randomized patients; 2) self-reported data may not be credible in an open-label trial; 3) no error adjustment for multiple testing in multiple symptom scores was made.

3.1.1.5 Efficacy Results and Conclusions

3.1.1.5.1 Study Population

A total of 141 patients were enrolled and randomized into Study 478 at 39 centers in Europe and at 1 center in Canada. The modified ITT population excluded 3 randomized patients from the BSC alone group for lack of post-randomization evaluation, and excluded 1 randomized patient from the BSC+OT group for being randomized but not treated. The modified per-protocol population excluded 14 patients (20.0%) in the BSC alone group for protocol deviations, and excluded 1 patient (1.4%) in the BSC+OT group for without treatment. All 14 excluded patients in the BSC alone group received 2nd-line chemotherapy outside of the protocol following randomization and withdrawal from the study.

Table 2 Study 478 Patient Distributions

	Treatment Group		Total
	BSC + OT	BSC alone	
Randomized	71	70	141
ITT Population	71	70	141
Modified ITT Population	70	67	137
Modified per-protocol population	70	56	126

Source: Table 6 of Study 478 clinical study report

3.1.1.5.2 Demographics and Other Baseline Characteristics

Table 3 summarizes the demographics and baseline characteristics of ITT population. The two treatment groups appear to be similar with respect to demographics and baseline characteristics.

Table 3 Demographic and Baseline Characteristics: ITT Population

Demographic and Baseline Characteristics	Treatment Group	
	BSC + OT N = 71	**BSC alone** N = 70
Time to progression from prior chemotherapy		
<=60 days	22 (31.0%)	20 (28.6%)
>60 days	49 (69.0%)	50 (71.4%)
Median	84 days	90 days
Performance status		
0	8 (11.3%)	6 (8.6%)
1	44 (62.0%)	41 (58.6%)
2	19 (26.8%)	23 (32.9%)
Liver metastases		
No	51 (71.8%)	56 (80.0%)
Yes	20 (28.2%)	14 (20.0%)
Sex		
Male	52 (73.2%)	51 (72.9%)
Female	19 (26.8%)	19 (27.1%)
Age (years)		
mean (standard deviation)	59.8 (9.0)	58.6 (8.2)
min – max	37 – 76	43 – 79
>= 65	24 (33.8%)	20 (28.6%)
Race		
White	70 (98.6%)	70 (100%)
Black	1 (1.4%)	0
Weight (kg)		
mean (standard deviation)	73.9 (14.2)	70.4 (13.4)
min – max	44 – 110	40 – 105
Maximum lesion diameter (cm)		
< 2	7 (9.9%)	2 (2.9%)
2 - < 5	34 (47.9%)	25 (35.7%)
5 – 10	19 (26.8%)	32 (45.7%)
> 10	2 (2.8%)	5 (7.1%)
Non-measurable	9 (12.7%)	6 (8.6%)
Prior cancer therapy		
Any prior therapy	46 (64.8%)	48 (68.6%)
Radiotherapy	38 (53.5%)	34 (48.6%)
Surgery	18 (25.4%)	20 (28.6%)
Immunotherapy	0	4 (5.7%)

3.1.1.5.3 Efficacy Results

3.1.1.5.3.1 Survival

Sponsor's survival results are summarized for the ITT population in Table 4. For the ITT population, median survival in the BSC alone group was 13.9 weeks compared with 25.9 weeks in the BSC + OT group. The difference between the groups in overall survival was statistically significant (p = 0.0104) based on the un-stratified log-rank test. The unadjusted hazard ratio for BSC + OT relative to BSC alone was 0.64 (95% C.I. 0.45, 0.90). The hazard ratio adjusted for the stratification factors was 0.61 (95% C.I.: 0.43, 0.87).

