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APPLICATION NUMBER:

20-981

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-981
Submission Code	000
Letter Date	April 11, 2007
Stamp Date	N/A
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Reviewer Name	Robert M. White, Jr., MD, FACP
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Established Name	Topotecan Hydrochloride
(Proposed) Trade Name	Oral Hycamtin
Therapeutic Class	Cytotoxic; topoisomerase I inhibitor
Applicant	GlaxoSmithKline
Priority Designation	P
Formulation	Oral
Dosing Regimen	2.3 mg/m^2/day for 5 consecutive days every 21 days
Indication	Treatment of patients with relapsed small cell lung cancer
Intended Population	Relapsed small cell lung cancer patients who have had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

One non-blinded, randomized, controlled trial, demonstrating the efficacy and safety of Hycamtin capsules for the treatment of patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are ≥ 45 days post cessation of first-line chemotherapy has been submitted and reviewed. The pivotal trial was multicenter with only non-United States sites. The data submitted demonstrated that Hycamtin capsules has a survival benefit in small cell cancer patients (who have had a complete or partial response to first-line chemotherapy and who are ≥ 45 days post cessation of first-line chemotherapy) in comparison to a best supportive care control arm.

Hycamtin capsules showed a consistent improvement in survival in comparison to best supportive care across the stratification factors (i.e., cessation from prior chemotherapy (days) (≤ 60 or > 60), liver metastases (absence or presence), performance status (ECOG) (0/1 or 2) and gender (male or female). Also, Hycamtin capsules showed improvement in survival with regard to age, stage of SCLC, and cessation from prior chemotherapy (days) (≤ 90 or > 90).

Based on the data submitted, Hycamtin capsules has satisfactorily demonstrated a consistent survival advantage compared to best supportive care in patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are ≥ 45 days post cessation of first-line chemotherapy in a randomized, non-blinded study.

In the Hycamtin capsules group, the frequency of grade 3 or 4 hematological toxicities followed the known profile of Hycamtin capsules: grade 3 or 4 neutropenia occurred in 61.2% of patients, grade 3 or 4 leukopenia in 40.6% of patients, grade 3 or 4 thrombocytopenia in 37.7% of patients and grade 3 or 4 anemia in 24.6% of patients. Similarly, the incidence of fever, febrile neutropenia, infection and sepsis were as expected following treatment with topotecan: fever or infection proximate to grade 4 neutropenia occurred in 4 (5.8%) patients. Sepsis was reported for 3 (4.3%) patients. The numbers of patients who experienced adverse events during the study was similar in each treatment group: 46 patients (68.7%) in the best supportive care group and 50 patients (71.4%) in the Hycamtin capsules group. The adverse events observed in the Hycamtin capsules group in study #478 study were consistent with other studies of Hycamtin capsules. A total of 18 patients (26.9%) in the best supportive care group and 18 patients (25.7%) in the Hycamtin capsules group had serious adverse events. The reported incidence of disease progression was higher in the best supportive care group (11 patients, 16.4%) than in the Hycamtin capsules group (5 patients, 7.1%). The incidence of serious thrombocytopenia (5 patients, 7.1%), leukopenia (3 patients, 4.3%) and neutropenia (3 patients, 4.3%) was higher in the Hycamtin capsules group, none of these events being reported in the best supportive group. In total, 1 patient (1.5%) in the best supportive care group and 11 patients (15.7%) in the

Hycamtin capsules group were withdrawn from the study due to adverse events in the modified intent-to-treat population. In the best supportive group, one patient withdrew, due to a pulmonary embolism. In the Hycamtin capsules group, the events most commonly leading to withdrawal were leukopenia, thrombocytopenia, pulmonary embolism and diarrhea. In the modified intent-to-treat population, 67 patients (95.7%) in the ASC alone group and 62 patients (88.6%) in the Hycamtin capsules were known to have died at any time. In the modified intent-to-treat population, 11 patients (15.7%) in the Hycamtin capsules died within 30 days of their last receipt of study medication; 51 patients (72.9%) died more than 30 days after last receipt of study medication. Three patients died within 30 days of their last receipt of study medication due to hematological toxicity and one due to nonhematological toxicity. Monitoring of non-hematological laboratory data and measurement of vital signs showed no results of clinical significance for the Hycamtin capsules group.

However, the demonstration of the survival benefit is based on only one randomized, control trial. Study #478 was not conducted under an IND; the FDA did not have knowledge about the study until notified about the pre-NDA meeting in August 2006. The study was conducted in Europe (and one site in Canada) and was under European authority. Study #478 did have challenges with regard to certain aspects of conduct of the trial (i.e., discrepancies in time to progression from the end of prior chemotherapy; liver metastases [presence or absence]; performance status; registration and randomization; and eligibility). Despite removal of 32 patients with discrepancies, the survival benefit of Hycamtin capsules in comparison to best supportive care remained. Also, on the Hycamtin capsules arm, the response rates for patients who were defined as having "sensitive" and "resistant" SCLC were the reverse of what would be expected from the literature and from the experience with intravenous topotecan; the "resistant" patients had a higher response rate than the "sensitive" patients.

Based on this review of NDA 20-981, Hycamtin capsules is clinically approvable for the treatment of patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy.

1.2 Recommendation on Postmarketing Actions

Not applicable

1.3 Summary of Clinical Findings

The regulatory conclusion is based on a single, randomized controlled trial.

- The study population was patients with small cell lung cancer (SCLC) who have had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy. Patients were randomized to either Hycamtin capsules or best support care only.

- The primary efficacy variable was overall survival. For the intent-to-treat population, median survival in the best support care group was 13.9 weeks compared with 25.9 weeks in Hycamtin capsules. The difference between the groups in overall survival was clinically and statistically significant (log-rank p=0.0104).
- For patients in the Hycamtin capsules, a response rate of 7.0% was recorded and stable disease was achieved in 44% of patients. Median time to progression for these patients was 16.3 weeks. In the best supportive care group 18 patients (25.7%) were alive after 6 months, compared to 34 patients (48.9 %) in the Hycamtin capsules group.
- The primary objective of the study has been met by demonstrating that second-line Hycamtin capsules extends survival in patients with relapsed resistant SCLC (who have had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy) by a clinically and statistically significant margin.

Brief Overview of Clinical Program

- Product name: Hycamtin capsules
- Class: cytoxic; topoisomerase I inhibitor
- Route of administration: oral
- Indication: Hycamtin capsules for relapsed small cell lung cancer patients who have had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy
- Number of pivotal efficacy and safety trials: Three randomized trials in relapsed small cell lung cancer were submitted to support the indication.
- Overall number of patients in the safety database: 682 patients from the thoracic integrated population plus 70 patients from the pivotal trial.

Efficacy

- Pivotal trial: An Open-Label, Multicentre, Randomised, Phase III Comparator Study of Active Symptom Control Alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant Small Cell Lung Cancer (SCLC) (study 478)
- Primary endpoint: overall survival
- Secondary endpoints: compare disease symptom control and quality of life; response rate and time to progression only on topotecan arm; and qualitative and quantitative toxicities of oral topotecan.
- Problems and/or issues with the efficacy study:
    - FDA did not have knowledge of the study at inception. FDA learned about the study after the study was completed.
    - The study was planned to accrue 220 patients; the study was stopped at 141 patients
    - Except for gender, all the stratification factors (time to progression from the end of prior chemotherapy; liver metastases [presence or absence]; performance status) had multiple discrepancies between what the investigator entered into the

registration and randomization system and what was in the NDA database. There were also eligibility, randomization, and staging discrepancies.

- The study began as a study of resistant SCLC after 1st-line chemotherapy and transitioned to a study to include both resistant and sensitive SCLC
- The patient population had an undefined entry criterion which cannot be labeled, i.e., patients not considered suitable for further intravenous chemotherapy. The reasons intravenous chemotherapy may not be suitable for a patient was not captured on the case report form.
- On the Hycamtin capsules arm, the response rates for patients who were defined as having "sensitive" and "resistant" SCLC were the reverse of what would be expected from the literature and from the experience with intravenous topotecan; the "resistant" patients had a higher response rate than the "sensitive" patients.
- The reviewer's efficacy conclusion: The data demonstrated a significant improvement in survival for patients on the oral topotecan arm compared to patients on the best supportive care arm. After removal of the known discrepant cases, there was still a survival benefit on the Hycamtin capsules arm.

Safety

Findings from the pivotal trial, Study #478

In the Hycamtin capsules group, the frequency of grade 3 or 4 haematological toxicities followed known profile of Hycamtin capsules: grade 3 or 4 neutropenia occurred in 61.2% of patients, grade 3 or 4 leukopenia in 40.6% of patients, grade 3 or 4 thrombocytopenia in 37.7% of patients and grade 3 or 4 anemia in 24.6% of patients. Similarly, the incidence of fever, febrile neutropenia, infection and sepsis were as expected following treatment with topotecan: fever or infection proximate to grade 4 neutropenia occurred in 4 (5.8%) patients. Sepsis was reported for 3 (4.3%) patients. The numbers of patients who experienced adverse events during the study was similar in each treatment group: 46 patients (68.7%) in the best supportive care group and 50 patients (71.4%) in the Hycamtin capsules group. The adverse events observed in the Hycamtin capsules group in study #478 study were consistent with other studies of Hycamtin capsules. A total of 18 patients (26.9%) in the best supportive care group and 18 patients (25.7%) in the Hycamtin capsules group had serious adverse events. The reported incidence of disease progression was higher in the best supportive care group (11 patients, 16.4%) than in the Hycamtin capsules group (5 patients, 7.1%). The incidence of serious thrombocytopenia (5 patients, 7.1%), leukopenia (3 patients, 4.3%) and neutropenia (3 patients, 4.3%) was higher in the Hycamtin capsules group, none of these events being reported in the best supportive group. In total, 1 patient (1.5%) in the best supportive care group and 11 patients (15.7%) in the Hycamtin capsules group were withdrawn from the study due to adverse events in the modified intent-to-treat population. In the best supportive group, one patient withdrew, due to a pulmonary embolism. In the Hycamtin capsules group, the events most commonly leading to withdrawal were leukopenia, thrombocytopenia, pulmonary embolism and diarrhea. In the modified intent-to-treat population, 67 patients (95.7%) in the ASC alone group and 62 patients (88.6%) in the Hycamtin capsules were known to have died at any time. In the modified intent-to-treat

population, 11 patients (15.7%) in the Hycamtin capsules died within 30 days of their last receipt of study medication; 51 patients (72.9%) died more than 30 days after last receipt of study medication. Three patients died within 30 days of their last receipt of study medication due to hematological toxicity and one due to nonhematological toxicity. Monitoring of non-hematological laboratory data and measurement of vital signs showed no results of clinical significance for the Hycamtin capsules group.

Dosing Regimen and Administration

- Hycamtin capsules 2.3 mg/m^2/day orally for 5 consecutive days every 21 days

Drug-Drug Interactions

Not applicable.

Special Populations

See Clinical Pharmacology review.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

- Oral HYCAMTIN is indicated for the treatment of patients with relapsed small cell lung cancer
- The recommended dose of Oral HYCAMTIN is 2.3 mg/m^2/day once daily for 5 consecutive days repeated every 21 days.
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2.2 Currently Available Treatment for Indications

The proposed indication is for small cell lung cancer patients who had a complete or partial response to first-line chemotherapy and who are $\geq$ 45 days post cessation of first-line chemotherapy. This indication covers two groups of patients: 1) sensitive disease patients, i.e., patients who had a complete or partial response to first-line chemotherapy and who are > 90 days post cessation of first-line chemotherapy; and 2) resistant disease patients, i.e., patients who had a complete or partial response to first-line chemotherapy and who are $\leq$ 90 days post cessation of first-line chemotherapy. Sensitive disease patients have the following options available: 1) intravenous topotecan (approved); and either cross-resistant cytoxic therapy or the prior chemotherapy regimen (depending on how long a patient is post cessation of first-line chemotherapy; the longer the duration from cessation of first-line chemotherapy, the more likely a patient may have a second response to the prior chemotherapy.). Resistant disease patients do not have any approved drugs available; at the time of sudy #478 initiation, best supportive care was an option for these patients. However, the intravenous topotecan indication includes a subset of responders to chemotherapy who are 60-90 days post cessation of first-line chemotherapy and this treatment is available for them.

2.3 Availability of Proposed Active Ingredient in the United States

The FDA approved Hycamtin for Injection as a single agent on May 28, 1996 (NDA 20-671) for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy and on November, 30, 1998 (NDA 20-671/S-004) for the treatment of patients with small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy.

2.4 Important Issues With Pharmacologically Related Products

Not applicable. If any, these have been addressed in the intravenous topotecan label.

2.5 Presubmission Regulatory Activity

REGULATORY SUMMARY OF APPROVAL STRATEGIES FOR ORAL TOPOTECAN

YEAR	INDICATION	OUTCOME OR COMMENT
1997	[redacted]	[redacted] b(4)
1997	randomized Phase II Study 065: IV vs. oral topotecan in sensitive small cell lung cancer **supportive study for NDA**	From 11/1998 meeting minutes: • The small cell lung cancer study is too small to be reassuring regarding efficacy • Activity of the oral formulation in the [redacted] • The Division recommends a confirmatory randomized controlled trial in sensitive small cell lung cancer comparing the two formulations. The sponsor could consider refining the dose. • [redacted] b(4) From 9/2006 meeting minutes: • ORRs were not statistically different between arms
1999	small cell lung cancer sensitive disease after the failure of initial chemotherapy: IV vs. oral topotecan in small cell lung cancer (study 396) **supportive study for NDA**	From 11/1998 meeting minutes: The Division recommends a confirmatory randomized controlled trial in sensitive small cell lung cancer comparing the two formulations. The sponsor could consider refining the dose. From 9/2006 meeting minutes: • ORRs were not statistically different between arms • GSK proposed to pool those results and show by noninferiority analysis that the ORR of oral topotecan is within 10% of

YEAR	INDICATION	OUTCOME OR COMMENT
		that of the IV formulation. From 4/2001 meeting minutes: • The FDA stated: Regarding your oral topotecan vs IV topotecan second-line study, please request a pre-NDA meeting to discuss issues related to this study prior to submission of an application for review.
2000	initiated randomized Phase III Study 478: oral topotecan + active supportive care vs. active supportive care only **pivotal study for NDA**	NO MEETING WITH FDA OR SPA
2001	[redacted]	[redacted] b(4)
2002	Combination of studies 065 and 396: IV vs. oral topotecan in small cell lung cancer	From 9/2006 meeting minutes: • ORRs were not statistically different between the arms
2006	[redacted]	
2006	To use Oral Topotecan Hydrochloride as treatment of patients with relapsed small cell lung cancer after failure of first-line therapy.	*This was the 1st time the FDA heard of this trial. In contrast to the studies mentioned above, this was the 1st time the FDA saw the protocol and the statistical plan. This is a completed study that was never a part of any of the before mentioned approval strategies.*

In summary, there is one pivotal trial + 2 supportive trials or two failed strategies that are unable to support a NDA on their own + one trial unknown to the FDA until eight months before submission of the NDA.

1 Also, there was study #078, an oral topotecan 1st-line study in extensive SCLC patients who were considered ineligible for standard therapy.

In the table below, there is a more detailed regulatory review.

