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Product name: **HYCAMTIN**
Procedure No. **EMEA/H/C/123/II/34**

SCIENTIFIC DISCUSSION

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Introduction

Topotecan (Hycamtin™) is a cytotoxic anti-cancer agent exerting its activity by the inhibition of the nuclear enzyme topoisomerase I. The resulting DNA damage induces apoptotic cell death predominantly in replicating cells such as tumour cells. Topotecan is registered in the European Union (EU), and 59 other countries around the world for the treatment of relapsed ovarian cancer following platinum-based therapy. In addition to the treatment of relapsed ovarian cancer, topotecan is registered for the treatment of relapsed small cell lung cancer (SCLC) in 39 countries worldwide. Around 230 000 patients have been treated with topotecan since market launch in May 1996 to November 2004.

The claimed new indication is:
"Relapsed small cell lung cancer (SCLC) in patients for whom re-treatment with the first line regimen is not considered appropriate".

Lung cancer is amongst the most commonly occurring malignant diseases. SCLC represents about 14% of all lung cancers and is a devastating disease with a long-term survival rate of around 5%. Most patients have extended disease already at first diagnosis. Despite this an initial response to chemotherapy is most often the case. However, the development of a therapy resistant disease is usually rapid.
The clinical evidence of today shows that patients with SCLC should be treated with a suitable first line regimen at initial presentation [cisplatin/ carboblatin plus etoposide or CAV (cyclophosphamide, Adriamycin [doxorubicin], and vincristine)], and should be considered for further therapy at relapse. A minority of patients have adequate Performance Score (PS) and a sufficiently long time to progression (TTP) following first line chemotherapy to be eligible for re-treatment with the first line regimen. The majority of patients need alternative therapy, and there is a great medical need for such new tolerated regimens for these patients.

IV topotecan has been evaluated in patients with relapsed SCLC at the same dose and schedule as is currently stated in the SPC for the treatment of relapsed ovarian cancer: 1.5mg/m^2/day for five consecutive days and repeated every 21 days according to bone marrow recovery.

Regulatory history of the application for Hycamtin in SCLC

In December 1997, an application was made to the Committee for Proprietary Medicinal Products (CPMP) for the addition of the treatment indication "patients with relapsed small cell lung cancer (SCLC)". The application was supported by a pivotal phase III study showing similarity of topotecan compared with cyclophosphamide, adriamycin and vincristine (CAV). The application was withdrawn in November 1998. The main hinder for approval was that patient benefit of second-line chemotherapy had not been scientifically proven in SCLC. Therefore superiority over an established comparator was required for approval.

A study was designed to address the reservations of the CPMP. A randomised phase III study, Study 478, was designed to show superiority of oral topotecan over Active Symptom Control (ASC) (=best supportive care) in the treatment of relapsed, resistant SCLC. It was considered unethical to include patients with relapsed SCLC unless their disease was "resistant" to the first line of therapy. Oral administration was considered more appropriate for such patients than intravenous administration given their poor survival expectation and disease symptom burden. Following preliminary discussions with the Swedish and French regulatory agencies, the protocol was reviewed by the CPMP. It was agreed that:

- the study design was adequate to prove the benefit of further chemotherapy to patients with relapsed SCLC;
- a positive outcome would support a second line indication for both IV and oral topotecan.

The dose of oral topotecan proposed for Study 478 was supported by data from a randomised phase II study (Study 065) which indicated that 2.3 mg/m^2 oral and 1.5 mg/m^2 intravenous (IV), daily for five days, every 21 days, were clinically similar in relapsed SCLC patients. As this study was not powered to show a statistical difference between the two routes of administration and the ratio of oral and IV doses was not based on kinetic data, the Committee advised an application to the IV licence should include:

- all available clinical data relevant to the oral to IV extrapolation, including data performed in ovarian cancer;
- a discussion of differences in the pharmacokinetics between the two formulations and the clinical relevance;
- pharmacological justification to support the claim of similarity in efficacy and safety of the two doses and routes of administration.

Recruitment to Study 478 proved to be more difficult than expected. Following consultations with the Rapporteur and the Co-Rapporteur, GSK submitted a second Type II variation application to register the treatment indication "small cell lung cancer (SCLC) after failure of first-line therapy" in November 2002. The application was withdrawn following an oral explanation. The outstanding objections were:

- the comparative regimen in the pivotal phase III study is not justified for a large percentage of patients;
- non-inferiority in overall survival cannot be concluded;
- superiority as regards other important measures of clinical benefit such as symptom control has not been established.

In October 2003, GSK met with the MPA and NAM to discuss the future conduct of Study 478 and the principals of extrapolating positive data from studies conducted with oral topotecan to the IV formulation. It was recognised that Study 478 was unlikely to complete as planned and agreed to GSK's proposal to conduct a final analysis at 125 events. Due to the maturity of the data the proposed analysis would have approximately 80% power and maintain alpha at 0.05. It was confirmed that a positive outcome from Study 478 would continue to support an application to register relapsed SCLC for both formulations. Previous agreements that positive data obtained with oral topotecan could be extrapolated to the IV formulation were reconfirmed, specifically:

- in general terms, extrapolation from oral to IV was more acceptable than IV to oral given the obvious differences in exposure;
- linearity for dose and exposure for each formulation should be demonstrated;
- pharmacokinetic data for all indications, not just SCLC, should be presented.

Non-clinical aspects

Since the dosing regimen proposed for treatment of relapsed small SCLC is identical to that currently registered in the EU for treatment of metastatic carcinoma of the ovary, i.e., 1.5 mg/m^2 administered by intravenous infusion over 30 minutes daily for 5 consecutive days, every 21 days, no additional nonclinical safety studies are considered necessary to support the current application.

Clinical aspects

Clinical Pharmacology

The doses and schedule of IV and oral capsule topotecan were defined in Phase I studies using identical selection criteria and definitions of dose-limiting toxicities in order to produce regimens with similar clinical profiles. In crossover studies at the therapeutic doses (1.5 mg/m^2/day (IV) or 2.3 mg/m^2/day (oral) x 5 every 21 days), the IV formulation has a greater AUC (1.7-fold) and C_{max} (5.4-fold) than the oral formulation. In these studies, IV topotecan had less inter-subject variability than oral topotecan as expected, due to the additional impact of absorption [i.e., bioavailability] on exposure [AUC, C_{max}] following oral administration.