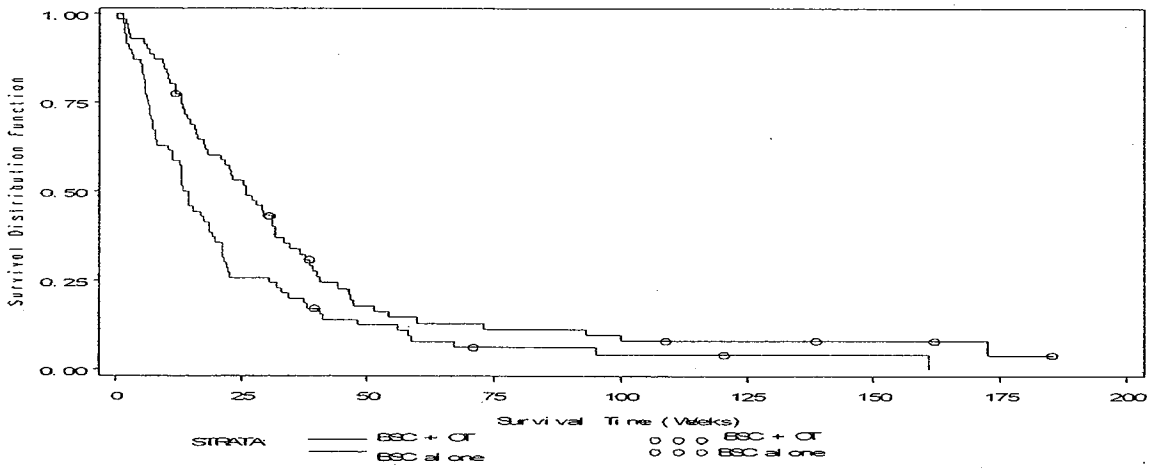
Table 4 Reviewer's Summary of Survival: ITT Population

Median survival (weeks)	**BSC + OT**	**BSC alone**
Median (95% CI)	25.9 (18.3, 31.6)	13.9 (11.1, 18.6)
Observed events	63 (88.7%)	67 (95.7%)
Hazard Ratio* (95% CI)	0.64 (0.45, 0.90)	
Log-rank p-value#	0.0104	

* Un-stratified hazard ratio for BSC+OT versus BSC alone

2-sided p-value from un-stratified log-rank test comparing survival between the two groups

Figure 2 Reviewer's Kaplan-Meier Curve for Survival (ITT Population)



Reviewer Comments:

1. The study was closed before the targeted 220 patients were recruited and survival analyzed with planned 168 events. If we view the survival analysis with observed 130 deaths as an interim analysis, the alpha allocated for this analysis should be 0.022, which is still greater than the log-rank p-value of 0.0104.

2. There is a concern that some study sites may not have entered correct information on time to progression since last chemotherapy at the time of randomization because the wording "duration of response" was used in the randomization procedure document. The reviewer re-calculated the stratified survival hazard ratio with time to progression since last therapy replaced by duration of response to prior therapy as a stratification factor. The re-calculated hazard ratio of 0.62 (95% CI: 0.43, 0.88) is similar to the one calculated based on randomization factors as specified in the final protocol.

3.1.1.5.3.2 Time to Progression (TTP)

Time to progression was assessed only for those patients in the BSC + OT group. Median time to progression in the BSC + OT group was 16.3 weeks (95% C.I.: 12.9, 20.0) with 59 out of the 71 patients (83.1%) had observed disease progressions.

Reviewer Comment:
The benefit of adding oral topotecan to best supportive care in terms of time to progression cannot be evaluated in this study as time to progression was not assessed in the BSC group for comparison.

3.1.1.5.3.3 Response Rate

Best response was also assessed only for those patients in the BSC + OT group. A response rate of 7.0% (95% C.I.: 2.33%, 15.67%) was observed and stable disease was determined in 43.7% of these patients.

Reviewer Comment:
The benefit of adding oral topotecan to best supportive care in terms of response rate cannot be evaluated in this study as response rate was not assessed in the BSC group for comparison.

3.1.1.5.3.4 Symptom Data

The applicant reported the rate of change from baseline per 3-month interval for EQ-5D symptom scores to be -0.20 for BSC alone group, and -0.05 for the BSC+OT group. The applicant conducted analysis for individual symptoms based on generalized estimation equations (GEE). Odds ratios from the GEE analysis were in favor of the BSC+OT over the BSC alone for symptom alleviation. The applicant also reported that mean visual analogue scores were numerically higher for patients in the BSC+OT group.

Reviewer Comment:
Analyses on symptom data will be viewed as only descriptive for the reasons: 1) the analyses were conducted using only a subset of randomized patients; 2) self-reported data may not be credible in an open-label trial; 3) no error adjustment for multiple testing in multiple symptom

scores was made; 4) the health outcome instruments used for the study have not been proven to be reliable and valid for assessing clinical benefit in patients with relapsed SCLC.