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
1993 IND filed	IND filed	Phase I oral topotecan study		
Feb. 26, 1997	End-of-phase-2 (EOP2)	[redacted]		
		cancer)		

b(4)

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
			absorption, ring opening (not absorbed) Low bioavailability may be due to open-ring form not well absorbed and the drug converts to different pH conditions.	
1997	initiated randomized Phase II Study 065	IV vs. oral topotecan in small cell lung cancer Study dates: March 1997– May 2000		
Nov. 5, 1998	EOP2	small cell lung cancer sensitive disease after the failure of initial chemotherapy.	a) Exposure to drug appears to be less with the oral formulation. b) The small cell lung cancer study is too small to be reassuring regarding efficacy. c) Activity of the oral formulation in the ——— b(4) d) The Division recommends a confirmatory randomized controlled trial in sensitive small cell lung cancer comparing the two formulations. The sponsor could consider refining the dose. The sponsor also discussed the results of their Oral Hycamtin studies in patients with	

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
1999	initiated randomized Phase III Study 396: IV vs. oral topotecan in small cell lung cancer	Study dates: Jan. 1999 –Sept. 2003		
Nov. 16, 2000	initiated randomized Phase III Study 478: oral topotecan + active supportive care vs. active supportive care only			**NO MEETING WITH FDA OR SPECIAL PROTOCOL ASSESSMENT**
April 18, 2001	EOP2			

b(4)

b(4)

2 **MEDICAL OFFICER NOTE: if this 1st-line study is being done in the same countries as study #478, a 2nd-line study, this may interfere with accrual to study #478.**

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
			The FDA stated: Regarding your oral topotecan vs IV topotecan second-line study, please request a pre-NDA meeting to discuss issues related to this study prior to submission of an application for review.	
Sept. 12, 2002	pre-NDA	relapsed SCLC Oral topotecan is proposed for use in relapsed SCLC.	You may combine safety data, but the efficacy data may either be presented separately or subjected to a Meta analysis. if you choose the latter approach, please discuss further with the Division statisticians.	The plan was to use studies #065 and #396. Clinical Pharmacology: Have you studied the dose proportionality of oral topotecan around the therapeutic dose? How do you plan to show the bioequivalence of formulation [redacted] This will be a fileability issue. Please resolve this issue with the Division before filing this application. b(4)
March 30, 2004	Early termination of Study #478		**No FDA meeting or notification**	
May 13, 2004	Revision of Patient Sample Size Change in Stratification Factor in the body of the protocol		**No FDA meeting or notification**	
February 21, 2006	EOP2	[redacted]		

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
			primary endpoint.	
September 12, 2006	Pre-NDA	To use Oral Topotecan Hydrochloride as treatment of patients with relapsed small cell lung cancer after failure of first-line therapy.3 Study dates: Nov. 2000– Sept. 2004	The apparent improvement in OS as described for Study 478 could be the basis for an approval pending review. QoL endpoints in open label studies are not interpretable. Furthermore: a. Different QoL instruments were used (study 478: PSA and EQ-5D; study 065: PSA; study 396: FACT-L). b. Multiple symptoms/dimensions were evaluated without adjustment for multiple comparisons.	*This was the 1st time the FDA heard of this trial. In contrast to the studies mentioned above, this was the 1st time the FDA saw the protocol and the statistical plan. This was a completed study that was never a part of any of the before mentioned approval strategies.* *The manuscript was sent to the Journal of Clinical Oncology on March 29, 2006; the article was accepted September 25, 2006* In Study 478, median OS in the oral topotecan arm was superior to that of patients receiving best supportive care (25.9 wks vs. 13.9 wks; log-rank p = 0.0104). In Studies 065 and 396, ORRs were not statistically different between arms; however, GSK proposes to pool those results and show by noninferiority analysis that the ORR of oral topotecan is within 10% of that of the IV formulation. An additional study (387) was conducted in patients

3 From the 8/16/2006 pre-NDA briefing document: "...a change in registration strategy from previous discussions with the Division. This shift in regulatory strategy is based on 1.) a survival advantage seen in patients with relapsed SCLC from a clinical trial that was conducted in Europe that has not been discussed with the Division, 2.) favorable reaction to these results from the EMEA, and 3.) input from clinical experts in this disease setting."

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
				with relapsed advanced non-small cell lung cancer (NSCLC).4 The acceptability of these studies to support the specific wording proposed for the indication would be a review issue . The incidence of toxic deaths among patients treated with oral topotecan was comparable to that among patients with IV topotecan or docetaxel. Hematologic toxicity was dose limiting and generally comparable to that of IV topotecan or docetaxel. The incidences of nausea and vomiting were higher than with IV topotecan or docetaxel, whereas the incidences of diarrhea and stomatitis were slightly lower. Neither tumor response nor TTP were assessed in the BSC arm of Study 478. From page 30 of the Briefing Document: "For patients in the BSC alone arm, radiological assessment of tumor response was not justified, as the predicted response rate was zero." On page 33: "TTP was not assessed for patients in the BSC alone arm of study 478 because

4 This may also be the 1st time that the FDA knew about this study.

DATE	meeting, Submission, or action	indication, protocol, issues	agreements or FDA recommendations	COMMENT
				radiologic assessment for clinical progression was not required for that arm." *Because of the differential assessment of response and TTP in the two treatment arms of Study 478 specifically, response and TTP would not be considered supportive secondary endpoints and would not be included in the labeling.* For patients in the Best Supportive Care alone arm, radiological assessment of tumor response was not justified as the predicted response rate was zero.
Dec. 1, 2006	Publication of Study 478 in *Journal of Clinical Oncology* (survival benefit)			
April 11, 2007	NDA submitted			
May 5, 2007	Medical Reviewer assigned			
Dec. 8, 2006-Sept. 4, 2007	Number of oral topotecan single patient INDs or compassionate use INDs: 0			

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See Chemist's Review (Brian Rogers, entered into DFS 10/10/2007)

3.2 Animal Pharmacology/Toxicology

See Pharmacologist/Toxicologist's Review (David McGuinn, entered into DFS 10/8/2007)

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The pivotal trial, study #478, supplied most of the data for this review. Also, clinical information was reviewed from studies #65 and #396, the literature, and the results of the Division of Scientific Investigations audits. In response to medical officer queries about the design and conduct of study #478, the Sponsor supplied additional information, including some source documents.

4.2 Tables of Clinical Studies

Table 2 Phase I Single-Agent Oral Topotecan R&D Trials

Study ID	Study Title	Indication	Number of patients	
			Oral Topotecan All Doses	Oral Topotecan 2.3 mg/m^2/day
047	Single-dose oral bioavailability and pharmacokinetics of topotecan	Solid Tumors	12	0
048	A Phase I study to determine the effect of food co-administration on the pharmacokinetics of oral Topotecan and to determine the absolute bioavailability of oral topotecan in patients with malignant solid tumors.	Bioavailability	18	18
049	A Phase I study to determine the maximum tolerated dose of topotecan following oral administration over 21 days in patients with malignant solid tumors	Solid Tumors	98	8
118	An open-label two period crossover study to compare the bioavailability of a single dose of oral topotecan in the presence or absence of ranitidine	Bioavailability	18	18
230	A study to determine the balance/excretion and pharmacokinetics of SKF 104864 (topotecan) given as oral (2.3 mg/m^2) or intravenous (1.5 mg/m^2) doses once daily for 5 days to patients with malignant solid tumors.	Mass-balance	11	11
565	A study to determine the bioequivalence of an oral formulation of topotecan containing the drug substance manufactured by new process relative to the current study formulation of topotecan in patients with advanced solid tumors	Lung	50	50
692	A study to determine the bioequivalence of an oral formulation of topotecan containing the drug substance manufactured by a new process relative to the current study formulation of topotecan in patients with advanced solid tumors (4C)	Solid Tumors	104	104
		Total	311	209

Table 3 Phase II/III Single-Agent Oral Topotecan R&D Trials

Study ID	Phase	Study Title	Indication	Number of patients	
				Oral Topotecan All Doses	Oral Topotecan 2.3 mg/m^2/day
078	IIA	An open-label, multicenter study of single agent oral topotecan daily x5 every 21 days for first line treatment in patients with extensive SCLC eligible for oral therap	SCLC	42	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
204	IIA	A Phase II study to determine the efficacy and safety of 2.3 mg/m^2 oral topotecan daily for 5 days every 21 days in patients with advanced non-small cell lung cancer	NSCLC	30	30
067/080	IIIA	An open-label, multicenter, randomized, Phase III, comparative Study of topotecan, as single-agent, second-line therapy administered intravenously or orally as five daily doses every 21 days in women with advanced ovarian cancer	Ovarian	135	135
151	IIB	An open-label, non-comparative, multicenter Phase II study of oral topotecan as single agent, second-line therapy administered for five days in patients with advanced ovarian cancer	Ovarian	116	116
203	IIA	A Phase II study to determine the efficacy and safety of 2.3 mg/m^2 oral topotecan daily for 5 days every 21 days in patients with advanced breast cancer	Breast	30	30
386	IIA	An open-label, multicenter , randomized, Phase II Study of 5 day oral topotecan vs. 21-day oral topotecan vs. CPT-11 (Irinotecan) for second-line therapy in patients with colorectal carcinoma	Colorectal	99	50
		Total		1134	1043

Studies that support [a]efficacy and [b]safety of oral topotecan in the NDA are shaded. (Please see Section 2.1 for descriptions of the studies that will support Efficacy and Section 2.2 for a description of the additional study that will support Safety).

Table 4 Phase I, II, and III Oral Topotecan R&D Trials with Combination Regimens

Study ID	Phase	Study Title	Indication	Number of patients	
				Oral Topotecan All Doses	Oral Topotecan 2.3 mg/m^2/day
101	I	A Phase I study to determine the maximally tolerated dose and sequence dependent effects of topotecan administered orally once per day for five days with a single intravenous dose of cisplatin, repeated every three weeks to patients with malignant tumor	Solid Tumors	61	6
250	I/II	Phase I/II study of oral topotecan and intravenous paclitaxel in patients with advanced non-small cell lung cancer (Phases I and II) and other advanced solid tumors	NSCLC	63	0
373	I/II	A Phase I/II study to determine the maximum tolerated doses of oral topotecan, carboplatin and paclitaxel administered every 21 days to patients with epithelial ovarian cancer stages IIb, IIc, III and IV	Ovarian	86	0
511	I	A Phase I study to assess the safety, tolerability and efficacy of oral Etoposide and oral Topotecan administered in combination to patients with small cell cancer who have not previously received chemotherapy	SCLC	19	0
389	IIIA	An open-label, multicenter, randomized, Phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive disease-small cell lung cancer.	SCLC	381	50
152	IIA	A Phase II study to determine the efficacy and safety of oral topotecan given once daily for 5 days with a single intravenous dose of cisplatin on Day 5 repeated every 21 days in patients with advanced non-small cell lung cancer	NSCLC	50	0
			Total	660	56

4.3 Review Strategy

Three randomized trials in relapsed small cell lung cancer were submitted to support the indication. The studies were:

- An Open-Label, Multicentre, Randomised, Phase III Comparator Study of Active Symptom Control Alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC (study 478)

- An open label multicentre, randomised , phase II comparator study of oral topotecan versus intravenous topotecan for second line therapy in sensitive patients with small cell lung cancer (study 65)

- An open-label, multicentre, randomised, phase III comparator study of oral topotecan versus intravenous topotecan for second-line therapy in patients with SCLC who have relapsed greater than or equal to 90 days after completion of first-line therapy (study 396).

The latter two studies were comparisons of the oral and intravenous formulations of topotecan but the results were not sufficient for approval of oral topotecan (see section 2.5, Presubmission Regulatory Activity). These studies were not reviewed and the results from these studies were removed from the proposed label. The results from study #478 were the basis for this review of the efficacy and safety of Hycamtin capsules. The review was limited to the review of the study protocol, the Sponsor's report of the results, and the reviewer's analyses of the study results.

4.4 Data Quality and Integrity

There were 40 sites and 38 investigators that accrued patients in study #478. There were 16 sites and 16 investigators that did not accrue patients.[5] The investigators/sites accrued at least one patient. There were no US sites. The closest country to the US was Canada which accrued one case on the topotecan arm. The Division of Scientific Investigations audited the following sites (the site identification was from Table 12.1.1 in the Study 478 report):

Country	center # investigator	topotecan arm randomized/completed study	supportive care randomized/completed study	Reason for audit
Bulgaria	072 Zekov	6/6	7/6	Large number of pts.
Croatia	081 Cucevic	3/3	4/2	Author[6]
Romania	101	6/4	8/4	Author

5 Response by Sponsor dated 7/17/2007 to a query.
6 O'Brien et al. J Clin Oncol 24: 5441-5447, 2006

Country	center # investigator	topotecan arm randomized/completed study	supportive care randomized/completed study	Reason for audit
	Ciuleanu			
United Kingdom	042 O'Brien	4/4	3/1	Author
Ukraine	092 Shparyk	5/5	3/0	Author

Based on a preliminary review of the protocol for study #478, the review division requested the Division of Scientific Investigations inspectors to audit the following additional items:

1. For each site to be inspected, determine which protocol the site was using during the course of the study. If the site used several versions of the protocol, please document when the site began using each protocol version (ie amendment). There seems to be discrepancies noted for which protocol version(s) were used at sites.

2. The protocol required that subjects enrolled into the study had a diagnosis of Small Cell Lung Cancer (SCLC). Please review pathology reports or any other source records to verify that the subject had SCLC prior to their enrollment in the study.

3. SCLC can be divided into two stages: (1) limited-stage disease is defined as tumor confined to one hemithorax and the regional lymph nodes or the stage is based on a judgment as to whether all detectable tumor can be encompassed within a tolerable radiotherapy port; and (2) Extensive-stage is disease beyond these bounds of limited-stage. For the extensive stage of the disease, the disease has spread (ie metastasis) to other parts of the body.

(a) The study being audited involves subjects who previously had SCLC and have now relapsed. Determine which stage of the disease (limited or extensive) the subject was noted to have at the beginning of the trial.

(b) Please examine source records to determine what stage of the disease (limited or extensive) the subject was noted to have had when they were first diagnosed with and treated for SCLC. According to the review division medical officer, the two stages of disease should be the same for subjects enrolled into the study.

4. The protocol required that subjects had relapsed SCLC. Thus, the subjects should have been diagnosed previously with SCLC and treated with chemotherapeutic agents. Please examine source records to ensure that there is documentation available to show that the subject had initially responded (i.e., a partial response or a complete response) to the first chemotherapeutic drugs given to them when they were initially diagnosed with SCLC. Also, please document the date when the subject was noted to have responded to the 1st chemotherapeutic drug, what the drugs were, and when the drugs were stopped.

5. The medical officer has requested that you obtain a copy of all of the subjects informed consent documents. In addition, please examine the informed consent (IC) documents to

ensure that the title and introduction paragraph has the word "Resistant". The IC's may be in a different language; thus please request that the translator show you specifically where the word "resistant" is in the title and introduction paragraph. There are concerns that the informed consent document did not specifically explain to subjects that this study was enrolling subjects with relapsed resistant SCLC.

6. Section 5.3.4 of the protocol stated that patients were to be stratified according to such things as (1) time to progression from end of prior chemotherapy (2) performance status (3) Gender and (4) Liver Metastases. The CRF does not contain a field to capture Time to progression from end of prior chemotherapy. For randomization purposes, please determine how each of the clinical investigators (CIs) determined Time to progression from end of prior chemotherapy and whether there is documentation in the source records to verify this for all subjects or whether the CIs used duration of response to prior chemotherapy (which was captured on the CRF) at the time of randomization.

7. According to an article published by some of the CI's, certain subjects received post study IV study drug. This conflicts with the protocol eligibility criterion-- Patients not considered suitable for further intravenous chemotherapy. Please examine source records to determine what route of administration (oral vs IV) was utilized for subjects post study. Below is a list of subjects who received post study chemotherapy (list not shown in this review). If subjects received post study drug, please document when it was administered, what the route of administration was used, and what the names of the drugs were.

The some of the results of the audits were integrated into the following sections: Financial Disclosures, Compliance with Good Clinical Practices, and the reviewer's analyses of the study results.

4.5 Compliance with Good Clinical Practices

Based on information in the protocol and an amendment to protocol, there may have been ethical challenges in the study.

Amendment 2

In August 2001 (after 22 patients were accrued), the protocol was amended. The entry criterion "relapse...45-90 days after cessation of first-line therapy (resistant patients)" was changed to "relapse... ≥45 days after cessation of first-line therapy (resistant and sensitive patients)." The definition of "resistant disease" was left up to the judgement of the investigator.[7]

7 Source: p. 135-136 of protocol in NDA

Information in the protocol

The protocol for study #478, study report, and other study #478 documents stated several times that it was unethical to accrue patients with relapsed sensitive SCLC (i.e., > 90 day TTP from the cessation of 1st-line chemotherapy) to the best supportive care arm. The following lists the examples.

- In original, amendment 1, of amendment 2, and of amendment 3 protocols: "For patients with relapsed SCLC that is considered to be sensitive to 1st-line therapy the clinical standard of care is re-induction with a standard combination chemotherapy. Randomisation of sensitive SCLC patients onto an ASC arm of a protocol is considered to be ethically unacceptable."[8,9,10,11]

- On page 20 of the study report: "For patients with relapsed SCLC that is considered to be sensitive to first-line therapy the clinical standard of care is re-induction with standard combination chemotherapy. Randomisation of sensitive SCLC patients onto an active symptom control arm of a protocol is considered to be ethically unacceptable."[12]

- On page 2 of the January 2006 EMEA report,[13] "It was considered unethical to include patients with relapsed SCLC unless their disease was "resistant" to the first line of therapy."