The disposition of topotecan is similar for both routes of administration, with a significant fraction of the dose reversibly hydrolysed to the carboxylate form. Topotecan is cleared predominantly renally with a minor component metabolised to the N-desmethyl metabolite. Mean exposure [metabolite/parent AUC ratio] to this metabolite is slightly higher following oral than IV administration, but it did not exceed 10% of the parent by either route.

The PK profile is dose proportional for both IV and oral topotecan. Despite the differences in AUC and C_{max}, plasma concentrations are similar between IV and oral topotecan at the therapeutic doses, from approximately two hours after dosing [start of infusion or oral administration]. Therefore, during a dosing interval, more than 90% of the concentration profile is similar between IV and oral administration. This similarity in concentration-time profiles by these routes is consistent with similar efficacy and overall clinical tolerability as has been shown in two randomised studies (Study 396 and 065), and may therefore be a better predictor than AUC or C_{max}.

A linear dose-PK relationship has been shown for both oral and IV administration of topotecan. The results from the two clinical studies 396 and 065 addressing the comparability between the two formulations/ modes of administration are discussed further below.

Further, preliminary bioavailability of topotecan was assessed using an oral drinking solution prepared from the reconstituted IV product, diluted in 200mls of 5% dextrose. The oral administration of 1.5mg/m2 on day 1 when compared to a 30 minutes infusion of 1.5mg/m2 on day 2 demonstrated a bioavailability of 30% with moderate inter-patient variability $\pm$ 7.7%. The oral drinking solution was well tolerated. The absolute bioavailability of oral topotecan determined using gelatin capsules compared to a 30 minute infusions was similar, 42% $\pm$ 13%.

Clinical Efficacy

Previous applications for the use of intravenous (IV) topotecan in relapsed small cell lung cancer (SCLC) have been based on six clinical studies evaluating intravenous (IV) topotecan.
A phase III comparative study with oral topotecan therapy against Active Symptom Control (ASC) (Study 478) in patients with relapsed, resistant SCLC has now been added to support the indication claim.

Two randomised trials (Studies 065 and 396) are submitted to show that IV topotecan is no less active than oral topotecan in relapsed sensitive SCLC.

Efficacy data from the integrated Total IV Topotecan (SCLC) population is also provided.

The Applicant states that all studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline (GSK) Group of Companies, which comply with the principles of

Good Clinical Practice (GCP). All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the Declaration of Helsinki. Where regulatory approval was required, this was obtained from the relevant health authority.

The phase II/III clinical trials in relapsed SCLC are presented below (Table 1):

Table 1 Summary of Phase II/III Clinical Trials – Topotecan in Relapsed Small Cell Lung Cancer

Protocol Phase / No.	Design	Population	Treatment	Efficacy Variables		No. treated patients	Country/ Centres	Study dates
				Primary	Secondary			
Phase III 478	Randomised, open-label, comparative	Resistant (PFI ≥ 45 days)[a]	Oral Topotecan + Active Symptom Control (ASC) vs ASC	Overall Survival	Response rate, time to progression (all non-comparative), 6-month survival rate, symptom assessment	Oral + ASC: 71 ASC alone: 70	Europe, N. America / 40	Nov 00 – Sept 04
Phase III 396	Randomised, Open-label, comparative.	Sensitive (PFI ≥ 90 days)	IV Topotecan vs Oral Topotecan	Response rate	TTE[c], Symptom assessment	IV: 151 Oral: 153	N. America, Europe, Australia, Asia / 83	Jan 99 – Sept 03
Phase III 090	Randomised, open-label, comparative	Sensitive (PFI ≥ 60 days)	IV Topotecan vs CAV[b]	Response rate, response duration	Time to response, time to progression, survival, symptom assessment	IV: 107 CAV: 104	N. America, Europe, S Africa / 45	Jun 95 – Mar 98
Phase II 065	Randomised, open-label, comparative	Sensitive (PFI ≥ 90 days)	IV Topotecan vs Oral Topotecan	Response rate, response duration, time to progression	Time to response, Survival, Symptom assessment	IV: 54 Oral: 52	Europe, Australia, South Africa / 31	Mar 97– May 00
Phase II 014EORTC	Open-label, non-comparative	Refractory / Sensitive	IV Topotecan	Response rate	TTE[c]	IV: 101	Europe / 22	Dec 92 - Feb 96
Phase II 014SB (092)	Open-label, non-comparative	Refractory / Sensitive	IV Topotecan	Response rate	TTE[c]	IV: 119	Europe / 35	Sep 93 - Feb 96
Phase II 053	Open-label, non-comparative	Refractory / Sensitive	IV Topotecan	Response rate, response duration, survival	Time to response, time to progression, symptom assessment	IV: 99	N. America / 32	Jun 94 – Jun 96
Total IV topotecan Population						IV: 631		

a. Patients not considered suitable for further intravenous chemotherapy
b. CAV = cyclophosphamide, doxorubicin, vincristine
c. TTE = Time To Event data which included: Time To Response, Response Duration, Time To Progression, Survival

Main clinical study(ies)

Studies 478, 396 and 090 are considered pivotal in addressing the crucial points for the establishment of an efficacy conclusion for topotecan in relapsed SCLC. The results from these studies will be discussed study by study in the results section below, while the phase II studies are regarded as supportive and the results from these are included and analysed in the integrated database for IV topotecan in SCLC.

Study populations:

- Study 478 was designed to recruit resistant patients, where **resistant** was defined as patients who had achieved a partial or complete response to first line therapy and progressed at least 45 days after completing first line therapy, who were not candidates for further IV chemotherapy but were considered of sufficient good health to tolerate treatment with single agent oral topotecan.

Potential reasons for exclusion from second-line i.v. chemotherapy

Each patient recruited into Study 478 received optimal and appropriate first-line chemotherapy, in accordance with local and national clinical practice and treatment guidelines and were not considered by their oncologist to be suitable for further IV chemotherapy.
Residual toxicity to the first-line regimen alone would not necessarily exclude a patient from further IV chemotherapy. It may exclude a patient from re-treatment with the same regimen but IV cross-over therapy would remain an option.
Screening data collected within the Case Report Form (CRF) for each patient does not specifically capture the reason why a patient was not considered a candidate for further IV chemotherapy.