3.1.1.5.4 Conclusions for Efficacy

Results from the NDA registration trial Study 478 indicate a survival benefit from addition of oral topotecan to best supportive care in patients with relapsed small cell lung cancer (SCLC). Median survival was 13.9 weeks (95% confidence interval [CI]: 11.1, 18.6 weeks) for patients under the best supportive care only, and was 25.9 weeks (95% CI: 18.3, 31.6 weeks) for patients treated with oral topotecan plus best supportive care. The unadjusted survival hazard ratio for best supportive care plus oral topotecan (BSC+OT) relative to best supportive care alone (BSC alone) was 0.64 (95% CI: 0.45, 0.90), and the un-stratified log-rank test for comparing survival curves between the two treatment groups was significant at a p-value of 0.0104. Issues related to the conduct of Study 478 such as study was closed earlier than planned, and some study sites may have failed to follow the stratification procedure, do not appear to alter the conclusion that oral topotecan appears to provide additional survival benefit to patients under best supportive care alone for relapsed SCLC.

3.1.2 Results from supportive studies 065 and 396

Studies 065 and 396 were designed as Phase 2 and Phase 3 trials, respectively, to evaluate the efficacy of oral topotecan (2.3 mg/m^2/day for 5 days, every 21 days) versus IV tpotecan (1.5 mg/m^2/day for 5 days, every 21 days) in SCLC patients who had relapsed >=90 days after completion of one prior regimen of chemotherapy.

Table 5 lists the summary of survival, response rate, and time to progression in SCLC patients treated with oral topotecan or IV topotecan based on data from studies 065 and 396. These results suggest patients treated with oral topotecan in general had better outcomes in Study 065, but had worse outcomes in Study 396, compared to patients treated with IV formulation of topotecan. It should be noted that Study 396 had failed its primary objective to demonstrate non-inferiority in response rate of oral topoptecan to IV topotecan based on a 10% margin of non-inferiority as the lower 95% confidence interval for the difference in response rate is -12.5%, which is < -10%.

Table 5 Summary Results on Oral Topotecan versus IV Topotecan Based on Data from Studies 065 and 396

	Study 065		Study 396	
	Oral topotecan (N = 52)	**IV topotecan (N = 54)**	**Oral topotecan (N = 153)**	**IV topotecan (N = 151)**
Median survival (weeks) (95% CI)	32.3 (26.3, 40.9)	25.1 (21.1, 33.0)	33.0 (29.1, 42.4)	35.0 (31.0, 37.1)
Hazard ratio (95% CI)	0.88 (0.59, 1.31)		0.88 (0.7, 1.11)	
Response rate (%) (95% CI)	23.1 (11.6, 34.5)	14.8 (5.3, 24.3)	18.3 (12.2, 24.4)	21.9 (15.3, 28.5)
Difference in response rate (95% CI)	8.3 (-6.6, 23.1)		-3.6 (-12.6, 5.5)	
Median time to progression (weeks) (95% CI)	14.9 (8.3, 21.3)	13.1 (11.6, 18.3)	11.9 (9.7, 14.1)	14.6 (13.3, 18.9)
Hazard ratio (95% CI)	0.90 (0.60, 1.35)		1.21 (0.96, 1.53)	

Source: Applicant's results from individual study reports. Results verified by the reviewer.

Reviewer's Comment:
Results from Studies 065 and 396 for comparing oral topotecan to IV topptecan are inconclusive since results from the two studies are contradictory, and the Phase III Study 396 have failed to demonstrate non-inferiority in response rate as pre-specified.

3.2 Evaluation of Safety

3.2.1 Statistical Methods for Safety Evaluations

The safety database for this NDA include all treated patients in studies 478, 065, 396 for relapsed small cell lung cancer, as well as treated patients in study 387 for non-small cell lung cancer. Safety of oral topotecan are assessed based on summary statistics on extent of exposure, incidence and severity of adverse, and incidence of serious adverse events. No formal hypotheses and statistical testing are used for safety evaluations.

3.2.2 Safety Results and Conclusions

Please refer to Clinical Evaluations of this application for safety results and conclusions.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The applicant had conducted survival analysis by gender as gender is an established prognostic factor for SCLC (see Table 27 of Study 478 report for detailed results). Summary results below show an approximately 14 weeks of median survival for both males and females in the BSC alone group, but an increase to 23 weeks of median survival for males, and an increase to 39 weeks of median survival for females in patients treated with oral topotecan in addition to best supportive care alone

The reviewer conducted subgroup analysis by age. Results shown below indicate a similar degree of survival benefit from addition of oral topotecan for both patients younger than 65 and patients older than 65 years of age.