Basis for treatment sensitive SCLC

The re-treatment of SCLC patients who have relapsed > 90 days after cessation of 1st-line chemotherapy is based, in part, on the following:

- "the sensitivity to the first-line treatment in combination with a progression free period of more than 3 months. For these patients, retreatment with the induction regimen is appropriate, for all others, it is 'trial and error' of single agents or combinations."[14]

- "Patients with a longer treatment-free interval may still have a high probability of achieving a second response to the same chemotherapy used in first-line chemotherapy"[15]

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8 SB Document Number: SKF-104864/RSD-1014C8/1; on pages 7 and 16
9 SB Document Number: SKF-104864/RSD-1014C8/2; on pages 7 and 16
10 SB Document Number: SKF-104864/RSD-1014C8/3; on pages 8 and 17
11 SK&F-104864/478 An Open-Label, Randomised, Phase III Comparator Study of Active Symptom Control Alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC - Amendment 3; pages 10 and 18
12 Clinical Study Report for Study SK&F-104864/478
13 SCIENTIFIC DISCUSSION. Product name: HYCAMTIN; Procedure No. EMEA/H/C/123/II/34; London, 6 January 2006
14 Postmus P. Second-line for small cell lung cancer: how-to-do-it? Lung Cancer. 2005 May;43(2):263-5
15 Tiseo M, Ardizzoni A. Current Status of Second-Line Treatment and Novel Therapies for Small Cell Lung Cancer. J Thorac Oncol. 2007;2: 764–772. The sources are from 1983, 1987, 1987, and 1988.

- 'in one prospective phase II study of single-agent tópotecan in relapsed SCLC, patients with disease-free intervals of more than 6 months obtained a response rate of 57%, similar to that obtained with combination reinduction chemotherapy"[16]

- IV topotecan and cytoxan, adriamycin, and vincristine (CAV) have activity in sensitive SCLC.

- "For patients who have relapsed after a three-month treatment free interval CAV is a clinical standard of care based principally on published data and clinicians experience."[17]

- "The longer the duration of response to first line therapy and the subsequent increased treatment-free interval, the greater is the indication for reinduction with first line therapy at relapse, provided that the patient can tolerate the therapy."[18]

Management of sensitive SCLC patients on best supportive care

The Sponsor appeared to support the randomization of sensitive patients to the best supportive arm on page 24 of the study report: "Patients who relapsed outside the 90 day window were still considered to have resistant disease, therefore the definition of "resistant" was left to the judgement of the investigator." In a response to a FDA query, on 9/6/2007, the Sponsor wrote, "However, for protocol purposes in this disease, patients conventionally have been recruited into a protocol based on a measured time from the last dose of first line chemotherapy rather the investigator's opinion that a given tumor may or may not respond to the administered chemotherapy."

The design of the study did not have close follow-up of the patients accrued to the best supportive care arm.

- Neither tumor response nor TTP were assessed routinely in the BSC arm of Study 478.
- From Page 30 of the Briefing Document (/2006): "For patients in the BSC alone arm, radiological assessment of tumor response was not justified, as the predicted response rate was zero."
- On Page 33: "TTP was not assessed for patients in the BSC alone arm of study 478 because radiologic assessment for clinical progression was not required for that arm."
- "Median time to progression was assessed only for those patients in the ASC + OT group since onerous monitoring of patients receiving ASC alone was inappropriate."[19]

16 Tiseo M, Ardizzoni A. Current Status of Second-Line Treatment and Novel Therapies for Small Cell Lung Cancer. J Thorac Oncol. 2007;2: 764–772

17 European Union Small Cell Lung Cancer Clinical Practice Survey Report, Final: 16 October 2002. SB Document Number: SKF-104864/RSD-101XB6/1

18 European Union Small Cell Lung Cancer Clinical Practice Survey Report, Final: 16 October 2002. SB Document Number: SKF-104864/RSD-101XB6/1

- Page 34 of the study report: "For patients randomised to receive ASC alone radiological assessment of tumour response was not justified as the predicted response rate was zero. Therefore radiological assessment of an apparent response is only applicable to patients randomised to receive oral topotecan."
- No analysis of interventions for hematological toxicity was performed for the ASC alone group. In the table below, none of the agents listed in the table above were administered to patients in the ASC alone group.

Table 22 Therapeutic Interventions for Hematological Toxicity Number (%) of Patients/Courses – Study 478

	Oral Topotecan + BSC	
	Patients (%)	Courses (%)
Intervention	n=70	n=276
Red blood cells	20 (28.6)	36 (13.0)
Platelets	5 (7.1)	6 (2.2)
G(M)-CSF	1 (1.4)	3 (1.1)
G-CSF as treatment	0	0
G-CSF as prophylaxis	1 (1.4)	3 (1.1)
Erythropoietin	2 (2.9)	4 (1.4)

In sensitive SCLC patients, who were randomized to best supportive care, a trial design that identified progressive disease as quickly as possible, may have removed them from the study, and then treatment with 2nd-line chemotherapy.

Informed consent

Patient who had sensitive disease were not provided adequate information as shown below:

- In the original protocol, 1st page of the informed consent refers to resistant SCLC, i.e., "the cancer has stopped responding so soon after the chemotherapy it may not respond to any further chemotherapy, this is referred to as resistant small cell lung cancer." This reference to resistant SCLC is also in the amended protocol submitted with the NDA. Patients with sensitive SCLC were misinformed if informed consent was rendered with this form.

- In the informed consent (p. 66 of the original protocol; 4. Alternative 4), the following statement appears to refer to the topotecan arm, "If the treatment with oral topotecan does not help control your disease, you may be offered other treatments." A similar offer should have been made to the Active Symptom Control arm.

- A sample of blank consent forms from the United Kingdom, which were provided by the Sponsor, documents that similar wording, regarding resistant disease: "patients with certain types of small cell lung cancer, resistant to treatment" and "the cancer has stopped

19 Page 71 of the study report in the NDA

responding soon after the chemotherapy it may not respond again, and this is called resistant small cell lung cancer."

- At a Bulgarian and Ukraine site, DSI inspectors found similar wording in the consent forms with regard to "resistant":

> "...it was confirmed that the ICF specifically contained explanation to subjects that the study was enrolling subjects with relapsed **resistant** SCLC. It was also noted that the title and introduction paragraph has the word "Resistant."[20]
>
> "The informed consent forms at this site contained the word "resistant" in one place in the title and two other places in the body of the consent form on the first page."[21]

The patients on best supportive care with sensitive SCLC

Below is a table with all the sensitive patients accrued to the best supportive care arm (n=34). Twelve patients had > 180 days TTP from end of 1st-line chemotherapy.

TTP from end of 1st-line chemotherapy, days	Patient #	arm	TTP from end of 1st-line chemotherapy, group
91	478.017.85350	Active Symptom Control	> 90 Days
96	478.043.11186	Active Symptom Control	> 90 Days
98	478.101.11188	Active Symptom Control	> 90 Days
102	478.072.11200	Active Symptom Control	> 90 Days
106	478.103.85454	Active Symptom Control	> 90 Days
109	478.074.85498	Active Symptom Control	> 90 Days
109	478.101.85463	Active Symptom Control	> 90 Days
116	478.091.11182	Active Symptom Control	> 90 Days
120	478.101.11231	Active Symptom Control	> 90 Days

20 PDF page 10. of the Food and Drug Administration Establishment Inspection Report of Pmf. Hristo Tsekov, University Multiprofile Hospital , St. Marina Varna; Inspection Start Date: 08/20/2007; Inspection End Date: 08/23/2007; Inspector: Dawn L Wydner

21 **E-mail From:** Saale, Mark; **Sent:** Wednesday, September 12, 2007 1:37 PM; **To:** Chu, Dan-My; **Subject:** RE: Inspection of Dr. Shparyk, Lviv, Ukraine

TTP from end of 1st-line chemotherapy, days	Patient #	arm	TTP from end of 1st-line chemotherapy, group
123	478.049.85511	Active Symptom Control	> 90 Days
124	478.074.85496	Active Symptom Control	> 90 Days
131	478.048.85421	Active Symptom Control	> 90 Days
134	478.121.85513	Active Symptom Control	> 90 Days
139	478.020.85537	Active Symptom Control	> 90 Days
140	478.042.11206	Active Symptom Control	> 90 Days
150	478.029.85387	Active Symptom Control	> 90 Days
161	478.101.85464	Active Symptom Control	> 90 Days
163	478.091.11181	Active Symptom Control	> 90 Days
164	478.094.00004	Active Symptom Control	> 90 Days
164	478.101.85465	Active Symptom Control	> 90 Days
167	478.101.11229	Active Symptom Control	> 90 Days
168	478.081.85504	Active Symptom Control	> 90 Days
181	478.081.85509	Active Symptom Control	> 90 Days
184	478.073.85490	Active Symptom Control	> 90 Days
188	478.044.85435	Active Symptom Control	> 90 Days
194	478.101.85457	Active Symptom Control	> 90 Days
207	478.081.85501	Active Symptom Control	> 90 Days
234	478.081.85502	Active Symptom Control	> 90 Days
245	478.102.85452	Active Symptom Control	> 90 Days
294	478.122.85517	Active Symptom Control	> 90 Days
369	478.063.85529	Active Symptom	> 90 Days

TTP from end of 1st-line chemotherapy, days	Patient #	arm	TTP from end of 1st-line chemotherapy, group
		Control	
445	478.034.85403	Active Symptom Control	> 90 Days
665	478.101.11187	Active Symptom Control	> 90 Days
1409	478.121.85518	Active Symptom Control	> 90 Days

Ethical issues include:

- randomizing to best supportive care sensitive SCLC patients, who have proven and accepted treatment options
- not having built into the protocol rapid procedures that would remove sensitive SCLC patients, who were randomized to the best supportive care arm, to treatment at disease progression
- the sensitive patients were not informed about their disease status and the options available to them.
- there was wording in the amendment and the inclusion criterion that was not clear about the study being open to sensitive patients

4.6 Financial Disclosures

Financial disclosure was submitted 4/11/2007; the documented was signed 3/22/2007. For study #478, the pivotal trial, there were 40 Primary Investigators and 49 Subinvestigators/Co-investigators. The completion of the study date was September 30, 2004. In the 4/11/2007 submission, source documents were not provided, except for the one investigator with financial information to disclose. The overall information was provided to FDA as illustrated in two samples below.

3 Page(s) Withheld

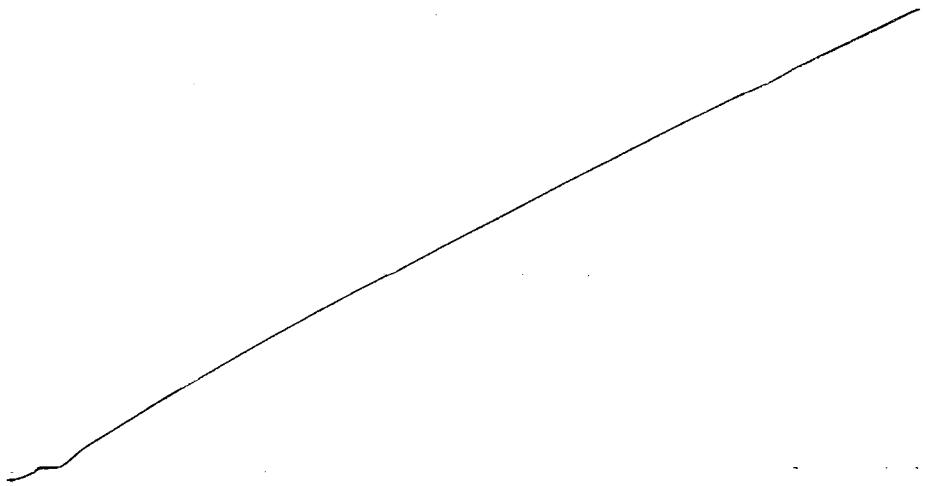
✓ Trade Secret / Confidential (b4)
PERSONAL PRIVACY INFORMATION (b6)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1



b(6)

IN CONCLUSION, the FDA analysis of financial disclosure does not rule in or rule out that bias affected the results of study #478.

5 CLINICAL PHARMACOLOGY

See the Clinical Pharmacologist's review (Sophia Abraham; entered into DFS 10/9/2007)

5.1 Pharmacokinetics

See above.

5.2 Pharmacodynamics

See above.

5.3 Exposure-Response Relationships

See above.

23 A Form 483 represents inspectional observations of the facility and does not represent a final FDA determination regarding compliance.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

HYCAMTIN capsules are indicated for the treatment of relapsed small cell lung cancer in patients with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy.

6.1.1 Methods

See section 4.1.
The pivotal trial, study #478, supplied most of the data for this review.

6.2 FDA Review of the protocol: Study #478

STUDY DESIGN OVERVIEW

MEDICAL OFFICER NOTE: This is an overview of the original protocol with amendments added in appropriate sections. A table of the amendments is included in the latter part of this overview.

Title: An Open-Label, Multicentre, Randomised, Phase III Comparator Study of Active Symptom Control Alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC (study 478).

MEDICAL OFFICER NOTE: The study is mistitled because as a result of the 2nd amendment, the study included both patients who relapsed 45-90 days (resistant) and > 90 days (sensitive) post 1st-line chemotherapy.

The title of the study report in the NDA is Study of ASC alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC.

Date issued: 07 February 2000 (original protocol; the study started to accrue patients with Amendment 1, July 2000)

MEDICAL OFFICER NOTE: There was no SPA for this protocol. The first time the FDA had knowledge of the existence of this study was in the August 2006 pre-NDA meeting package. There was an EOP2 in 11/98 to discuss the treatment of patients with small cell lung cancer sensitive disease after the failure of initial chemotherapy. The next EOP2 was in 4/2001, i.e., [redacted] th

b(4)

b(4)

Specifically, the need for a SPA for this indication was included in the minutes, i.e., "Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT in bolded block letters at the top of your cover letter."

In response to a Medical Officer query, the Sponsor responded about this issue on 7/10/2007 with: a) "The proposals presented in this Briefing Document reflect a change in registration strategy from previous discussions with the Division. This shift in regulatory strategy is based on 1.) a survival advantage seen in patients with relapsed SCLC from a clinical trial that was conducted in Europe that has not been discussed with the Division, 2) favorable reaction to these results from the EMEA" and b) "In that submission, we included the final protocol for Study 478. Since Amendment 3
included the details of all changes from the original protocol, we did not send the earlier versions to the FDA. Thus, no date and serial number of the submission to the FDA that contained the original protocol can be provided, as the original protocol was not previously submitted to the FDA. This study was initiated at the request of the EMEA to help support the registration of IV Hycamtin in SCLC in Europe."

Again, the protocol was first submitted to the FDA on August 15, 2006. The case report forms were not amended during the course of the study because no changes in data collection were indicated as a result of the protocol amendments.

Rationale of the Study: According to the Sponsor, the European Agency for the Evaluation of Medicinal Products considered the patient benefit derived from 2nd-line chemotherapy in patients with relapsed SCLC to be scientifically unproven. Demonstration of a statistically superior patient benefit either between two chemotherapeutic regimens or compared to no active anticancer treatment would be required to prove and support the application of 2nd-line chemotherapy in relapsed SCLC. The most efficient methodology identified was to compare an active chemotherapeutic regimen against palliative Active Symptom Control (ASC).

For patients with relapsed SCLC that were considered to be *sensitive* to 1st-line therapy the clinical standard of care is re-induction with a standard combination chemotherapy. *Randomisation of sensitive SCLC patients onto an ASC arm of a protocol was considered to be ethically unacceptable* (italics are from the medical officer).

MEDICAL OFFICER NOTE: italics inserted by reviewer. It is noted that with the introduction of Amendment 2 (8/2001), sensitive SCLC patient may be randomized to the ASC arm. It is unclear how it was ethical to accrue sensitive SCLC patients when the 1st-line drugs that the patient responded to and IV topotecan were available.

To demonstrate that patient benefit can be derived from 2nd-line chemotherapy a study was proposed in patients with relapsed *resistant* SCLC that *were not candidates for further intravenous chemotherapy but are considered of sufficient good health to tolerate treatment with single agent oral topotecan* (p. 7 of the original protocol). The Sponsor claimed that "*Patients with resistant relapsed SCLC would not tolerate five daily infusions (of topotecan) repeated every 21 days.*(p. 8 of the protocol) " This proposal was based on the very poor prognosis of patients with resistant SCLC and that it was standard practice in many centers to manage the patients with palliative care alone. In addition there was evidence from the IV topotecan development program that patients with resistant SCLC could benefit from treatment with topotecan. The oral formulation of topotecan has been selected for this protocol because of its greater convenience and apparent milder hematological toxicity profile .