Study 478: Potential reasons for exclusion from second-line intravenous chemotherapy

Potential Reason	Relevance to Study 478 Population
A very short Time To Progression (TTP) of 90 days following an initial response to first-line chemotherapy.	58% of patients in the ASC + Oral topotecan arm and 51% in the ASC alone arm had a TTP from first-line of < 90 days. Until the completion of Study 478, clinically significant survival benefit had not been demonstrated in resistant SCLC thus palliating symptoms without administering further chemotherapy would have been an appropriate treatment option.
A relatively short TTP from first-line chemotherapy and residual toxicity to the first-line regimen.	13% of patients in the ASC + topotecan arm and 10% in the ASC alone arm reported residual toxicity attributed to their first-line chemotherapy. Assessing what influence these residual toxicities had on treatment options would be conjecture however sustained toxicities associated with the first-line chemotherapy will influence the choice/option of both the clinician and the patient.
The patient's personal choice not to receive further intravenous chemotherapy.	Data captured within the CRF for each patient may allow the potential reason why a patient was not considered a candidate for further intravenous chemotherapy to be identified, but it does not capture the full consultation process or individuals opinions.

A bit more than 50% of patients in Study 478 had a relapse within 90 days. A minority of patients (13%) had residual toxicity and another 13% had received two types of chemotherapy prior to the entry to study 478. In conclusion, the majority of patients fulfil the requirement of not being suitable for re-treatment with the first line.

- Studies 396, 065, and 090 were designed to recruit sensitive patients, where **sensitive** was defined as patients who had progressed ≥ 90 days (Studies 396 and 065) or ≥ 60 days (Study 090) after having a documented response to first line therapy.
- Studies 014EORTC, 014SB(92), and 053 were designed to recruit sensitive or refractory patients, where sensitive was defined as progression ≥ 90 days after having a documented response to first line therapy and **refractory** was defined as patients who
    - received at least one full course of treatment and progressed during first line therapy, or
    - received at least two full courses of treatment, responded initially (partial or complete response) or achieved stable disease, but progressed within 3 months (90 days) of completing first- line therapy.

As overall survival was the primary endpoint in Study 478, patients were not required to have a bidimensionally measurable disease for inclusion in this study. In the other six studies, where response rate was the primary endpoint, all patients were required to have a least one measurable indicator lesion at baseline.

The other principal eligibility criteria, which were similar across all seven studies, are summarised in Table 2.

Table 2 Summary of Eligibility Criteria from All SCLC Studies

Criterion	Study						
	478	**396**	**090**	**065**	**014 EORTC**	**014SB (092)**	**053**
≥18 years	✓	✓	✓	✓	✓[a]	✓[a]	✓
Only one previous chemotherapy regimen	✓	✓	✓	✓	✓	✓	✓
≤ 2 performance status (ECOG scale)	✓	✓	✓	✓	✓	✓	✓
Resistant patients only	✓[b]						
Sensitive patients only		✓[c]	✓[d]	✓[c]			
Sensitive or Refractory patients					✓[e]	✓[e]	✓[e]
Extensive disease or limited disease	✓	✓	✓	✓	✓	✓	✓
Bidimensionally measurable disease[f]		✓	✓	✓	✓	✓	✓
Asymptomatic neurological metastases (if applicable)[g]	✓	✓	✓	✓	✓	✓	✓

a. For studies 014EORTC and 014SB (092) patients > 75 years were excluded
b. Time to (disease) progression (TTP) from first line treatment ≥ 45 days
c. TTP from first line treatment ≥ 90 days
d. TTP from first line treatment was reduced from ≥ 90 days to ≥ 60 days to increase patient recruitment
e. Sensitive: TTP ≥ 90 days; Refractory: TTP < 90 days

Treatment schedules

The starting dose of **oral topotecan** (for Study 478, and as a comparator to IV topotecan in Study 396) was selected on the basis of a phase I study of oral topotecan in patients with malignant solid tumours which concluded that the maximum tolerated dose was 2.3mg/m^2/day for 5 days every 21 days.

Study 049 (A phase I study to determine the maximum tolerated dose of topotecan following oral administration over 5, 10 or 21 days in patients with malignant solid tumours) evaluated the pharmacokinetics across a broad dose range, from 0.15 mg/m^2 to 2.9 mg/m^2 (0.3 to 5.5 mg), and demonstrated dose proportionality. The pharmacokinetics of oral topotecan has been shown to be linear in this dose range.
The initial study of oral topotecan, Study 047, evaluated a dose of 1.5 mg/m^2 given by oral administration of the intravenous solution; however, after Study 049, clinical trials to evaluate oral topotecan have generally used the maximum tolerated dose determined by that study, 2.3 mg/m^2.
Study 065 comparing oral with IV topotecan in recurrent SCLC confirmed the clinical appropriateness of this dose selection.

Extensive testing of **IV topotecan** over a range of dosing schedules from single day administration every 21 days to continuous 21 day infusions identified once-daily dosing for 5 days every 21 days as an appropriate regimen. The starting dose of IV topotecan was chosen on the basis of Phase I studies. This dose was subsequently approved as the registered dose for the treatment of relapsed ovarian cancer. In all studies IV topotecan was administered as a 30-minute intravenous infusion at an initial dose of 1.5mg/m^2/day for 5 days every 21 days.
CAV (cyclophosphamide, Adriamycin [doxorubicin], and vincristine), used as a comparator in Study 090, was administered at the standard initial dose of cyclophosphamide 1000mg/m^2 plus doxorubicin 45mg/m^2 plus vincristine 2mg/m^2 every 21 days, with the maximum permitted doses being 2000mg/m^2, 100mg/m^2, and 2mg/m^2, respectively. Dose modification criteria were specified for reductions in the dose of cyclophosphamide and/or doxorubicin and/or vincristine.

Methods

Efficacy endpoints:

Table 3 Primary and Secondary Endpoints for all SCLC Studies

	Study Number						
Endpoint	**478**	**396**	**090**	**065**	**014 EORTC**	**014SB (092)**	**053**
Survival	**P**	S	S	S	S	S	**P**
Response rate	S[d]	**P**	**P**	**P**	**P**	**P**	**P**
Time to response	-	S	S	S	S	S	S
Response duration	-	S	**P**	**P**	S	S	**P**
Time to Progression	S[d]	S	S	**P**	S	S	S
Patient Symptom Assessment / Quality of life	S[a, b]	S[c]	S[a]	S[a]	-	-	S[a]

P = primary, S = secondary
a. GSK patient symptom assessment scores
b. EuroQol (EQ-5D) global health score
c. Assessed using Functional Assessment of Cancer Therapy-G and Lung Cancer Subscale (FACT-L)
d. Not comparative – oral topotecan/ASC only

Survival: the time from first administration of study drug (randomisation in Study 478) until death due to any cause.