Subgroup analysis by race was not performed since there was only one non-white participant in Study 478.

Table 6 Treatment Comparisons by Gender and Age (ITT Population, Study 478)

Factor	Group	BSC + OT			BSC alone			Hazard Ratio * (95% CI)
		n	# Event	Median OS	n	# Event	Median OS	
Gender	Male	52	48	23.3	51	49	13.3	0.80 (0.53, 1.19)
	Female	19	15	38.7	19	18	14.4	0.43 (0.21, 0.88)
Age	< 65 yrs	47	42	25.7	50	47	13.2	0.69 (0.45, 1.05)
	>= 65 yrs	24	21	27.6	20	20	15.7	0.57 (0.31, 1.06)

* Hazard ratio for BSC + OT versus BSC in overall survival

4.2 Other Special/Subgroup Populations

The applicant had also performed survival analyses by performance status, liver metastases, and time to progression from the end of prior therapy (detailed results were listed in tables 28-30 of Study 478 report). The reviewer performed additional subgroup analyses by whether the patient received platinum-containing regimens. Results on these subgroup analyses as summarized in Table 7 suggest a survival benefit from addition of oral topotecan across subgroups.

Table 7 Summary of Survival by Selected Factors (ITT Population, Study 478)

Factor	Group	BSC + OT			BSC alone			Hazard Ratio * (95% CI)
		n	# Event	Median OS	n	# Event	Median OS	
Performance status	0 or 1	52	46	29.2	47	44	18.6	0.70 (0.46, 1.07)
	>=2	19	17	20.9	23	23	7.7	0.46 (0.24, 0.87)
Liver metastases	Absent	51	43	30.9	56	53	14.4	0.58 (0.38, 0.87)
	Present	20	20	13.3	14	14	7.9	0.61 (0.30, 1.24)
Time to progression #	≤ 60 days	22	19	23.3	20	20	13.2	0.51 (0.26, 0.97)
	> 60 days	49	44	27.7	50	47	14.4	0.71 (0.47, 1.07)
Time to progression #	≤ 90 days	41	36	22.7	36	36	13.1	0.62 (0.39, 0.98)
	> 90 days	30	27	31.6	34	31	15.9	0.65 (0.39, 1.10)
Prior platinum regimens	Yes	54	49	27.3	53	51	14.4	0.65 (0.39, 1.10)
	No	17	14	22.7	17	16	12.7	0.65 (0.39, 1.10)

* Hazard ratio for BSC + OT versus BSC alone in overall survival

Time from the end of prior therapy to disease progression

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

1) Study 478 was closed before the required target sample size was achieved. A total of 141 instead of targeted 220 patients were recruited. Survival analysis was performed with 130 deaths compared to originally planned 168 deaths, resulting a reduction in power from targeted 90% to 81% for testing the survival superiority hypothesis with addition of oral topotecan. Reason for closing the trial early, as claimed by the applicant, was due to poor recruitment in this trial and several centers withdrawing their participation (please refer to Appendix I for study accrual rate as provided by the applicant). To evaluate the impact of closing the study early, the reviewer compared the p-value of 0.0104 from un-stratified log-rank test to an alpha of 0.022 for the survival analysis with observed 130 deaths as an interim analysis. Since 0.0104 is less than 0.022, the survival comparison between oral topotecan and BSC alone remains statistical significant with fewer events.