MEDICAL OFFICER NOTE: There is no definition of "not candidates for further intravenous chemotherapy." Why wouldn't patients with resistant SCLC tolerate five days of IV topotecan? The local and national clinical practice in Europe may not be congruent with US clinical practice, i.e., where oral topotecan will be used if approved for marketing.

There may be a contradiction between the protocol's claim that resistant SCLC cannot tolerate five days of IV topotecan (p. 8 of the original protocol) and the claim about the evidence from the IV topotecan development program that patients with resistant SCLC can benefit from treatment with topotecan (pp. 13-14).

Although the oral formulation may have decreased hematological toxicity, this may be more of a function of the 40% bioavailability and the subsequent substitution of increased diarrhea for hematological toxicity.

Also, according to the O'Brien article, "Some patients who were randomly assigned to receive BSC alone withdrew consent and elected to receive standard intravenous chemotherapy. In all, 13 patients in each arm (18.3% on BSC and 18.6% on topotecan) received poststudy chemotherapy either alone or in combination with other therapy."24 Whatever the criteria was that the investigator used to indicate that the patient was unsuitable for further IV chemotherapy, either the 26 patients, the investigator or another physician, or a combination disagreed with that assessment and gave these patients IV chemotherapy at a worse time in the natural history of their disease.

24 O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cuceviá B, Juhasz G, Thatcher N, Ross GA, Dane GC, Crofts T. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7

Primary Objective

- To compare the overall survival between patients with resistant SCLC who receive Active Symptom Control alone to those who receive Active Symptom Control in combination with Oral Topotecan.

Secondary Objectives

- 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.
- To evaluate the qualitative and quantitative toxicities of oral topotecan.

Planned number of patients: 220; approximately 110 to be randomized into ASC alone arm and 110 into the ASC plus oral topotecan arm.

Stratification:

- Duration of response to prior chemotherapy (≤ 60 days or > 60 days)

MEDICAL OFFICER NOTE: There is no scientific and clinical basis for this as a stratification factor. It appears to come from an article by von Pawel and co-authors, "we compared single-agent topotecan with CAV in patients who progressed at least 60 days after initial therapy.25 The study was originally designed to recruit patients with at least 90 days between completion of first-line therapy and progression, but early in the study the criteria were amended to make topotecan available to a larger proportion of relapsed SCLC patients."26

When did this stratification factor change from Duration of response to prior chemotherapy (≤ 60 days or > 60 days) (original protocol) to time to progression from end of prior chemotherapy (≤ 60 days or > 60 days) (p. 28 of Clinical Study Report for Study SK&F-104864/478)?

25 This was confirmed in the Sponsor's response to a query dated 7/19/2007: "The duration of response to prior therapy (greater than or less than 60 days) was used as a stratification criterion in the pivotal study supporting registration of Hycamtin...for Injection in patients with relapsed small cell lung cancer (SCLC) sensitive disease[von Pawel, 1999]. In the Sponsor's response to a query dated 8/3/2007, the Sponsor corrected this statement with: "Our statement that "the duration of response to prior therapy (greater than or less than 60 days) was used as a stratification criterion in the pivotal study supporting registration of [IV] Hycamtin" was incorrect. The reviewer is correct that the study described in the 1999 von Pawel publication identifies the only stratification factors as the extent of disease and performance status."

26 von Pawel et al. J Clin Oncol 17:658-667, 1999

Stratification factors in the pivotal and supportive studies

47827	39628	06529
Duration of response to prior chemotherapy30: ≤ 60 days or > 60 days	**duration of response to prior chemotherapy:31: ≤ 6 months or > 6 months**	**Duration of response to prior chemotherapy32: 3-6 months or > 6 months**
Gender	**Sex**	
Liver metastases (present or absent)	**liver metastases: present or absent**	**Liver metastases: present or absent**
Performance status (0/1 or 2)		
		Staging: limited or extensive disease

Perhaps on 8/29/2001, with Amendment 2 to the protocol, the stratification factor should have changed to: progression from end of prior chemotherapy: 45-90 days vs. > 90 days.

In Appendix J, Procedures for Central Patient Registration and Randomization, in the original protocol, the following variations of the stratification criterion were used:

- **patient's duration of response to first-line chemotherapy in days from cessation of first line therapy until documented relapse (p. 88)**
- **The duration of the patient's response to first-line chemotherapy was...(p. 89)**
- **patient's duration of response to first-line chemotherapy (p. 90)**

In Appendix 10, Procedures for Central Patient Registration and Randomization, in the protocol submitted in the NDA, the following stratification criterion was used:

- **the time in days from discontinuation of first line chemotherapy to relapse (p. 80)**

According to a response by the Sponsor 6/8/2007, the Topo 478 CRF was not amended during the course of the study. The CRF submitted to the FDA is the only version."

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27 Source: p. 26 of original protocol

28 Source: p. 40 of study report in NDA. The publication has the stratification factor as, "duration of response to first-line therapy (progression ≤6 months or > 6 months) (*J Clin Oncol 25:2086-2092, 2007*)

29 Source: p. 46 of study report in NDA. The publication has the stratification factor as :"duration of response to prior chemotherapy after cessation of first-line chemotherapy (3 to 6 months or ≥ 6 months)" (van Pawel et al. J Clin Oncol. 19: 1743-1749, 2001)

30 Page 28 of study report in NDA has "time to progression from end of prior chemotherapy"

31 The label has "relapsed ≥ 90 days *after completion of one prior regimen of chemotherapy.*"

32 The label has "relapsed ≥ 90 days *after completion of one prior regimen of chemotherapy.*"

In the figure below, the CRF (p. 2) captures date of recurrence, end date for 1st-line chemotherapy, and duration of response to 1st-line chemotherapy. It does not capture TTP from cessation of 1st-line chemotherapy. TTP from cessation of 1st-line chemotherapy can be calculated (date of recurrence - end date of 1st-line chemotherapy). There is no entry line for this number. Did the investigator's calculate this and provide it for randomization?

HISTORY OF SMALL CELL LUNG CANCER

Date of the histological diagnosis of primary disease ☐☐ ☐☐ ☐☐ Day Month Yr

Date of first documentation of recurrence ☐☐ ☐☐ ☐☐ Day Month Yr

Stage of current disease, (mark one box only)

[1] ☐ Limited Disease

[2] ☐ Extensive Disease

PREVIOUS CHEMOTHERAPY FOR SMALL CELL LUNG CANCER

Has the patient had only one prior chemotherapy regimen for small cell lung cancer?

☐ No ⟶ *If 'No' patient is not eligible for the study*

☐ Yes ⟶ *If 'Yes' please record first line regimen below*

Previous Regimen	Dose (units)	Start Date Day Mth Yr	End Date Day Mth Yr	1st Line Response: Complete Response (1)	1st Line Response: Partial Response (2)	Duration of response (weeks)
		☐☐ ☐☐ ☐☐	☐☐ ☐☐ ☐☐	☐	☐	☐☐

The figure below shows the difference between using duration of response vs. TTP post 1st-line chemotherapy as a stratification factor. Using duration of response, results in a patient stratified as one in a good prognostic group (> 60 days). Using TTP post 1st-line chemotherapy, results in a patient stratified as one in a poor prognostic group (≤ 60 days). However, this is the same patient.

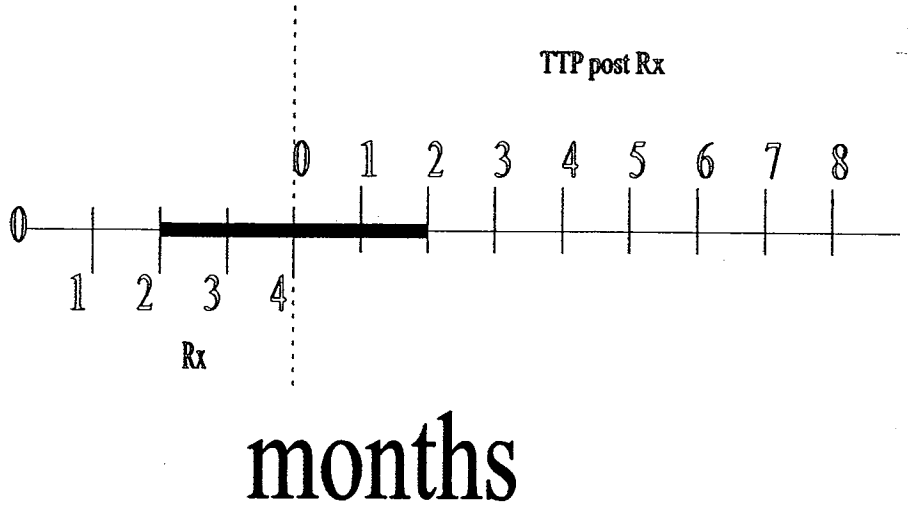


Figure: the difference between stratification factors: duration of response vs. TTP post Rx. The vertical, dashed line represents when 1st-line chemotherapy was stopped. The heavy horizontal line represents the beginning and the end of an objective response to 1st-line chemotherapy.

- Performance status (0/1 or 2)
- Gender
- Liver metastases (present or absent)

STUDY DESIGN OVERVIEW

MEDICAL OFFICER NOTE: The following paragraph was added to the protocol submitted in the NDA:

> **"For patients' randomised to receive ASC alone radiological assessment of tumour response is not justified as the predicted response rate is zero: Therefore radiological assessment of an apparent response is only applicable to patients' randomised to receive oral Topotecan. Furthermore to minimise the potential and inappropriate burden to the patient, frequent radiological assessment of response is not required in this protocol. Radiological**

assessment is only required after 3 courses of treatment, in the absence of any signs or symptoms of progressive disease, and thereafter only to confirm an apparent response or if clinically indicated to confirm disease progression."

Inclusion criteria *(italics* represent criteria at issue)

- Written informed consent
- Age at least 18 years old.
- Patients who have received one prior chemotherapy regimen only.
- Alternating or sequential use of different regimens without interruption in first line treatment is considered as one prior regimen).
    - Documented *partial or complete response to first-line therapy.*
- Documented *relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy*

  MEDICAL OFFICER NOTE: On August 29, 2001, amendment 2 changed the original 45-90 day window for disease relapse (an inclusion criterion) to ≥45 days, because the original window was proving to be too rigid.

- *Patients not considered suitable for further intravenous chemotherapy.*

  MEDICAL OFFICER NOTE: This is subject to investigator bias. This becomes even more problematic when the study was opened up to patients whose disease relapsed > 90 days after cessation of first-line therapy—patients who could be treated with IV topotecan or CAV or platininum/VP-16. Considering the physiological status of the patients who were eligible for this study, it is far from clear how these patients who *"not considered suitable for further intravenous chemotherapy,"* were defined from investigator to investigator. According to the published report of the study, 13 patients each from both arms (or ~18%) received poststudy chemotherapy or chemotherapy + other therapy (e.g., radiotherapy)—at a time when there disease may have been worse.

- Performance status of 0,1 or 2 (ECOG Scale).
- Patients considered to have adequate bone marrow reserve to potentially tolerate chemotherapy with oral topotecan.
- At least 4 weeks since last surgery (a lesser period is acceptable if deemed in the best interest of the patient).
- At least 24 hours since last radiotherapy treatment.
- At least 3 months since last immunotherapy treatment
- A probable life expectancy of at least 2 months.
- Patients of reproductive potential must agree to practice an effective contraceptive method. Examples include: for females, oral contraceptives or IUD for 3 months prior to

the start of the study medication or diaphragm plus spermicide; and for males: condom plus spermicide.

- Screening laboratory values required:
  - haemoglobin ≥ 9.0 g/dl (after transfusion if needed)
  - WBC ≥ 3,500/mm3
  - neutrophils ≥ 1,500/mm3
  - platelets ≥ 100,000/mm3
  - creatinine clearance ≥ 60ml/min (Cockcroft and Gault creatinine clearance formula)
  - serum bilirubin ≤ 2.0 mg/dl (34 umol/l)
  - SGOT/AST, SGPT/ALT, and Alkaline Phosphatase ≤ 2 times the upper limit of normal if liver metastases are absent by abdominal CT or MRI scan or ≤ 5 times the upper limit of normal if liver metastases are present.

Exclusion criteria

- Clinical signs or symptoms of brain and/or leptomeningeal metastases confirmed by CT or MRI brain scan. A patient with brain and/or leptomeningeal metastases on CT or MRI scan may be included only if he/she is asymptomatic on neurologic exam and is not receiving corticosteroid therapy to control symptoms.
- Concomitant malignancies or previous malignancies other than SCLC within the last five years, with the exception of adequately treated basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or stage A low grade prostate cancer.
- Active uncontrolled infection.
- Concurrent severe medical problems unrelated to the malignancy that would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy.
- Treatment with an investigational drug within 30 days or five half-lives prior to entry into the study, whichever is longer.
- Concurrent other chemotherapy, immunotherapy, radiotherapy, or investigational therapy for the treatment of small cell lung cancer.(Concurrent radiation for palliation of bone metastases and CNS lesions is not permitted unless discussed with the medical monitor.)
- Patients with uncontrolled emesis, regardless of etiology.
- Patients with active peptic ulcer, diabetes mellitus which is complicated by gastrointestinal neuropathy which has effected motility, chronic gastritis, significant ascites, or clinical evidence of any other GI conditions (removal of a portion of the stomach, or patients who have a history of recent obstruction of the GI tract) or drugs (e.g., cisapride) which would alter absorption or GI motility. The investigator should ensure that patients with other unlisted presenting conditions or drugs that could affect the absorption of oral topotecan are not enrolled.
- Prior treatment with topotecan

MEDICAL OFFICER NOTE: If study #389, a 1st-line study, is being done in the same countries as study #478, a 2nd-line study, this may interfere with accrual to study #478.

Also, there may be another conflict with accrual in studies 389 and 478. Study #389 is an extensive disease in 1st-line SCLC. Study #478 could influence results of study #389 because patients in the control arm of study #389 (i.e., cisplatin/VP-16) could be eligible for study #478; patients randomized to the topotecan arm may have neutralized any survival effect in study #389. The table below demonstrates that there were shared study countries in studies #389 and #478.

INVESTIGATOR	STUDY 389 CISPLATIN-TOPOTECAN/CISPLATIN-VP-16	STUDY 478 TOPOTECAN/.BSC
Bulgaria	There were no investigators who accrued patients in 478 but 69 patients were randomized to 389	10/11
Canada	There were no investigators who accrued patients in 478 but 36 patients were randomized to 389 (2/2 patients accrued by two 389 investigators who did not accrue to 478)	1/0
Hungary	2/3 2/2 1/5	1/1 1/1 0/1
Netherlands	Two investigators who did not accrue patients to 478, accrued 3/3 patients to 389	
Russia	6/3 One investigator who did not accrue patients to 478, accrued 16/13 patients to 389	1/0
Slovakia	No investigators who accrued patients in 478 but 16 patients randomized to 389	0/2
United Kingdom	8/4 2/4 One investigator who did not accrue patients to 478, accrued 1/0 patients to 389	0/2 3/4

- History of allergic reactions to compounds chemically related totopotecan.

- Women who are pregnant or lactating.
- Patients of child bearing potential refusing to practice adequate contraception.

Study procedures (see table below)

{ TC "5.2 Outline of Study Cycle Procedures "\f C\l 2}5.2 Outline of Study Cycle Procedures

Study Procedures	Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Pre-next visit
Informed Consent	♦								
Medical History	♦								
Interim History									♦
Physical Examination	♦								♦
Vital Signs	♦								♦
Patient Symptom Assessment / EQ-5D Health questionnaire	♦								♦
Performance Status	♦								♦
CBC/Differential/Platelets[1]	♦	♦3,4					♦3	♦3	♦
Routine Chemistries [2]	♦	♦3,4						♦3	♦5
Urinalysis	♦								♦
Serum Pregnancy Test	♦								
ECG (12-lead)	♦								♦6
Disease Status									
Chest X-ray, CT or MRI	♦								
Abdominal CT, MRI or US	♦								
Neurologic Assessment	♦								
Head CT or MRI	♦7								
Radionuclide Bone Scan	♦7								
Lesion(s) Assessed by PE or photograph	♦								
Eligibility Criteria	♦								
Review of Toxicity Grades									♦8
Randomised arm									
Active Symptom Control									
Or									
Active Symptom Control + Oral Topotecan		♦9	♦9	♦9	♦9	♦9			
Review of Disease Status									♦3,10, 11

1-Haemoglobin, haematocrit, RBC, WBC, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelets

2-Sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, BUN, uric acid, creatinine, alkaline phosphatase, LDH, SGOT-AST, SGPT-ALT, total bilirubin, direct bilirubin, total protein, albumin

3-Applicable only to patients randomised to receive oral topotecan and ASC.