Response rate: the percentage of patients who had a complete or partial response.
- Complete response (CR) was defined as complete disappearance of all known measurable and evaluable disease determined by two measurements not less than 4 weeks apart.

- A partial response (PR) was defined as a greater than 50% decrease in the sum of the products of the greatest length and perpendicular width of all measurable lesions for at least 4 weeks with no simultaneous increase in a known lesion (> 25%), appearance of new lesions or increase in evaluable disease during this period.
- Stable disease (SD) was defined as a state of response which is less than partial or progression and lasts for at least 8 weeks.

Investigators monitored and reported the response to treatment through application of the WHO response criteria. Scans for all patients with a partial or complete response underwent independent radiological review. In the phase III studies and Study 065 the independent radiologists were blinded to the respective treatment group.

Time to response: the time from initiation of study drug until the first documented complete or partial response.

Response duration: the time from the initial documented response to the first sign of progression.

Time to progression (TTP): the time from initiation of study drug (from randomisation in Study 478) until the first documented sign of disease progression or death due to progressive disease. Disease progression was defined as a greater than 25% increase in a single measurable lesion; reappearance of measurable disease; clear worsening of evaluable disease; appearance of any new lesions; or significant worsening of a condition presumed to be related to malignancy.

Quality of Life (QoL) assessment: In Studies 478, 396, 090, 065 and 053 disease related symptom improvement was assessed using Patient Symptom Assessment to access the following symptoms at baseline and at the end of each course of treatment: Shortness of Breath; Cough; Chest Pain; Coughing up Blood; Loss of Appetite; Interference with Sleep; Hoarseness; Fatigue (Studies 478, 090 and 065 only) and Interference with Daily Activities (Studies 478, 090 and 065 only).
Study 396 used the patient completed FACT-L questionnaire to assess disease related symptoms at baseline and at the end of each course of treatment. FACT-L is a validated 44-item self-reporting instrument consisting of five sections: physical well-being, social/family well-being, emotional well-being, functional well-being, and an index specific to lung cancer and its associated symptoms.

In Study 478, quality of life was assessed using the EuroQoL (EQ-5D) health questionnaire including the Visual Analogue Scale. The EQ-5D is a 16-item self-reporting instrument consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression divided into three levels of perceived problems (level 1: no problems; level 2: some problem; level 3: extreme problem). Unique health states are defined by combining response levels from each of the five dimensions. The Visual Analogue Scale uses a thermometer-style scale on which patients rate their overall health state from zero (worst imaginable) to 100 (best imaginable).

Statistics

Study 478: To demonstrate survival superiority with the addition of oral topotecan to Active Symptom Control (ASC), 110 patients per treatment group were required. This sample size was calculated using a two-sided nonparametric log-rank test which assumed all patients were followed for a fixed length of time, that the hazard ratio was constant over time and the estimated median survival time was 12 weeks for the ASC group, with an anticipated survival time of 20 weeks for the topotecan + ASC group. The sample size calculation was based on a minimum follow-up period for all patients of 30 weeks or until death, a 5% risk of erroneously claiming superiority, and a 90% chance of successfully declaring superiority.

Due to protracted recruitment and diminishing number of centres and countries willing to participate in this study, this study was terminated early after randomising 141 patients. Because the study was terminated early, the power was reduced from the original 90%; the final analysis was to be performed when at least 125 deaths had occurred providing 80% power to successfully declare superiority of oral topotecan + ASC over ASC alone in the presence of a true underlying difference, using the same assumptions as in the original sample size calculation.

The intent-to-treat (ITT) population, comprised all randomised patients, and was the primary population for analyses of demography and efficacy.
The modified ITT population, comprised all randomised and treated patients in the topotecan/ASC group and all randomised patients in the ASC group who had at least one evaluation, and was the primary population for safety and QoL.

Kaplan-Meier estimates for survival were presented. Patients were censored for these analyses if the event in question had not occurred at the time of reporting or the patient was lost to follow-up. Overall survival was also analysed using a Cox regression model.

"Survival" was chosen for study 478 and is considered as the only acceptable primary endpoint in confirmatory studies in SCLC.

Study 396: A sample size of 300 patients (150 per treatment group) was not based on formal statistical criteria, but rather the practical limitations of feasible enrolment rates and study completion time. These provided 71% power to show that the upper limit of the 95% confidence interval (CI) for the difference in response rate (oral minus IV topotecan) between formulations excluded values larger than 10%, assuming that the response rate following second-line treatment with IV topotecan in patients with SCLC is 19%.

The ITT population comprised all randomised patients who received at least one dose of study medication (IV or oral topotecan), and was the primary population for analysis of efficacy.

An estimated percentage difference in response rate between oral and IV topotecan and a two-sided 95% CI based on normal approximation of binomial distribution were presented. As the goal was to demonstrate non-inferiority of oral to IV topotecan, the lower limit of the 95% CI was compared against the pre-specified non-inferiority limit (10%).

Study 090: Assuming response rates following second-line treatment with IV topotecan and CAV of 33% (based on previous GSK experience with IV topotecan) and 28% [Shepherd, 1987], respectively, a sample size of 200 patients was required to provide 90% probability that the lower 95% confidence limit for the difference between treatments excluded values larger than 14% (the magnitude of a clinically important difference in this population) in favour of CAV.

The ITT population comprised all randomised patients who received at least one dose of study medication (IV topotecan or CAV), and was the primary population for analysis of efficacy.

Response rates and the estimated percentage difference in response rates between treatment groups (IV topotecan and CAV) along with 95% CIs based on normal approximation of binomial distribution were presented. As the goal was to demonstrate non-inferiority of IV topotecan to CAV, the lower limit of the 95% CI was compared against the pre-specified non-inferiority limit (14%).

Total IV Topotecan Population: The ITT population for the integrated analysis comprised all randomised patients in the IV topotecan treatment group of Studies 396, 090, 065, 014EORTC, 014SB(092) and 053. Data from Study 396 using the initial cut-off date were included in this population. The similarity in design and patient populations allows pooling of the data from the six studies that

included an IV topotecan group (the Total IV topotecan population). These analyses are descriptive in nature. Kaplan-Meier plots for survival were displayed for the Total IV topotecan population by sensitivity (sensitive vs. refractive and separately, <90 days, 90-180 days, >180 days).