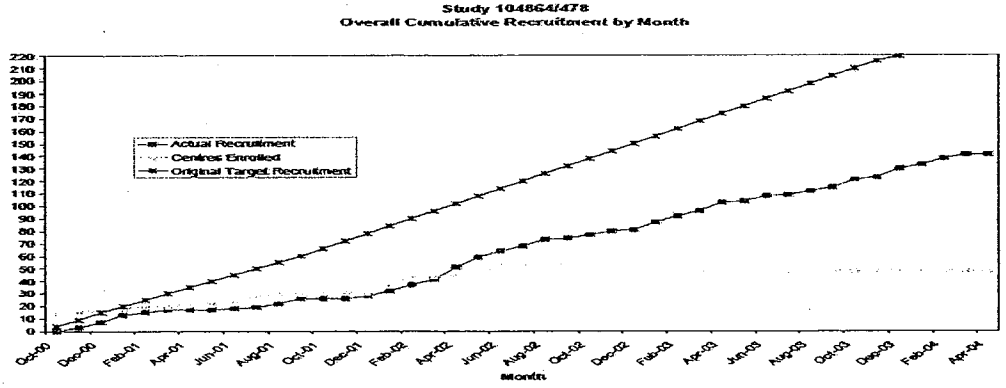
2) In the original protocol dated 07 Feb. 2000, duration of response to prior chemotherapy was listed as a randomization factor along with performance status, gender, and liver metastases. However, duration of response to prior chemotherapy was replaced by time to progression since prior chemotherapy in protocol amendment 03 dated 13 May 2004. According to applicant's response, number of days from discontinuation of first-line chemotherapy to relapse was asked when an investigator called in the randomization system per Procedures for Central Patient Registration and Randomization of the protocol, and the protocol was amended to reflect what was actually captured (please see Appendix II for the required information entered for randomization). To address the concern that duration of response may have been entered instead of time to progression in some patients, the reviewer calculated the survival hazard ratios adjusting for original protocol specified stratification factors or for the amended stratification factors, and results are similar (survival hazard ratio [95% CI] = 0.62 [0.43, 0.88] if adjusted for the factors as specified in original protocol; = 0.61 [0.43, 0.87] if adjusted for the factors as specified in amended protocol).

5.2 Conclusions and Recommendations

Results from the NDA registration trial Study 478 indicate a survival benefit from addition of oral topotecan to best supportive care in patients with relapsed small cell lung cancer (SCLC). Median survival was 13.9 weeks (95% confidence interval [CI]: 11.1, 18.6 weeks) for patients under the best supportive care only, and was 25.9 weeks (95% CI: 18.3, 31.6 weeks) for patients treated with oral topotecan plus best supportive care. The unadjusted survival hazard ratio for best supportive care plus oral topotecan (BSC+OT) relative to best supportive care alone (BSC alone) was 0.64 (95% CI: 0.45, 0.90), and the un-stratified log-rank test for comparing survival curves between the two treatment groups was significant at a p-value of 0.0104. Issues related to the conduct of Study 478 such as study was closed earlier than planned, and some study sites may have failed to follow the stratification procedure, do not appear to alter the conclusion that adding oral topotecan to best supportive care appears to provide survival benefit to patients with relapsed SCLC.

APPENDIX I Study 478 Accural Rate and Recruitment by Month

Monthly Accrual Rate
Study 104864/478



Study 104864/478
Recruitment by Month

Month-Year	Patients Enrolled	Original Target Rate	Month-Year	Patients Enrolled	Original Target Rate
Oct 00	0	4	Dec-02	1	150
Nov-00	3	9	Jan-03	6	156
Dec-00	4	15	Feb-03	5	162
Jan-01	6	20	Mar-03	4	168
Feb-01	2	25	Apr-03	7	174
Mar-01	2	30	May-03	1	180
Apr-01	0	35	Jun-03	4	186
May-01	0	40	Jul-03	1	192
Jun-01	1	45	Aug-03	3	198
Jul-01	1	50	Sep-03	3	204
Aug-01	3	55	Oct-03	6	210
Sep-01	4	60	Nov-03	2	216
Oct-01	0	66	Dec-03	7	220
Nov-01	0	72	Jan-04	3	
Dec-01	2	78	Feb-04	5	
Jan-02	4	84	Mar-04	3	
Feb-02	5	90	**Total**	**141**	
Mar-02	4	96			
Apr-02	10	102			
May-02	8	108			
Jun-02	5	114			
Jul-02	4	120			
Aug-02	5	126			
Sep-02	2	132			
Oct-02	2	138			
Nov-02	3	144			

APPENDIX II Study 478 Information to be Entered for Randomization

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Original protocol Feb. 2000

Appendix J: Procedures for Central Patient Registration and Randomization

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Please enter the five digit CRF number, followed by the pound/hash key. [GEN_49]

The CRF number is... (#####). [Gen_62] If this is correct, press 1. If this is incorrect, press 3. [GEN_34

(if 1, continue)

(if 3, go to 7)

Please enter the patient's date of birth (specific to the country)

Enter 2 digits for the day, then 2 digits for the month, and then 4 digits for the year of birth. [GEN_83]

The patient's date of birth is {1 January 1990}. [S28]

If this is correct, press 1. If this is incorrect, press 3. [GEN_34]

(if 1 continue)

(if 3 go to 9)

Please enter the patient's duration of response to first-line chemotherapy in days from cessation of first line therapy until documented relapse(please enter three digits i.e for 75 days enter 075). [S54]

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/s/

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