4-Performed only if these parameters were abnormal at last determination or measurements were done >7 days ago.

5-Only required for patients receiving oral topotecan if Day 15 results reflect clinically significant deterioration from baseline.

6-Perform at screening and after final course only, unless clinically indicated.

7-Performed if clinically indicated.

8-Dose modification of oral dose based on toxicity criteria described in section 5.5.3

9-Oral topotecan 2.3mg/m2/day

10-Disease status documented at baseline must be repeated at the end of 3 courses or if clinically indicated using the same radiological methodology.

11-Patients with a response (PR/CR) after 3 courses should be assessed after at least 28 days to confirm the response.

MEDICAL OFFICER NOTE: On 6/8/2007, the Sponsor was queried about the whereabouts in the NDA of the photographs of lesions. On 6/8/2007, the Sponsor responded with: "The Pre-NDA meeting on 12 September 2006. On Page 9 of 18 of the official meeting minutes from you (e-mail from 28 September, minutes dated 18 September 2006), Question 6 includes "Radiological assessments from these studies [478, 065, and 396] were collected on film and are not available in digital format. Will the FDA request copies of the radiographic assessments to evaluate response? FDA Response: No, tumor measurements submitted in the raw datasets will be adequate." Apparently, the Sponsor has mistaken radiographs for photographs. In section 9.3, the following was written: "A skin lesion must have one diameter ≥ 1 cm and must be confirmed by photograph."

Only the topotecan arm have CBC/differential/platelets and routine chemistries performed @ days 1, 8 (hematology only), 15, and pre-next visit (routine chemistries only). Only the topotecan arm a Review of Disease Status evaluation at the pre-next visit. In the Outline of Study Cycle Procedures table in the protocol in the NDA, the row for Review of Disease Status was replaced with only the topotecan arm evaluated @ the Pre-next visit, as indicated, by chest x-ray, CT or MRI, Abdominal CT, MRI or US, Neurologic Assessessment, Lesion(s) Assessed by PE or photograph, Head CT or MRI, and/or Radionuclide Bone Scan.

Study Procedures were to be done within 2 weeks of Randomisation

Treatment arms

Oral Topotecan
In addition to Active Symptom Control, 2.3 mg/m2/day of oral topotecan for 5 consecutive days every 21 days.33

Active symptom control.
Assessment and optimal palliation of symptoms following relapse at least every 21 days.

Definition of active symptom control or best supportive care: best supportive care would include the use of medications (including analgesics for pain, antibiotics for intercurrent infections, steroids and appetite stimulants, antidepressants) as well as the use of procedures such as radiotherapy to specific troublesome sites of disease, transfusion support for anaemia, the use of deep relaxation therapy and palliative surgical procedures such as the drainage of effusions.

33 On page 33, it states that it was recommended to treat with oral topotecan for at least 4 cycles.

MEDICAL OFFICER NOTE:
In the Outline of Study Cycle Procedure table, the tests that are applicable only to the topotecan arm, i.e., review of disease status, CBC/differential/platelet count, and routine chemistries, appear to not support the purpose of active symptom control, e.g., detecting intercurrent infections, transfusion support for anemia, drainage of effusions, radiotherapy for troublesome sites of disease, and detecting paraneoplastic syndromes associated with SCLC (e.g. ADH and ACTH syndromes). Also, failure to review disease status may delay removal of the patient from study and the patient moving on to other active therapy.

There was no provision in the protocol for the administration of hematological growth factors.

Patients' randomized to receive Active Symptom Control alone were to attend the clinic at the same frequency as the topotecan arm in order to maintain a comparable access to medical staff and procedures.

Method of Randomization
Study participants were to be randomly assigned to Active Symptom Control alone or Active Symptom Control with oral topotecan. A dynamic randomisation schedule would be employed to stratify study participants with respect to four criteria. These are:
1) Duration of response to prior chemotherapy (≤ 60 days or > 60 days)

MEDICAL OFFICER NOTE: There is no scientific and clinical basis for this as a stratification factor. It appears to come from an article by von Pawel and co-authors, "we compared single-agent topotecan with CAV in patients who progressed at least 60 days after initial therapy. The study was originally designed to recruit patients with at least 90 days between completion of first-line therapy and progression, but early in the study the criteria were amended to make topotecan available to a larger proportion of relapsed SCLC patients."34

When did this stratification factor change from Duration of response to prior chemotherapy (≤ 60 days or > 60 days) (original protocol) to time to progression from end of prior chemotherapy (≤ 60 days or > 60 days) (p. 28 of Clinical Study Report for Study SK&F-104864/478)?

34 von Pawel et al. J Clin Oncol 17:658-667, 1999

Stratification factors in the pivotal and supportive studies

47835	39636	06537
Duration of response to prior chemotherapy38: ≤ 60 days or > 60 days	**duration of response to prior chemotherapy:39: ≤ 6 months or > 6 months**	**Duration of response to prior chemotherapy40: 3-6 months or > 6 months**
Gender	**sex**	
Liver metastases (present or absent)	**liver metastases: present or absent**	**Liver metastases: present or absent**
Performance status (0/1 or 2)		
		Staging: limited or extensive disease

On 8/29/2001, with the amendment to the protocol, the stratification factor should have changed to: progression from end of prior chemotherapy: 45-90 days vs. > 90 days.

In Appendix J, Procedures for Central Patient Registration and Randomization, in the original protocol, the following stratification criterion was used:

- **patient's duration of response to first-line chemotherapy in days from cessation of first line therapy until documented relapse (p. 88)**
- **The duration of the patient's response to first-line chemotherapy was...(p. 89)**
- **patient's duration of response to first-line chemotherapy (p. 90)**

In Appendix 10, Procedures for Central Patient Registration and Randomization, in the protocol submitted in the NDA, the following **stratification criterion was used:**

- **the time in days from discontinuation of first line chemotherapy to relapse (p. 80)**

According to a response by the Sponsor (6/8/2007), the Topo 478 CRF was not amended during the course of the study. The CRF submitted to the FDA is the only version."

2) Performance status (0/1 or 2)

35 Source: p. 26 of original protocol
36 Source: p. 40 of study report in NDA
37 Source: p. 46 of study report in NDA
38 Page 28 of study report in NDA has "time to progression from end of prior chemotherapy"
39 The label has "relapsed ≥ 90 days *after completion of one prior regimen of chemotherapy.*"
40 The label has "relapsed ≥ 90 days *after completion of one prior regimen of chemotherapy.*"

3) Gender
4) Liver metastases at baseline (present or absent)

Randomisation employed the method of Freedman and White. Randomisation was administered by a centralised automated patient registration and randomisation system. The investigator's identification, center number, CRF number and the assessment of eligibility per the inclusion/exclusion criteria was required for proper randomisation. Based on the stratification characteristics, as well as the accrued treatment assignments, the patient would be assigned a randomisation number and a study arm.

Following Completion of 3 Courses of Treatment (or if clinically indicated)

Full disease status assessment using the same radiological methodology employed at baseline.

- Documentation of disease status included date of assessment, description of lesion site, dimensions, and type of diagnostic study used.
- If a patient met the tumor assessment criteria for complete or partial response, another complete tumor assessment was required at least 28 days later to confirm the response.
- If a patient met the tumor assessment criteria for progressive disease the patient should be withdrawn from treatment with oral topotecan, unless it was considered by the principle.

Procedure for Dosing in Course 2 and Subsequent Courses.

The next treatment course were to begin on schedule providing the following criteria are met by day 21 of the previous treatment course:

Hemoglobin $\geq$ 9.0g/dl (after transfusion, if needed)
Neutrophils $\geq$ 1,000/mm3
Platelets $\geq$ 100,000/mm3
There was no clinically significant non-hematologic drug related toxicity.
If the patient failed to meet the above criteria the next treatment course were to be delayed until the criteria is met. If treatment was delayed, the patient was assessed at least on a weekly basis.

Dose Modification

Dose Escalation
The daily dose of oral topotecan could be increased by 0.4 mg/m2/day if, during the previous course there was no toxicity greater than grade 2. Maximum dose permitted is 3.1 mg/m2/day

Dose Reduction.
Following a treatment course, toxicity grades were to be reviewed and the dose for the next course reduced, if appropriate, according to the following schedule.

Haematologic Toxicity	
Neutrophil Nadir	**Modification**
Neutrophils < 500/mm^{3}associated with fever/infection or lasting ≥ 7 days.	Reduce the daily dose of oral topotecan by 0.4 mg/m^2/day.
Neutrophils 500 – 900/mm^3 lasting beyond day 21 of the treatment course.	Reduce the daily dose of oral topotecan by 0.4 mg/m^2/day.
Platelet Nadir	**Modification**
Platelets < 25,000/mm^3.	Reduce the daily dose of oral topotecan by 0.4 mg/m^2/day.

If the platelet count reached levels at which the patient was believed to be at risk of hemorrhage (especially if surgery was to be performed or anticoagulants administered) platelet transfusion should be considered.

MEDICAL OFFICER NOTE: There was no provision in the protocol for the administration of hematological growth factors.

Non-Haematologic Toxicity	
CTC Grade	**Modification**
Grade 3-4 (excluding grade 3 nausea or grade 3/4 vomiting)	Reduce the daily dose of oral topotecan by 0.4 mg/m^2/day. If the disease does not respond to reduced dose or if the patient cannot swallow or keep-down topotecan despite adequate anti-emesis, withdraw from study.

The minimum dose of oral topotecan was 1.5 mg/m2/day. If, at the minimal dose, the treatment course was delayed greater than two weeks beyond day 21, the patient would be withdrawn from treatment with oral topotecan.

Treatment Duration

It was recommended that patients would be treated with at least four courses of oral topotecan.treatment duration, depending on the investigators discretion and if it was in the patients best interest. Patients withdrawn from treatment with oral topotecan were to continue to return to the center for continuation of Active Symptom Control until it was considered inappropriate and the patient's care was transferred to local medical support groups.

For patients randomized to receive oral topotecan it was recommended that patients take their capsules either two hours after eating or at least 30 minutes before eating. Oral topotecan was administered to the patient in the clinic on day 1 and the patient sent home with the topotecan capsules for the remaining four days of dosing.

Active Symptom Control Alone Arm

Following completion of screening and randomization to receive Active Symptom Control alone patients will be invited to return to the clinic on at least a 21-day cycle.

At each of the scheduled visits:

1. Patients were asked to complete the Patient Symptom Assessment and the EQ-5D Health questionnaire prior to any other assessment at each prenext visit.
2. Interim medical history and physical exam, including neurologic examination.
3. Assessment of performance status.
4. Complete documentation of all significant current medical conditions and all associated measures taken to control the symptoms and palliate the patient.

Treatment Duration

Patients were to continue to return to the center for continuation of Active Symptom Control until it is considered inappropriate and the patient's care is transferred to local medical support groups.

Procedures for Patient Withdrawal

Oral Topotecan Arm Only

The investigator assessed each patient for evaluability, and characterize the Best Overall Response achieved by the patient while on study treatment according to the WHO Criteria.

A 12-lead ECG was performed at the last treatment course that the patient had received. Patients with abnormal clinical or laboratory findings at the end of the study that were felt to be treatment related will be followed until the condition resolved or until the laboratory findings were not considered clinically significant.

MEDICAL OFFICER NOTE: There appears to be no procedures for withdrawal for the active symptom control only arm, particularly, for progressive disease. The CFR has withdrawal for lack of efficacy (progressive disease as a criterion).

All Patients
Following the last clinic visit associated to the study patients were followed at regular intervals (at least every 2 months) until death to determine survival and time to progression if applicable.

Dosage and Formulation(s)
Oral Topotecan
Oral topotecan was supplied as capsules containing topotecan HCL, equivalent to 0.25mg or 1.00 mg of the anhydrous free base.

Reasons for withdrawal from active therapy
A patients would be considered to have be withdrawn from the study if the principle reason for ending study treatment fall into one of the following categories:
- Adverse event (including inter current illness, unacceptable toxicity)
- Deviation from protocol (including non-compliance)
- Lost to follow-up
- Patient withdrawn at her own request, for reasons other than those above.

The reason for withdrawal must be entered on the Case Report Form.

> **MEDICAL OFFICER NOTE: In a Sponsor communication dated July 17, 2007, the Sponsor stated that "The 83 page case report form (CRF) for Study 478 contained in the NDA submitted on April 11, 2007...comprises information collected for Cycle 1 and subsequent cycles of participation in the study. The investigators also were provided with supplementary CRF pages that were to be used as needed. These supplemental pages collected information regarding Serious Adverse Events, Death, Quality of Life, and Post-Study Minimal Follow-up information. GSK acknowledges that a complete version of the black CRF inadvertently was not included in...the NDA."**

Procedure Following Withdrawal
Patients with abnormal clinical or laboratory findings at the end of the study that were felt to be treatment-related were to be followed until the condition resolves.
Patients were be monitored every 2 months following study completion or withdrawal, using a single page questionnaire, to determine survival and time to progression, if applicable.

Target Sample Size
The primary aim of the study was to answer the question, whether the addition of oral topotecan to active symptom control led to prolonged overall survival.
Ho: overall survival with ASC only = overall survival with ASC + topotecan
H1: overall survival with ASC only ≠ overall survival with ASC + topotecan
According to this hypothesis, tests concerning the primary end point were to be performed as two-sided tests.
Using reported results from Spiro, the estimated median survival with Active Symptom Control alone was expected to be 12 weeks. Estimated median survival

with Active Symptom Control and oral topotecan therapy was 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 were
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 were to be the nonparametric log-rank test. It is assumed that all patients were followed for a fixed length of time, and that the hazard ratio was constant over time
- Minimum follow-up time for all patients: 30 weeks or until death.

MEDICAL OFFICER NOTE: There is no indication of the number of events that would trigger the final analysis. At best, the final analysis may have occurred with a minimum of 30 weeks follow-up.

In the Amendment 3 protocol submitted in the NDA, the number of events deficiency was corrected: "Due to protracted recruitment and a diminishing number of centres and countries able to participate, the protocol was closed early after recruiting 140 subjects. Because the trial was closed before the required sample size was achieved, the power of the study is reduced from the original 90%. As power calculations in a time-to-event setting are event-driven, the final analysis will be performed when 125 events have occurred, providing 80% power to successfully declare superiority in the presence of a true underlying difference."

Also, according to the amended protocol, the number of events (deaths) was 168 in the original protocol.

Although the study was amended to include patients TTP from prior chemotherapy of > 90 days (sensitive disease), expected medians for the Active Symptomatic Control and the ASC + oral topotecan arms were not changed in the protocol in the NDA.

Instead of having 220 resistant (TTP from prior chemotherapy $\leq$ 90 days) SCLC patients as entered planned, we have 77 resistant patients + 64 sensitive (TTP from prior chemotherapy > 90 days) SCLC patients.

Planned Efficacy Evaluation

In addition to survival, for patients randomized to receive treatment with oral topotecan the response rate and response duration for patients with measurable or evaluable only disease, as defined below, were to be evaluated.

MEDICAL OFFICER NOTE: The following paragraph was in the protocol submitted in the NDA in section 9.3:
"For patients' randomised to receive ASC alone radiological assessment of tumour response is not justified as the predicted response rate is zero: Therefore radiological assessment of an apparent response is only applicable to patients' randomised to receive oral Topotecan. Furthermore to minimise the potential and inappropriate burden to the patient, frequent radiological assessment of response is not required in this protocol. Radiological assessment is only required after 3 courses of treatment, in the absence of
any signs or symptoms of progressive disease, and thereafter only to confirm an apparent response or if clinically indicated to confirm disease progression."

Measurable disease - Bidimensionally measurable lesions (indicator lesions) with early defined margins by diagnostic studies, (CT or MRI scan must have had one diameter ≥ 1 cm and one diameter ≥ 2 cm, chest X-ray or ultrasound must have had both dameters ≥ 2 cm), palpable tumour masses (e.g. lymph nodes in the neck) should have been measured by an imaging technique, if possible. If imaging was not possible, and the mass was to be measured clinically, it must have two palpable diameters ≥ 2 cm. A skin lesion must have had one diameter ≥ 1 cm and must have been confirmed by photograph. Lesions measured by physical examination alone were required to have confirmation by a second physician.
Non-measuurable, Evaluable Only disease - Undimensionally measurable lesions, lesions with margins that were not clearly defined, palpable lesions with one diameter ≤ 2 cm, lesion that was palpated but not measured, hepatomegaly.
Non-measurable, non-evaluable disease - ascites, pleural effusion, pericardial effusion, bone or bone marrow metastases, leptomeningeal metastases, lymphangitic metastases, lesions irradiated within the last 6 weeks.