RESULTS

Table 4 Demographic and disease characteristics: Studies 478 and 396

	478		396	
Demographic characteristic	**Oral topotecan +ASC**	**ASC alone**	**IV topotecan**	**Oral topotecan**
Total no. of patients	71	70	151	153
Gender (M/F)	52/19	51/19	96/55	98/55
Age (yr)				
≤ 40 n (%)	1 (1)	0	3 (2)	0
41-64 n (%)	46 (65)	50 (71)	84 (56)	88 (58)
≥ 65 n (%)	24 (34)	20 (29)	64 (42)	65 (43)
Mean	60 yrs	59 yrs	62.0	63 yrs
Min-Max	37-76	43-79	35-82	41-82
Prior therapy n (%)				
Chemotherapy	71 (100)	70 (100)	151 (100)	153 (100)
Immunotherapy	0	4 (6)	1 (1)	1 (1)
Surgery	18 (25)	20 (29)	53 (35)	53 (35)
Radiotherapy	38 (54)	34 (49)	116 (76)	116 (76)
Performance status n (%)				
≤1	52 (73)	47 (67)	133 (88)	133 (87)
2	19 (27)	23 (33)	18 (12)	20 (13)
Extent of disease n (%)				
Limited	23 (32)	27 (39)	45 (30)	51 (33)
Extensive	48 (68)	43 (61)	106 (70)	102 (67)
Missing	0	0	0	0
Liver Metastases n (%)	20 (28)	14 (20)	43 (29)	44 (29)
TTP from 1st-line chemotherapy				
Median	12.0 weeks	12.9 weeks	27 weeks	25.2 weeks

Study 478

Time to Progression (TTP) from first-line therapy

The two treatment groups were similar in terms of key established prognostic factors. The median TTP from first line chemotherapy was 84 days for the oral topotecan plus ASC group and 90 days for the ASC alone group.

Only four (6%) patients in each arm had relapsed < 45 days after completing their first-line chemotherapy; of these eight patients, six had a TTP that was between 34 to 44 days.
In the ASC+ oral topotecan arm 23% of patients had a TTP of between 91 and 180 days compared to 31% in the ASC alone arm. A further 20% and 17% respectively had a TTP of > 180 days.

Study 478: TTP from first-line chemotherapy: ITT population

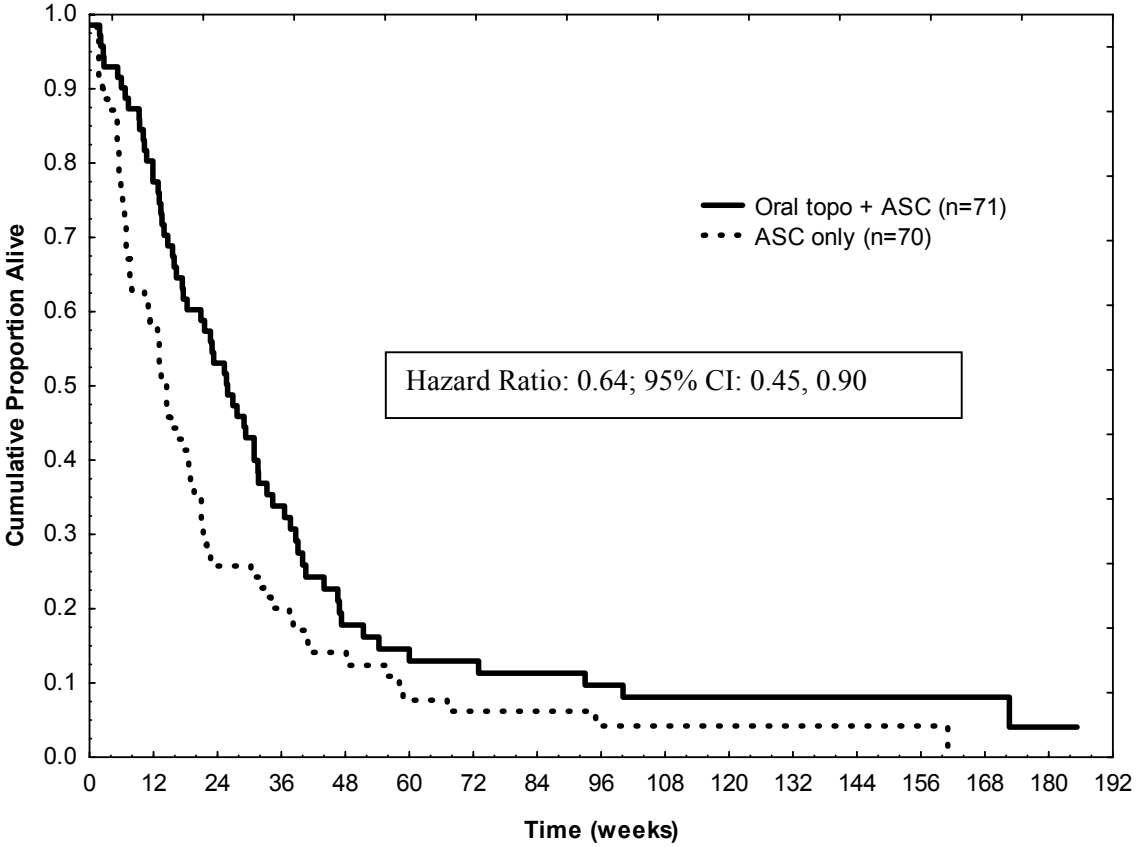
TTP From 1st-line Chemotherapy	ASC + Oral topotecan	ASC alone
	N=71	N=70
< 45 days*	6%	6%
45 – 90 days	52%	45%
91 – 180 days	23%	31%
> 180 days	20%	17%

* Actual TTP for the 8 pts < 45 days were (ASC+ Oral topo, 34, 39, 43 and 44) (ASC alone, 14, 43, 16 and 43)

Overall survival (ITT)

In the ITT Population, treatment with oral topotecan plus ASC approximately doubles the median survival time in these patients, topotecan plus ASC: 25.9 weeks (95% CI 18.3, 31.6); ASC alone: 13.9 weeks (95% CI 11.1, 18.6) (log-rank p=0.0104). The median survival of patients receiving ASC alone closely mirrors the survival described in the literature for untreated SCLC. The unadjusted hazard ratio for oral topotecan plus ASC versus ASC alone was 0.638 (95% CI: 0.45, 0.90) (Figure 1).

Figure 1 Overall Survival, Study 478: Kaplan-Meier Estimates (Intent-to-Treat (ITT) population)



The survival advantage for oral topotecan plus ASC over ASC alone is maintained in the subset analysis based on *a priori* stratification by TTP (≤ or > 60 days) from first line chemotherapy. In the subset of patients with a TTP ≤ 60 days median survival times were 23.3 weeks and 13.2 weeks for topotecan plus ASC (n=22) and ASC alone (n=20), respectively (overall survival HR: 0.499, 95% CI: 0.264, 0.942, p=0.0357). In the subset of patients with a TTP > 60 days median survival times were 27.7 weeks and 14.4 weeks for topotecan plus ASC (n=49) and ASC alone (n=50), respectively (overall survival HR: 0.696, 95% CI: 0.464 to 1.052, p=0.0975).

QoL and disease-related symptom benefits were associated with active chemotherapy (data not shown in AR).

Survival by first-line chemotherapy regimen

The Applicant performed a subgroup analysis of those patients who received CAV, platinum, etoposide or other first-line treatments in Study 478. The efficacy of topotecan in patients with relapsed, resistant SCLC was consistent irrespective of the first-line regimen.

Median survival and Hazard Ratios consistently favour Active Symptom Control (ASC) + oral topotecan; the subgroup analysis does not demonstrate any inconsistency. Although the number of patients within the respective sub-sets are small and the analysis was *ad hoc*, the data are consistent with the ITT population analysis which demonstrated clinical and statistical superiority of chemotherapy over ASC alone (p=0.0104).

Study 478: Overall survival by first-line chemotherapy regimen

First-Line Regimen	ASC + Oral topotecan	ASC alone
Platinum/etoposide followed by CAV	n=10	N=9
Median (weeks)	35.4	7.7
(95% CI)	12.9-46.9	5.1-14.4
CAV/ACE/CDE	n=17	N=17
Median (weeks)	22.7	7.7
(95% CI)	12.9-36.6	5.1-22.4
Platinum/etoposide	n=44	N=44
Median (weeks)	25.8	18
(95% CI)	17.6-33.3	13.1-21.1
Overall (Total ITT Population)	N=71	N=70
Median (weeks)	25.9	13.9
(95% CI)	18.3-31.6	11.1-18.6

Survival according to Performance Score (PS)

Median survival according to Performance Score (PS) in Study 478

Survival	ASC + OT	Treatment Group	ASC alone
ITT Population	N=71		N=70
Median Survival	25.9 weeks		13.9 weeks
95% C.I.	18.3 - 31.6		11.1 – 18.6
Log-rank p-value		0.0104	
Hazard Ratio (95% C.I.)		0.638 (0.45, 0.90)	
6 months survival n (%)	34 (49)		18 (26)
1yr survival n (%)	10 (14)		8 (11)
Performance status 0/1	n=52		n=47
Median	29.2 weeks		18.6 weeks
95% C.I.	21.6 - 38.7		13.1 – 21.4
Log-rank p-value		0.0968	
Hazard Ratio (95% C.I.)		0.704 (0.464, 1.069)	
6 months survival n (%)	28 (54)		15 (32)
1yr survival n (%)	9 (17)		7 (15)

Performance status 2	n=19		N=23
Median	20.9 weeks		7.7 weeks
95% C.I.	13.4 - 26.9		5.3 – 13.1
Log-rank p-value		0.0146	
Hazard Ratio (95% C.I.)		0.489 (0.260, 0.918)	
6 months survival n (%)	6 (32)		3 (13)
1yr survival n (%)	1 (5)		1 (4)

As would be expected, the natural course of the untreated disease is that patients with better PS have a longer survival without treatment than patients with worse PS (18.6 weeks versus 7.7 weeks, respectively).

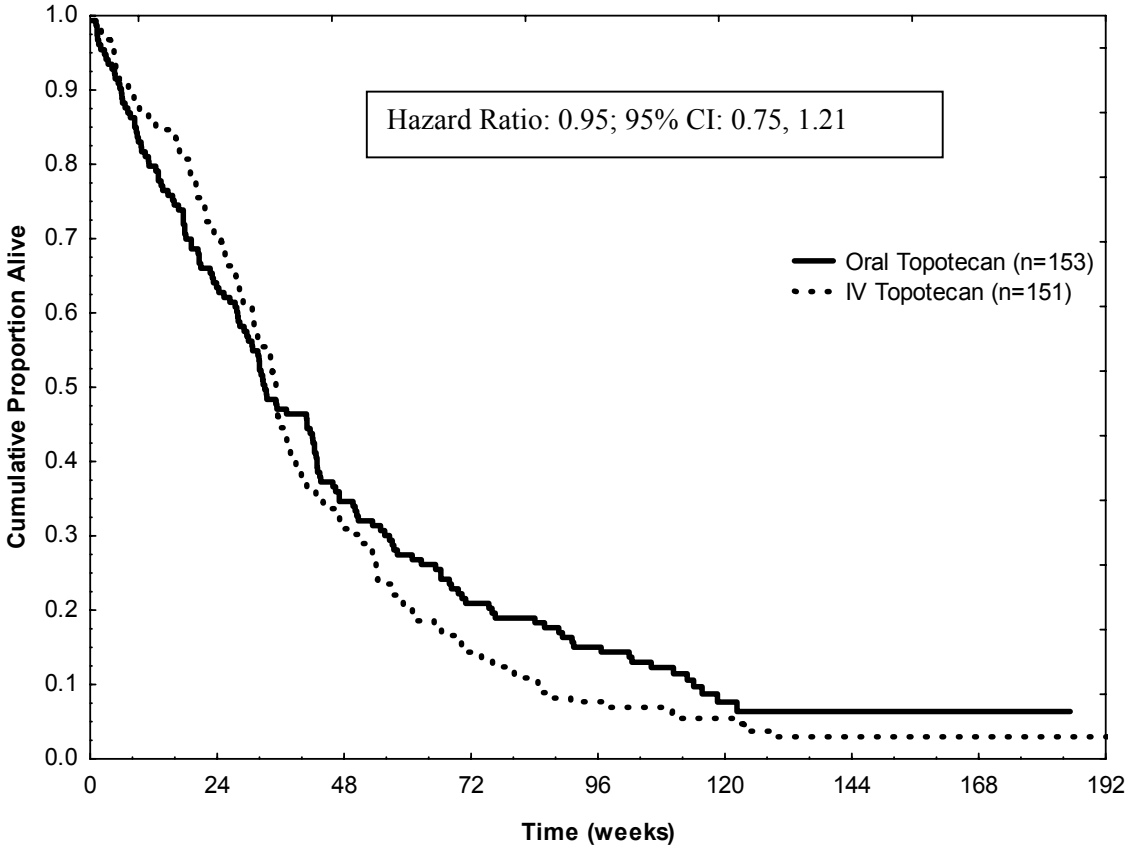
Both populations (PS 0/1 and PS 2) experience survival benefit following treatment with active chemotherapy. For patients with PS 0/1 the median survival following active chemotherapy was 29.2 weeks and for patients with PS 2, the median was 20.9 weeks. The magnitude of the survival benefit was similar in the two groups and median survival was extended by about 12 weeks.