Response rate (RR) - the percentage of patients achieving either a complete or partial response. Categories of tumor response were defined as follows:
Complete response (CR) - complete disappearance of all known measurable and evaluable disease determined by two measurements not less than four weeks apart.
Partial response (PR) - greater than a 50% decrease in the sum of the products of the greatest length and perpendicular width of the largest measurement of all measurable lesions for at least four weeks with no simultaneous appearance of new lesions or increase in evaluable disease during this period.
Stable (SD) - any change in tumor size, or lack thereof, for a period of at least eight weeks, which was less than partial response yet did not indicate tumour progression.
Progression - *greater than a 25% increase in the smallest measurement of a single measurable lesion,* reappearance of measurable disease, *clear worsening of evaluable disease,* appearance of any new lesions including brain metastases even if there was response outside of the brain or s significant worsening of conditions presumed to be related to malignancy.

MEDICAL OFFICER NOTE: See italics above. The protocol submitted to the NDA has: ... *greater than 25% increase in the sum of the products of the measurable disease...clear worsening of evaluable only disease...*

Not evaluable (NE) - Any patient who could not be classified by one of the four preceding definitions.
Response duration - time from initial documented response to the first documented sign of progression.

Primary Efficacy Variables
The primary indicator of drug efficacy is overall survival.
Survival - the time from randomization to the date of death (all-cause mortality).

Secondary Efficacy Variables
Patient Symptom Assessment - The effect on symptoms of disease would be assessed using Patient Symptom Assessment scores.

Methods of Analysis
The primary endpoint of the trial would be analyzed confirmatively considering an overall level of $p <= 0.05$ as statistically significant.

All other parameters would be evaluated in an explorative or descriptive manner, providing means, ranges, standard deviations and/or confidence intervals. If additional p-values were calculated, they would be presented explicitly without referring to hypotheses or a significance level. No error adjustment for multiple testing would be performed. Thus the p values would reflect the comparison-wise error and not the experiment-wise error. All p values were to be two-sided if not stated otherwise. The statistical methods described in this section were suited for the data and distributions usually expected in this type of trials. The suitability was to be checked after data entry. If necessary, the statistical method were to be modified accordingly. Adjustment for prospective stratification factors were be performed. Demographic and prognostic baseline data were to be checked for homogeneity between treatment groups. In case of relevant imbalances of other important prognostic factors the statistical model would be adjusted in order to achieve best possible comparability of the groups, and the results would be critically reviewed in comparison to the unadjusted models. Time-to-event endpoints will be estimated by the product limit (Kaplan-Meier) method and compared using the logrank test. In addition, comparisons between regimens would be made via proportional-hazards regression to allow for adjustments of influential baseline variables. Analytical results would include the estimated risk-ratio with 95% confidence intervals and associated probabilities for the effects of treatment and stratification factors. The risk-ratio for treatment would express the rate of event occurrence among patients randomised to oral topotecan and ASC relative to those receiving ASC alone. A separate model, which included a time-dependent treatment covariate, would be examined in an effort to validate the proportional-hazards assumption. For the ASC + topotecan

arm, analytical results would include the estimated response rate with corresponding 95% confidence interval.

Interim Analysis
No interim analysis was planned.

> **MEDICAL OFFICER NOTE: the study was stopped early based on the scenario described by the Sponsor: "Due to protracted recruitment and a diminishing number of centres and countries able to participate, the protocol was closed early after recruiting 140 subjects. Because the trial was closed before the required sample size was achieved, the power of the study is reduced from the original 90%. As power calculations in a time-to-event setting are event-driven, the final analysis will be performed when 125 events have occurred, providing 80% power to successfully declare superiority in the presence of a true underlying difference."**

Patient Symptom Assessment
The pre-next course scores from the Patient Symptom Assessment questionnaire would be compared to scores at screening, and trends in differences between groups would be analysed.
EQ-5D Health Questionnaire
The five dimensional classification of health states from the first part of the EQ-5D was used to describe up to 243 health states. The respondent's health state was derived by combining the responses to the questions for the five dimensions of health into a five digit code. These codes are then converted into health state value scores using tables of values that have been generated based on data collected from surveys of the public.
For the thermometer responses, a three digit code number between 0 and 100 was read off the "thermometer," from the exact point where the respondent's line crossed the scale. For example, a line drawn across 46 on the scale of 0 to 100 would be coded 046. The average baseline health state scores and distributions of scores and thermometer ratings from the EQ-5D would be compared to scores at the subsequent pre-next course visits, and differences between treatment groups would be described.

> **MEDICAL OFFICER NOTE: Except for one patient from Canada, the study population is European. It is unclear how this study population correlates with a heterogenous American population who develops small cell lung cancer..**

Patient Population/Data Sets to be Evaluated
The principal focus of this protocol was to be the intent-to-treat population. This population consisted of all randomized patients and would be assessed for safety and efficacy. A second population, the protocol-defined population, were to be assessed only for efficacy. Patients having a documented protocol violation which might preclude an appropriate efficacy evaluation would be excluded from the protocol-defined population.

Patients who died during therapy would be counted as having progressive disease unless there was a clinical or autopsy diagnosis of drug-related death or death due to an unrelated cause.

Safety Evaluation

An objective of this study was to assess the qualitative and quantitative toxicities experienced by the patients on the two study arms. The quantitative evaluation would be limited to four Hematological toxicities: neutropenia, thrombocytopenia, leukopenia, and anemia. Each will be expressed with respect to the nadir observed during each course of topotecan administration. Qualitative toxicities would be expressed in terms of the NCIC Common Toxicity Criteria. This evaluation would compare the incidence of reported
toxicities between treatment regimens. Clinical interpretation would be based on review of displays of reported toxicities by worst CTC grade and by investigator
reported relationship of the event to study medication. All subjects who were randomised would be assessed for safety and toxicity.

SUMMARY OF PROTOCOL

PARAMETER	PROTOCOL
regimens	○ 2.3 mg/m2/day of oral topotecan for 5 consecutive days every 21 days Vs. ○ Active symptom control
Primary endpoint	• Overall survival
Secondary endpoints	• compare disease symptom control and quality of life. • response rate and time to progression only on topotecan arm • qualitative and quantitative toxicities of oral topotecan.
Sample size	Randomize 220-→*141*
Statistics	Active Symptom Control, the estimated median survival: 12 weeks oral topotecan arm, the estimated median survival: 20 weeks. Stratify: • Duration of response to prior chemotherapy (≤ 60 days or > 60 days)→ *Time to progression from end of prior chemotherapy* (≤ 60 days or > 60 days) • Performance status (0/1 or 2) • Gender • Liver metastases (present or absent)
Final analysis	Minimum follow-up time for all patients: 30 weeks or until death→*125 deaths*
Cross-over design & potential impact on primary endpoint	None
Interim analysis	None
Inclusion	• Patients who have received one prior chemotherapy regimen only. ○ Documented *partial or complete response to first-line therapy.*

PARAMETER	PROTOCOL
	• Documented *relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy→≥ 45 days after cessation of first-line therapy* • *Patients not considered suitable for further intravenous chemotherapy.*
Exclusion	• Prior treatment with topotecan

AMENDMENTS

DATE	AMENDMENT	RATIONALE	CUMMULATIVE # OF PATIENTS ACCRUED AT TIME OF AMENDMENT	# OF PATIENTS ACCRUED AFTER AMENDMENT TO NEXT AMENDMENT
2/7/2000	None: original protocol		--	--
7/14/2000	Amendment 1; Routine issues; effective date41 The definition of progressive disease given in protocol was not consistent with current R&D Topotecan protocols. The definition has been updated from: 1) greater than a 25% increase in the smallest measurement of a single measurable lesion *to* greater than 25% increase in the sum of the products of the measurable disease and 2) clear worsening of evaluable disease *to* clear worsening of evaluable only disease. To clarify the requirement for tumour imaging and the rationale for exclusion of concurrent radiotherapy and to change the definition of progressive disease. Added to Study Design and Planned Efficacy Evaluation sections: For patients' randomised to receive ASC alone radiological assessment of tumour response is not justified as the predicted response rate is zero: Therefore radiological assessment of an apparent response is only applicable to patients' randomised to receive oral Topotecan. Furthermore to minimise the potential and inappropriate burden to the patient, frequent radiological assessment of response is not required in this protocol. Radiological assessment is only required after 3 courses of treatment, in the absence of any signs or symptoms of progressive disease, and thereafter only to confirm an apparent response or if clinically indicated to confirm disease progression. The dialogue for the telephone randomization procedure was updated for the new external provider,		0	22
8/29/2001	Amendment 2: changed 45-90 day window for disease relapse (an inclusion criterion) to ≥45 days, because the original window was proving to be too rigid.42'43 To change the definition of resistant disease44 plus, the	the original window was proving to be too rigid.	22 (1 of 22 patients were > 90 days)	119

41 Source: 8/2006 meeting package

DATE	AMENDMENT	RATIONALE	CUMMULATIVE # OF PATIENTS ACCRUED AT TIME OF AMENDMENT	# OF PATIENTS ACCRUED AFTER AMENDMENT TO NEXT AMENDMENT
	definition of "resistant" has been left to the judgement of the investigator. 45 **MEDICAL OFFICER NOTE: "Consequently, some of the patients enrolled after the implementation of the amendment had a time to progression of >90 days from the end of prior chemotherapy." How is randomizing patients to the active symptom control, whose time to progression from the end of prior chemotherapy was >90 days, *ethical*? According to the original protocol (p. 7 & 16), "Randomisation of sensitive SCLC patients onto an ASC arm of a protocol is considered to be ethically unacceptable."46 The Sponsor claims that "In the limited number of countries that could participated in protocol 478 there is an increasing trend to prescribe further chemotherapy not only to patients with sensitive disease but also to those with resistant disease."47** **Also, perhaps with this amendment to the protocol, the stratification factor should have changed to progression from end of prior chemotherapy: 45-90 days vs. > 90 days.**			
5/7/2004	Amendment 3: changed the stratification factor duration of response to prior chemotherapy (≤ 60 days or > 60 days) to time to progression from end of prior chemotherapy (≤ 60 days or > 60 days)48 **MEDICAL OFFICER NOTE: On page 24 of the study report, this change in the stratification factor is not mentioned in the discussion of Amendment 3** To introduce a final analysis when a defined	The continued evolution in evidence based clinical practice that has occurred whilst study 478 has been ongoing have only exacerbated the difficulties with recruitment. In the limited number of countries that could participated in protocol 478 there is an increasing trend to	141 (last patient accrued March 2004)	0

42 Source: 8/2006 meeting package
43 Source: p. 135-136 of protocol in NDA
44 Source: p. 1 of protocol in NDA
45 Source: p. 135-136 of protocol in NDA
46 From the 8/2006 meeting package, protocol pages 10 & 18; page 20 of study #478 study-report.
47 Source: p. 137 of protocol in NDA
48 Source: p. 218-221 of 8/2006 meeting package; page 138 of the protocol in NDA
49 Hycamtin: Lung Cancer MPA / NAM / GSK Meeting (16 October 2003) Final Minutes; Sent by GSK and dated 7/10/2007

DATE	AMENDMENT	RATIONALE	CUMMULATIVE # OF PATIENTS ACCRUED AT TIME OF AMENDMENT	# OF PATIENTS ACCRUED AFTER AMENDMENT TO NEXT AMENDMENT
	number of events have occurred; i.e., 125 events. **MEDICAL OFFICER NOTE: Although the study was amended to include patients, who had a TTP from prior chemotherapy of > 90 days (sensitive disease), in Target Sample Size section, the expected median survivals for the Active Symptomatic Control and the ASC + oral topotecan arms were not changed in the protocol in the NDA. This change in median survivals may have had a change in the statistics of the study and the number of patients required to complete the study.**	prescribe further chemotherapy not only to patients with sensitive disease but also to those with resistant disease. The slow recruitment rate has however resulted in the maturing of the survival data as the study has continued and it is predicted that a final analysis when 125 events (deaths) have occurred will provide sufficient evidence with respect to the primary endpoint. **(See recruitment Table and Figure in the MEDICAL OFFICER NOTE below)** B[b]y May 2004 only 141 patients out of the required 220 had been enrolled and several participating centres had withdrawn. Continuation of enrolment at the current rate would mean that recruitment would not be complete until late 2006. **MEDICAL OFFICER NOTE: Based on extrapolation of Linear (Actual Recruitment) (Figure below) to the original planned accrual of 220 patients, recruitment would have been completed in February 2006 or early 2006. Also, it is noted that the last patient was accrued in March 10, 2004, i.e., "by May 2004 only 141 patients out of the**		

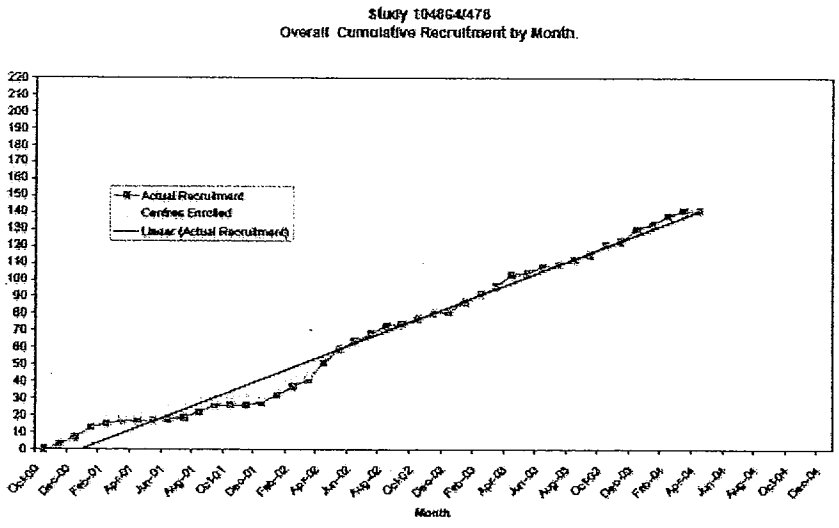
DATE	AMENDMENT	RATIONALE	CUMMULATIVE # OF PATIENTS ACCRUED AT TIME OF AMENDMENT	# OF PATIENTS ACCRUED AFTER AMENDMENT TO NEXT AMENDMENT
		required 220 had been enrolled and several participating centres had withdrawn." What happened to accrual of patients in April 2004 and early May 2004? Importantly, there were 118 deaths by May of 2004. **On October 16, 2003, GSK spoke with the EMEA about terminating the study.49**		

MEDICAL OFFICER NOTE: An e-mail response from GSK dated 6/8/2007: "I can confirm from our EU colleagues that 'the Topo 478 CRF was not amended during the course of the study. The CRF submitted to the FDA is the only version.'" This applies to amendment, regarding, the original 45-90 day window for disease relapse that was changed to ≥45 days, The CRF, page 13, Eligibility Checklist, has "a documented relapse of limited or extensive SCLC between 45 and 90 days after cessation of first-line therapy" as a criterion.

MEDICAL OFFICER NOTE: Below is a table with the month-by-month accrual provided by the Sponsor on July 17, 2007. The slow recruitment rate claimed by the Sponsor is not apparent. The Medical Officer query also requested month-by-month accrual for studies #065 and #396. For both of these other studies the Sponsor provided a column labeled "Target Rate." A "Target Rate" was not provided for study #478. Also, below is figure with the cumulative recruitment by month. Again, the slow recruitment rate claimed by the Sponsor is not apparent.