Study 396

The two treatment groups were similar in terms of key established prognostic factors. The median TTP from first line chemotherapy was 25.2 weeks (176 days) for the oral topotecan group and 27.1 weeks (190 days) for the IV topotecan group. Thus, this is a more sensitive population than in Study 478.

Median survival times in Study 396 were 33.0 weeks (95% CI 29.1, 42.4) for oral topotecan and 35.0 weeks (95% CI 31.0, 37.1) for IV topotecan. The hazard ratio of oral topotecan relative to IV topotecan for survival was 0.95 (95% CI: 0.75, 1.21). Comparison of survival outcomes was not confounded by post-study third-line chemotherapy as a similar proportion of patients in both treatment groups received third-line therapy (chemotherapy, IV: 35.1%, oral: 32.7%).
Survival data from Study 396 is illustrated in Figure 2. Survival curves from the randomized Phase II Study 065 support these Phase III data (overlapping curves, data not shown).

Figure 2 Plot of Kaplan-Meier Estimates for Survival (Study 396, ITT Population)



The response outcomes of Studies 396 and 065 are summarised in Table 5.

Table 5 Outcomes from two randomised studies on oral versus IV topotecan in patients with relapsed sensitive SCLC (Protocols 396 and 065, ITT populations)

	Study 396		Study 065	
Response	**Oral topo N=153 n (%)**	**IV topo N=151 n (%)**	**Oral topo N=52 n (%)**	**IV topo N=54 n (%)**
Total Response (CR+PR)	28 (18.3)	33 (21.9)	12 (23.1)	8 (14.8)
95% CI	(12.2, 24.4)	(15.3, 28.5)	(11.6, 34.5)	(5.3, 24.3)
Difference (oral-IV) (95% CI) (%)	-3.6 (-12.6, 5.5)		8.26, (-6.6, 23.1)	
Stable Disease	27 (17.6)	35 (23.2)	10 (19.2)	16 (29.6)

Symptom palliation associated with IV topotecan was similar to the symptom palliation achieved with oral topotecan (see Table 6).

Table 6 **Symptom Palliation: oral topotecan versus IV topotecan: Study 396; ITT population; Mean change from baseline across courses in symptom scores**

Symptom	Treatment Group			
	Oral Topotecan	**IV Topotecan**	**Oral – IV Topotecan**	**p-value**
Nausea	-0.36 (-0.51, -0.20)	-0.37 (-0.53, -0.21)	0.01 (-0.20, 0.23)	0.89
Pain	-0.02 (-0.20, 0.17)	-0.06 (-0.25, 0.13)	0.04 (-0.22, 0.30)	0.75
Shortness of breath	0.02 (-0.15, 0.19)	0.005 (-0.18, 0.19)	0.002 (-0.23, 0.26)	0.89
Cough	0.12 (-0.05, 0.29)	0.22 (0.06, 0.37)	-0.10 (-0.33, 0.13)	0.40
Chest tightness	-0.04 (-0.20, 0.12)	0.02 (-0.14, 0.19)	-0.07 (-0.29, 0.16)	0.56
Quality of life	-0.31 (-0.51, -0.12)	-0.31 (-0.47, -0.14)	-0.009 (-0.26, 0.25)	0.94

NB: A positive change indicates improvements in score and quality of life and a negative change indicates deterioration in score and quality of life.

Results showed no substantive differences in average change from baseline between oral and IV treatment groups. There was no apparent difference between treatments in change from baseline in total FACT-L scores, TOI scores, individual well-being subscale scores, including the lung cancer scale, or scores for most individual symptoms.

Study 396 showed that no advantage is seen with either formualation of topotecan. The treatment schedules of both formulations were chosen based on MTD, and the results regarding response rate (1st end point) achieved in the 396 trial show that the activity is very similar. The point estimates favour IV treatment. Survival and QoL data from both studies are supportive.

Study 090

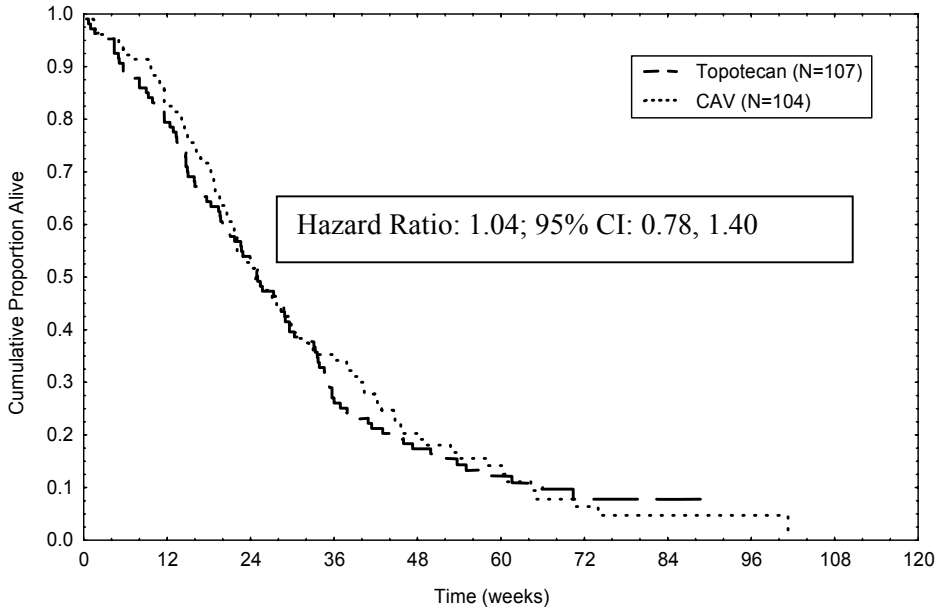
The outcome of the randomised comparison between IV topotecan and the CAV combination chemotherapy in relapsed sensitive SCLC is summarised in Table 7.