Study 104864/478
Recruitment by Month

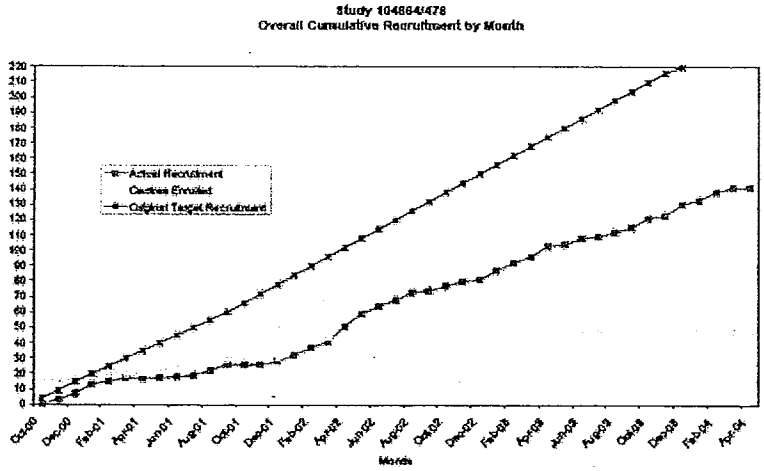
Month-Year	Pts Enrolled	Month-Year	Pts Enrolled
Nov-00	3	Dec-02	1
Dec-00	4	Jan-03	6
Jan-01	6	Feb-03	5
Feb-01	2	Mar-03	4
Mar-01	2	Apr-03	7
Apr-01	0	May-03	1
May-01	0	Jun-03	4
Jun-01	1	Jul-03	1
Jul-01	1	Aug-03	3
Aug-01	3	Sep-03	3
Sep-01	4	Oct-03	6
Oct-01	0	Nov-03	2
Nov-01	0	Dec-03	7
Dec-01	2	Jan-04	3
Jan-02	4	Feb-04	5
Feb-02	5	Mar-04	3
Mar-02	4		
Apr-02	10	Total	141
May-02	8		
Jun-02	5		
Jul-02	4		
Aug-02	5		
Sep-02	2		
Oct-02	2		
Nov-02	3		



Below is the Sponsor's response to a request for the target rates.

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			



6.3 A Post-Hoc Special Protocol Assessment

For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive and clinically meaningful efficacy findings so that a second trial would be ethically or practically impossible to perform.

Deficiencies and Issues

- Protocol amendments and early termination would have prompted discussions with the FDA.
- The unsuitability for further IV chemotherapy eligibility criterion (but considered able to tolerate treatment with single agent oral topotecan) should have been defined or deleted. Documentation of unsuitability should have been collected.
- Radiographic disease assessments in both study arms (need for tumor assessments on control is to detect PD and move on to other therapy) would have been required.
- The case report forms should have captured poststudy therapy and the route of administration.
- A mechanism to document response to 1st-line therapy and not just checking-off a box on the case report form would have been suggested, i.e., dates for the start of response and the confirmation of response.
- In the original definition of resistant SCLC, i.e., 45-90 days TTP post 1st-line chemotherapy, FDA would have pointed out that patients in the 60-90 day category are "considered sensitive" in the IV topotecan label and are eligible for IV topotecan and CAV.
- Although the study was amended to include patients, who had a TTP from prior chemotherapy of > 90 days (sensitive disease), the expected medians for the Active Symptomatic Control and the ASC + oral topotecan arms were not changed in the protocol in the NDA. The sample size and power calculations also should have been re-done with the change in eligibility.
- When the Sponsor changed the eligibility criteria to include patients >90 days from 1st-line therapy, the FDA would have reminded them of the following comment in the protocol: *Randomisation of sensitive SCLC patients onto an ASC arm of a protocol is considered to be ethically unacceptable.*
- If sensitive patients were enrolled on the BSC arm, how is it ethical not to assess tumor progression in these patients in order for them to rapidly be taken off study and treated with the regimen that gave them their first response or another cross-resistant regimen?
- A placebo controlled, double blind design would have been suggested.
- The FDA would have suggested adding US sites, particularly sites that could accrue blacks and Latinos. The IV topotecan label states "The effect of race on topotecan pharmacokinetics has not been studied." IV topotecan has indications for ovarian, small cell lung cancer, and cervical cancer. Oral topotecan has similar wording in the proposed label; i.e., "There are insufficient data to determine an effect of race on pharmacokinetics of oral topotecan."

- There may have been differing standards for clinical care and definitions of sensitive and resistant SCLC in Europe and the US (e.g., from EMEA document <90 days from 1st-line therapy defined resistant disease but the label for IV topotecan in the US considered sensitive to first-line chemotherapy responders who then subsequently progressed >/=60 days after completion of first-line therapy).
- There was no scientific or clinical basis for a stratification factor of duration of response of ≤ 60 days or > 60 days).
- The Sponsor amended the stratification factor from duration of response to prior chemotherapy (≤ 60 days or > 60 days) to TTP from prior chemotherapy (≤ 60 days or > 60 days) after all the patients were accrued to the study.
- In Appendix, J Procedures for Central Patient Registration and Randomization, in the original protocol, the following required amending for uniformity:
    - patient's duration of response to first-line chemotherapy in days from cessation of first line therapy until documented relapse (p. 88)
    - The duration of the patient's response to first-line chemotherapy was...(p. 89)
    - patient's duration of response to first-line chemotherapy (p. 90)

  On page 90, randomization 26 has oral topotecan and *intravenous* topotecan.50

  On 8/29/2001, with the Amendment 2 to the protocol, the stratification factor may have been changed to progression from end of prior chemotherapy: 45-90 days vs. > 90 days.
- There was no indication of the number of events that would trigger the final analysis. At best, the final analysis may have occurred with a minimum of 30 weeks follow-up. The protocol should have indicated the number events for the final analysis. This was corrected with Amendment 3 which was introduced after all the patients were accrued to the study.
- In the protocol, there was a contradiction between the claim that resistant SCLC patients cannot tolerate five days of IV topotecan and the claim about the evidence from the IV topotecan development program that resistant SCLC patients can benefit from treatment with topotecan. This required clarification.
- Procedures for withdrawal for the active symptom control only arm were not clearly delineated.
- If the FDA had known about study #478, FDA may have pointed out that the activation of study #389 (i.e., a 1st-line extensive SCLC study with cisplatin/oral topotecan vs. cisplatin/VP-16) in the same countries/centers as study #478 may negatively impact accrual to study #478.
- In the original protocol, the 1st page of the informed consent refers to resistant SCLC, i.e., "the cancer has stopped responding so soon after the chemotherapy it may not respond to any further chemotherapy, this is referred to as resistant small cell lung cancer." This reference to resistant SCLC was also in the informed consent in Amendment 3 protocol submitted with the NDA. Patients with sensitive SCLC were misinformed if informed consent was rendered with this document. Also, patients with sensitive SCLC had other

50 This is corrected in Amendment 3 protocol submitted in the NDA.

alternative therapy available, particularly, sensitive SCLC patients who were randomized to the active symptom control arm.

- In the informed consent (p. 64 of the original protocol), the following would have been amended. "Half of the patients will not receive any further chemotherapy but will receive medical treatment and support to alleviate and control the symptoms of the small cell lung cancer." Patient should have be informed that they would be permitted to seek further treatment at the time of disease progression.
    - In the informed consent (p. 66 of the original protocol; 4. Alternative 4), the following statement appears to refer to the topotecan arm, "If the treatment with oral topotecan does not help control your disease, you may be offered other treatments" A similar offer should have been made to the Active Symptom Control arm.
- According to the SUMMARY CHART OF PROCEDURES in the CRF, lesions were assessed by physical exam or photograph only at baseline. This would have been expanded.
- On page 2 of the CRF, the date of first documentation of recurrence should be the date of first documentation of recurrence or progression.
- Liver metastases (present or absent) was a stratification factor. This was not captured specifically in the CRF but was derived from baseline lesion data.
- In section 8.2 of the original protocol, lack of efficacy or progressive disease is not listed as grounds to withdraw a patient from therapy. On page 34 of the CFR, this was included.
- On page 13 of the CRF, Eligibility Checklist, criterion #5, requiring between 45 and 90 after cessation of first-line therapy would have been changed to $\geq$ 45 days after cessation of first-line therapy after the introduction of Amendment 2.
- On page 35 of the CRF, it is not clear how lack of efficacy or progressive disease was to be a criterion for withdrawal if it is not addressed in the original protocol.
- In the CRF, duration of response to 1st-line chemotherapy should have been in days and not weeks.
- CRF should have collected why patients were not considered suitable for further intravenous chemotherapy.
- CRF should have collected poststudy chemotherapy, drug names, and route of administration. In the case of the ASC patients, they would have been eligible for 2nd-line chemotherapy which presumably would have impact on survival (i.e., IV topotecan, CAV, and other regimens (?).
- Amendment 02 (August 2001), changing the 45-90 day window for relapse of resistant to $\geq$ 45 days and permitting the definition of "resistant" left to the judgement of the investigator, would have been challenged.
- It appears that the amendment, changing the stratification factor duration of response to prior chemotherapy ($\leq$ 60 days or > 60 days) to time to progression from end of prior chemotherapy ($\leq$ 60 days or > 60 days), was made after all the patients (i.e., n=141) were accrued to the study.
- FDA may have recommended an independent data monitoring committee.

Based on the multiple deficiencies noted above, the design, follow-up, planned analysis, and ethics of the study are problematic. The protocol submitted to the NDA (Amendment 3) does not appear to have been executed or IRB-approved during the time that patients were accrued to the study, i.e., the Amendment 3 protocol was issued three months after the last patient was accrued to study #478. No patients were accrued under the Amendment 3 protocol. Thus, the question is whether the apparent survival benefit with oral topotecan is a function of drug or a function of one or a combination of the methodological challenges in the protocol.

6.4 The Sponsor's Efficacy Findings of Study #478

Title: An Open-Label, Multicentre, Randomised, Phase III Comparator Study of ASC alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC

STUDY #478 (tables and figures are from the Sponsor's 8/2006 meeting package); other information taken from the study report in the NDA.

Initiation Date: 16 Nov 2000
Early Termination Date: 30 Mar 2004
Revision of Patient Sample Size and Change in Stratification Factor51: 13 May 2004
Completion Date: 30 Sep 2004
Date of Report: April 2005

Indication Studied: Relapsed, resistant small cell lung cancer (proposed).

> **MEDICAL OFFICER NOTE: Early in the trial when the eligibility criteria was amended to include patients with relapse of $\geq$ 45 days post cessation of 1st-line chemotherapy. According to the literature (see Disease Background section), patients, who relapse > 90 days post cessation of 1st-line chemotherapy, are defined to have sensitive disease.**
>
> **On page 20 of the study report, it is clear that the Sponsor is writing about and means resistant SCLC.**
>
> **On page 24 of the study report: "Patients who relapsed outside the 90 day window were still considered to have resistant disease, therefore the definition of "resistant" was left to the judgement of the investigator."**

This study was carried out at 40 centres 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 (12).

51 The change in the stratification factor is not in the study report.

MEDICAL OFFICER NOTE: There were 16 sites not listed in the NDA that did not recruit patients to the study. The sites were in Canada (3), Netherlands (6), Russia (2), Slovakia (1), and the United Kingdom (4).

Rationale: Five consecutive days of infusion with intravenous topotecan was considered too intrusive for this poor prognosis population in the absence of proof of benefit.

Demographics

Seventy-one patients were entered on the oral topotecan + BSC arm; 70 patients were entered on the BSC alone. The baseline characteristics appeared balanced, except for trends in favor of the topotecan arm in performance status, maximum lesion diameter, and response to 1st-line chemotherapy and in favor the BSC alone arm in staging and liver metastases. The numbers for the populations are in the table below.

	ASC	ASC + ORAL TOPOTECAN
ITT	70	71
Modified ITT52	67	70
Modified per protocol population53	56	70

52 These were randomized patients who had at least one evaluation after randomization.
53 This was the modified ITT population, excluding patients having a documented protocol violation which precluded an appropriate efficacy evaluation. **MEDICAL OFFICER NOTE: These patients included 14 patients randomised to ASC but subsequently received chemotherapy and one patient randomised to the oral topotecan arm but not treated.**

Baseline Characteristic	Study 478	
	Oral Topotecan + BSC	BSC Alone
	N=71	N=70
	n (%)	n (%)
Age, yrs		
18 – 40	1 (1.4)	0
41-64	46 (64.8)	50 (71.4)
≥65	24 (33.8)	20 (28.6)
mean	59.8	58.6
Race		
Caucasian	70 (98.6)	70 (100.0)
Black	1 (1.4)	0
Asian	0	0
Other	0	0
Gender		
Male	52 (73.2)	51 (72.9)
Female	19 (26.8)	19 (27.1)
ECOG PS		
0	8 (11.3)	6 (8.6)
1	44 (62.0)	41 (58.6)
2	19 (26.8)	23 (32.9)
Staging at Baseline		
Limited	23 (32.4)	27 (38.6)
Extensive	48 (67.6)	43 (61.4)
Missing	0	0
Maximum Lesion Diameter		
<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-evaluable	9 (12.7)	6 (8.6)
Response to 1st Line Chemotherapy		
CR	22 (31)	19 (27)
PR	49 (69)	51 (73)
SD	0	0
missing	0	0
Prior Radiotherapy	38 (53.5)	34 (48.6)
Liver Metastases		
Present	20 (28.2)	14 (20.0)
Absent	51 (71.8)	56 (80.0)

BSC = best supportive care; N = number of patients in the treatment arm; n = number of patients in the subgroup; ECOG = Eastern Cooperative Oncology Group; PS = performance status; CR = complete response; PR = partial response; SD = stable disease.

On entry to the study, 53 patients (75.7%) in the ASC alone group and 49 patients (69.0%) in the ASC + OT group had ongoing medical conditions associated with their SCLC

All patients had received prior chemotherapy. The most frequently received prior chemotherapeutic agents were platinum (cisplatin or carboplatin), 80% in the ASC + OT group and 77% in the ASC alone group and etoposide, 76% in the ASC +OT group and 74%, in the ASC alone group. In total 76% of patients in both groups received platinum

based combination chemotherapy 1st-line, mostly in combination with etoposide. Those who did not, received either a CAV or CAE based regimen.

Table 7 Time to Progression from End of First-Line Therapy – Study 478

TTP	Oral Topotecan + BSC n(%)	BSC Alone n(%)
≤90 days (≤3m)	41 (57.7)	36 (51.4)
>90 days (>3m)	30 (42.3)	34 (48.6)
≤60 days (≤2m)	22 (31.0)	20 (28.6)
>60 days (>2m)	49 (69.0)	50 (71.4)
Median (days)	84	90

TTP: time to progression from end of fist line chemotherapy.

MEDICAL OFFICER NOTE: Using 60 days as the stratification dividing lines provided a more balanced distribution of patients than 90 days post hoc. This is in view that in the original protocol the stratification factor was duration of response (≤ 60 days vs. >60 days) and was changed to TTP post Rx (≤ 60 days vs. >60 days) after the accrual of patients to the study had ceased.

In the modified ITT population, patients in the ASC + OT group received a median of four courses (range 1 to 10). *Patients in the ASC alone group were not treated but were followed for the equivalent of a median of three courses.*

By the fourth cycle, nearly half the patients were no longer receiving topotecan.

Table 8 Number of patients at each treatment course: modified ITT population[1]

Course	Treatment Group ASC + OT N=70
1	70
2	59
3	50
4	37
5	25
6	20
7	6
8	4
9	4
10	1

Data source: Table 14.3.1

1. Patients in the ITT population who received at least one dose of study treatment (see Section 6.4).

The topotecan arm patients remained on study longer than the best supportive care patients.

Table 9 Time on study for each treatment group

Treatment Group ASC alone N=70				Treatment Group ASC + OT N=71			
ITT population							
N	Median (weeks)	Min	Max	n	Median (weeks)	Min	Max
70	7.80	0.1	55.1	71	12.30	0.1	31.0
Modified per-protocol population							
N	Median (weeks)	Min	Max	n	Median (weeks)	Min	Max
56	7.05	0.1	27.0	70	12.35	1.9	31.0

Data source: Table 14.4.1, Table 14.4.2

Patient and study drug compliance was over 90%.

Table 16 Compliance with receipt of oral topotecan (number (%) of patients): modified ITT population

Overall Compliance	Oral Topotecan	
	Patient Compliance[1] N=70	Study Medication Compliance[2] N=70
< 80%	1 (1.4%)	1 (1.4%)
80 – < 90%	0	0
90 – 100%	69 (98.6%)	46 (65.7%)
> 100%	0	22 (31.4%)
Not evaluable[3]	0	1 (1.4%)

Data source: Tables 12.18.1, Table 12.19.1

1. Patient compliance defined as 100 times (sum of number of capsules taken across courses)/(sum of number of capsules dispensed across courses), where number of capsules taken = number of capsules dispensed – number of capsules returned
2. Study medication compliance defined as 100 times (sum of actual doses taken across courses)/(sum of recommended dose across courses), where recommended dose is (scheduled amount times BSA)
3. Patients with incomplete data for at least one course of treatment.

According to the Sponsor, overall survival was the primary endpoint in this study. The key results were as follows:

- The oral topotecan + BSC arm showed statistically significantly better overall survival compared with the BSC alone arm (p=0.0104).
- Median survival for oral topotecan + BSC arm was 86% higher than BSC alone arm (25.9 weeks vs. 13.9 weeks).
- The unadjusted hazard ratio for oral topotecan + BSC relative to BSC alone was 0.638 (95% CI: 0.45, 0.90), indicating a 36% reduction in the risk of death for patients in the oral topotecan + BSC arm.
- The adjusted hazard ratio (adjusted for stratification factors of gender, PS, liver metastases, and TTP from first-line chemotherapy) for oral topotecan + BSC relative to BSC alone was 0.608

(95% CI: 0.43, 0.87), indicating a 39% reduction in the risk of death for patients in the oral topotecan + BSC arm.

Table 10 Summary of Overall Survival – Study 478 ITT Population

Survival	Oral Topotecan + BSC (n=71)	BSC Alone (n=70)
Median, weeks (95% CI)	25.9 (18.3, 31.6)	13.9 (11.1, 18.6)
Observed (%)	63 (88.7)	67 (95.7)
Censored (%)	8 (11.3)	3 (4.3)
Log-rank p-value	0.0104	
Unadjusted HR (95% CI)	0.64 (0.45, 0.90)	
Adjusted HR (95% CI)[1]	0.61 (0.43, 0.87)	

1. Adjusted for protocol-defined stratification factors - gender, performance status, liver metastasis, time to progression from prior chemotherapy (≤60 days vs. >60 days).

CI = confidence interval; HR = hazard ratio.

Figure 1 Kaplan-Meier Survival Estimates - Study 478

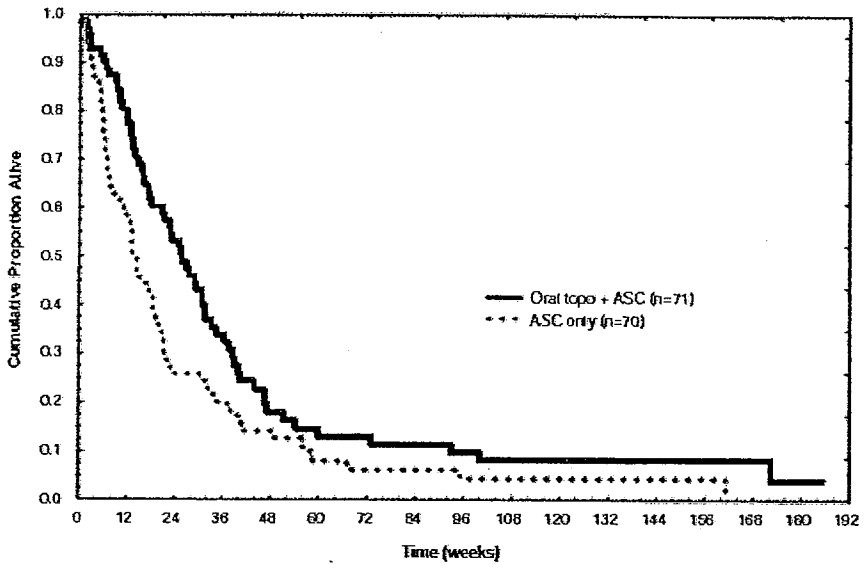


Table 11 Summary of Overall Survival
Subgroup Analysis
TTP </=90 or >90 Days from End of Prior Chemotherapy

	Oral Topotecan + BSC (N=71)	BSC Alone (N=70)
TTP ≤90 days		
Number of patients in the subgroup	41	36
Median (wks) (95% CI)	22.7 (13.6, 30.9)	13.1 (7.1, 18.6)
Censored events (%)	12	0
Hazard ratio (95% CI):	0.61 (0.38, 0.98)	
TTP >90 days		
Number of patients in the subgroup	30	34
Median (wks) (95% CI)	31.6 (21.6, 38.7)	15.9 (11.1, 21.9)
Censored events (%)	10	9
Hazard ratio (95% CI):	0.66 (0.39, 1.11)	

TTP = time to progression.
N=patients in the randomized group.

In the ASC alone group of the Modified per protocol population none of the patients received 2nd-line chemotherapy and therefore demonstrate the natural course of untreated SCLC at relapse.

MEDICAL OFFICER NOTE: The modified ITT population included 14 patients randomized to ASC but subsequently received chemotherapy and one patient randomised to the oral topotecan arm but not treated.

Table 18 Summary of survival: modified per-protocol population

Survival (weeks)	Treatment Group	
	ASC alone N=56	ASC + OT N=70
Median (95% C.I.)	12.8 (7.1, 14.4)	25.9 (18.3, 31.7)
Observed events	55 (98.2%)	62 (88.6%)
Censored events	1 (1.8%)	8 (11.4%)
Log-rank p-value	< 0.0001	

Data source: Table 13.1.1.2

Best response and median time to progression was assessed only for patients in the ASC + OT group. A response rate of 7.0% was achieved and stable disease was seen in a further 43.7% of patients.

MEDICAL OFFICER NOTE: There was no breakdown of response by resistant or sensitive SCLC patients. This breakdown was in the O'Brien et al article although there were no comments about it.54

54 O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cuceviá B, Juhasz G, Thatcher N, Ross GA, Dane GC, Crofts

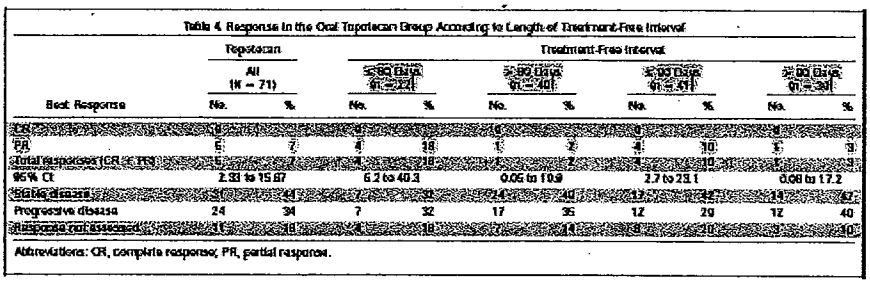


Table 4. Response in the Oral Topotecan Group According to Length of Treatment-Free Interval

	Topotecan		Treatment-Free Interval							
	All (N = 71)		≤ 90 Days (n = 22)		> 90 Days (n = 40)		> 90 Days (n = 41)		> 90 Days (n = 39)	
Best Response	No.	%	No.	%	No.	%	No.	%	No.	%
CR	0		0		0		0		0	
PR	5	7	4	18	1	2	4	10	1	3
Total response (CR + PR)	5	7	4	18	1	2	4	10	1	3
95% CI	2.33 to 15.87		6.2 to 40.3		0.05 to 10.9		2.7 to 23.1		0.08 to 17.2	
Stable disease	31	44	7	32	14	35	17	41	13	33
Progressive disease	24	34	7	32	17	35	12	29	12	40
Response not assessed	11	16	4	18	8	20	8	20	3	10

Abbreviations: CR, complete response; PR, partial response.

On the topotecan arm, sensitive patients (> 90 days treatment-free interval) had a response rate of 3% and resistant patients (≤ 90 days treatment-free interval) had a response rate of 10%. This was the reverse of what would have been predicted.

Median time to progression in the ASC + OT group was 16.3 weeks. In the ASC alone group, 18 patients (25.7%) were alive after 6 months compared with 34 patients (48.9%) in the ASC + OT group.

Summary of Kaplan-Meier estimate of time to progression: ITT population

Time to progression (weeks)	Treatment Group ASC+ OT N=71
Median (95% C.I.)	16.3 (12.9, 20.0)
Observed events	59 (83.1%)
Censored events	12 (16.9%)

Data source: Table 13.4.1.1

T. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7

Table 21 Post-study cancer therapy (number (%) of patients): ITT population

Therapy	Treatment Group	
	ASC alone N=70	ASC + OT N=71
Chemotherapy[1]	13 (18.6%)	13 (18.3%)
Radiotherapy alone	1 (1.4%)	7 (9.9%)
Surgery alone	0	1 (1.4%)
Unknown	2 (2.9%)	3 (4.2%)
No subsequent therapy	20 (28.6%)	33 (46.5%)
No post study follow-up data	34 (48.6%)	14 (19.7%)

Data source: Table 13.2.1

1. Represents third line chemotherapy for the ASC + OT group and second line for the ASC alone group

MEDICAL OFFICER NOTE: There was another patient (#478.042.85414) not listed in the FLWUP database but listed in the PV database. This brings the total of ASC patients who received post-study chemotherapy to 14 or 20%. Also, there is a difference in the meaning of receiving post-study chemotherapy—ASC alone patients were listed as protocol violators and the ASC + oral topetecan, who received post-study chemotherapy, were not listed as protocol violators.

According to the Sponsor, "A small but similar proportions of patients from each treatment group received subsequent chemotherapy. Based on the data presented above it would appear that a higher proportion of patients in the ASC + OT group received no subsequent therapy. In fact in both groups a number of patients died during or within a very short period of time of completing the treatment phase of the protocol. As a consequence these patients did not progress into the Post Study Monitoring phase which follows withdrawal and during which any post study cancer therapy was documented. The large majority of these patients did not receive any post study cancer therapy with a few patients being lost to follow-up."

Table 22 Palliative care for SCLC symptoms; modified ITT population

Therapy	Treatment Group			
	ASC alone		ASC + OT	
	Patients	Courses	Patients	Courses
N	67	276	70	348
Medications	55 (82.1%)	133 (48.2%)	42 (60.0%)	98 (28.2%)
Radiotherapy	17 (25.4%)	23 (8.3%)	10 (14.3%)	11 (3.2%)
Transfusions	7 (10.4%)	10 (3.6%)	23 (32.9%)	39 (11.2%)
Other Procedures	9 (13.4%)	12 (4.3%)	6 (8.6%)	6 (1.7%)

Data source: Table 14.9.1

Below is a course-by-course tabulation for the categories of palliative care.

Table 23 Palliative medications for SCLC symptoms (number (%) of patients) by course; modified ITT population

	Treatment Group			
	ASC alone N=67		n	ASC + OT N=70
Courses with medications	133 (48.2%)			98 (28.2%)
Course	n		n	
Baseline	67	36 (53.7%)	70	30 (42.9%)
1	67	35 (52.2%)	70	25 (35.7%)
2	49	24 (49.0%)	59	16 (27.1%)
3	36	15 (41.7%)	50	12 (24.0%)
4	26	11 (42.3%)	37	6 (16.2%)
5	13	7 (53.8%)	27	6 (22.2%)
6	5	2 (40.0%)	20	1 (5.0%)
7	3	1 (33.3%)	6	2 (33.3%)
8	3	1 (33.3%)	4	0
9	3	1 (33.3%)	4	0
10	1	0	1	0
11	1	0	0	NA[1]
12	1	0	0	NA[1]
13	1	0	0	NA[1]

Data source: Table 14.9.1

1. Not applicable: no patients in this group had more than 10 courses

Table 24 Palliative radiotherapy for SCLC symptoms (number (%) of patients) by course; modified ITT population

Course		Treatment Group		
		ASC alone N=67		ASC + OT N=70
Courses with palliative radiotherapy		23 (8.3%)		11 (3.2%)
Course	n		n	
Baseline	67	3 (4.5%)	70	6 (8.6%)
1	67	11 (16.4%)	70	1 (1.4%)
2	49	4 (8.2%)	59	0
3	36	3 (8.3%)	50	1 (2.0%)
4	26	2 (7.7%)	37	1 (2.7%)
5	13	0	27	2 (7.4%)
6	5	0	20	0
7	3	0	6	0
8	3	0	4	0
9	3	0	4	0
10	1	0	1	0
11	1	0	0	NA[1]
12	1	0	0	NA[1]
13	1	0	0	NA[1]

Data source: Table 14.9.1

1. Not applicable: no patients in this group had more than 10 courses

Below are tables, comparing palliative care in both arms.

Table 25 Post-randomisation palliative medications received by at least 5% of patients in either group (number (%) of patients): modified ITT population

Concomitant Medication[1]	Treatment Group	
	ASC alone N=67	ASC + OT N=70
At least one medication	53 (79.1%)	42 (60.0%)
Dexamethasone	19 (28.4%)	14 (20.0%)
Tramadol	3 (4.5%)	11 (15.7%)
Paracetamol	11 (16.4%)	8 (11.4%)
Sodium chloride	5 (7.5%)	8 (11.4%)
Furosemide	4 (6.0%)	7 (10.0%)
Morphine sulphate	15 (22.4%)	6 (8.6%)
Diclofenac	3 (4.5%)	6 (8.6%)
Methyl prednisolone	6 (9.0%)	5 (7.1%)
Metoclopramide	4 (6.0%)	5 (7.1%)
Codeine	3 (4.5%)	5 (7.1%)
Aminophylline	8 (11.9%)	4 (5.7%)
Codeine phosphate	7 (10.4%)	4 (5.7%)
Diazepam	4 (6.0%)	4 (5.7%)
Theophylline	3 (4.5%)	4 (5.7%)
Fentanyl	6 (9.0%)	2 (2.9%)
Prednisolone	6 (9.0%)	2 (2.9%)

Data source: Table 14.10.1

1. Medications received represent use for that term only and does not take account of salts; numbers given are most frequent and do not take account of multiple ATC classifications

Table 26 Post-randomisation palliative medical procedures (number (%) of patients): modified ITT population

Medical procedure	Treatment Group	
	ASC alone N=67	ASC + OT N=70
Aspiration pleural cavity	3 (3.0)	2 (2.9%)
Paracentesis	1 (1.5)	1 (1.4%)
Paracentesis abdomen	0	1 (1.4%)
Spinal laminectomy	0	1 (1.4%)
Bladder catheterisation	1 (1.5)	0
Chest X-ray	1 (1.5)	0
Open reduction of fracture	1 (1.5)	0
Pericardial drainage	1 (1.5)	0
"Sepsis"	1 (1.5)	0
Stent occlusion	1 (1.5)	0
Ultrasound abdomen	1 (1.5)	0

Data source: Table 14.11.1

Below is a subgroup analysis by gender. Topotecan appears to have more effect in females than in males.

Table 27 Summary of survival, by gender: ITT population

Survival (Weeks)	Treatment Group	
	ASC alone N=70	ASC + OT N=71
Females (n)	19	19
Median (95% C.I.)	14.4 (6.6, 21.1)	38.7 (16.3, 73.0)
Observed events	18 (94.7%)	15 (79.0%)
Censored events	1 (5.3%)	4 (21.1%)
Log-rank p-value	0.0173	
Males (n)	51	52
Median (95% C.I.)	13.3 (10.3, 19.7)	23.3 (15.9, 29.3)
Observed events	49 (96.1%)	48 (92.3%)
Censored events	2 (3.9%)	4 (7.7%)
Log-rank p-value	0.2702	

Data source: Table 13.1.1.3

Below is a subgroup analysis by performance status. Topotecan appears to have more effect in patients with ECOG performance status 2. The patients with performance status 2 in the ASC alone arm have a particularly poor median survival.

Table 28 Summary of survival, by performance status: ITT population

Survival (Weeks)	Treatment Group ASC alone N=70	ASC + OT N=71
Performance status 0 or 1 (n)	47	52
Median (95% C.I.)	18.6 (13.1, 21.4)	29.2 (21.6, 38.7)
Observed events	44 (93.6%)	46 (88.5%)
Censored events	3 (6.4%)	6 (11.5%)
Log-rank p-value	0.0968	
Performance status 2,	23	19
Median (95% C.I.)	7.7 (5.3, 13.1)	20.9 (13.4, 26.9)
Observed events	23 (100%)	17 (89.5%)
Censored events	0	2 (10.5%)
Log-rank p-value	0.0146	

Data source: Table 13.1.1.4

Below is a subgroup analysis by presence or absence of liver metastases. Topotecan appears to have more effect in patients without liver metastases. The patients with liver metastases in the ASC alone arm have a particularly poor median survival.

Table 29 Summary of survival, by presence or absence of liver metastases: ITT population

Survival (Weeks)	Treatment Group ASC alone N=70	ASC + OT N=71
Liver metastases absent	56	51
Median (95% C.I.)	14.4 (12.7, 21.0)	30.9 (23.3, 39.1)
Observed events	53 (94.6%)	43 (84.3%)
Censored events	3 (5.4%)	8 (15.7%)
Log-rank p-value	0.0071	
Liver metastases present	14	20
Median (95% C.I.)	7.9 (3.4, 18.6)	13.3 (9.4, 25.3)
Observed events	14 (100%)	20 (100%)
Censored events	0	0
Log-rank p-value	0.1674	

Data source: Table 13.1.1.5