Table 7 Overall Efficacy Results (Study 090; ITT Population)

	IV Topotecan N=107	CAV N=104
Response Rate n(%)		
Complete Response	0	1 (1.0)
Partial Response	26 (24.3)	18 (17.3)
Total Response	26 (24.3)	19 (18.3)
95% CI	(16.17, 32.43)	(10.84, 25.70)
Difference (IV-CAV) (95% CI)	6.0 (-5.9, 18.0)	
Stable Disease	21 (19.6)	12 (11.5)
Time To Event Outcomes		
Time To Progression, Weeks		
Median (95% CI)	13.3 (11.4, 16.4)	12.3 (11.0, 14.1)
Min-Max	0.4-55.1	0.1-75.3
Survival, Weeks		
Median (95% CI)	25.0 (20.6, 29.6)	24.7 (21.7, 30.3)
Min-Max	0.4-90.7	1.3-101.3
Hazard Ratio (95% CI)	1.04 (0.78, 1.40)	
6 month Survival Rate[d], % (95% CI)	47.3 (37.8-56.8)	47.6 (37.9-57.4)
1 Year Survival Rate[d], % (95% CI)	15.5 (8.5-22.4)	17.9 (10.2-25.7)

Figure 3 shows the plot of Kaplan-Meier estimates for survival for the Study 090 for the ITT population. Comparison of survival outcomes was not confounded by an imbalance of post study therapy since approximately 20% of patients on both arms received post study 3rd-line chemotherapy.

Figure 3 Plot of Kaplan-Meier Estimates for Survival (Study 090, ITT Population)



Cox-regression analysis, unadjusted for prognostic factors, revealed that the hazard rate for survival in IV topotecan patients was similar to CAV patients (hazard ratio: 1.04; 95% CI: 0.78, 1.40, IV topotecan relative to CAV).

Analysis performed across trials (pooled analyses and meta-analysis)

The overall survival results by disease status (sensitive, resistant, refractory) are presented below in the pooled analysis.

The efficacy data from six studies with IV topotecan (Studies 396, 090, 065, 014EORTC, 092 and 053) are presented individually, and the integrated Total IV topotecan (SCLC) population (which included data from all six studies) are presented in Table 8.
The data for the integrated Total IV topotecan (SCLC) population by relative sensitivity to first line chemotherapy is presented in Table 9.

Table 8 Best Overall Response to Treatment (Total IV Topotecan (SCLC) Population)

	Phase III Studies		Phase II Comparative	Phase II Non-comparative			Total IV topotecan (SCLC) population[1]
	396 N=151	090 N=107	065 N=54	014EORTC N=101	014SB(092) N=119	053 N=99	N=631
Response							
Total response (CR+PR), %	21.9	24.3	14.8	17.8	7.6	9.1	16.3
Stable Disease[2], %	23.2	19.6	29.6	18.8	13.4	25.3	20.9
Survival							
Median (Weeks)	35.0	25.0	25.1	26.0	21.7	27.3	27.4
95% CI	(31.0, 37.1)	(20.6, 29.6)	(21.1, 33.0)	(20.9, 29.6)	(16.9, 28.6)	(21.4, 29.9)	(25.4, 29.6)
1-Year Rate, %	28.9	15.5	16.7	17.8	15.6	17.2	19.8

1. The sensitivity to prior chemotherapy was missing for one patient
2. If the tumour is measured objectively and WHO Response Criteria are applied rigorously, it has been shown that stabilisation of disease can be regarded as a clinical response, and so tumour regressions and stabilisations for no less than 56 days are included in this table.

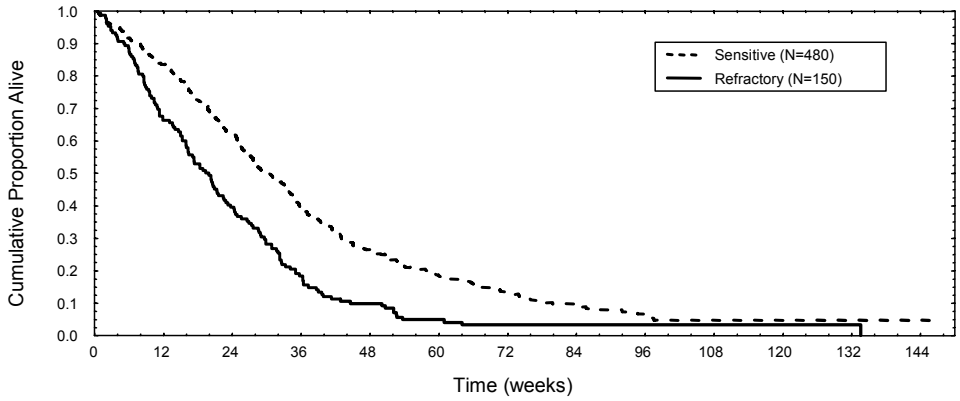
Table 9 **Best Overall Response to Treatment by Sensitivity to Prior Chemotherapy (Total IV Topotecan (SCLC) Population)**

Response	Sensitive to Prior Chemotherapy N=480	Refractory to Prior Chemotherapy N=150
Total response (CR+PR), %	20.2	4.0
95% CI	(16.6, 23.8)	(0.86, 7.14)
Stable disease, %	22.5	16.0

1. The sensitivity to prior chemotherapy was missing for one patient
2. The IV refractory population included some patients whose disease had never responded to first line therapy – a particularly poor prognostic group

Predictably, and as demonstrated in the literature on this subject, patients with sensitive SCLC had a higher response rate than patients with resistant disease. Figure 4 shows survival curves from the Total IV topotecan (SCLC) population, presented according to the pre-defined stratification factor; TFI $\leq$90 days (refractory) or TFI >90 days (sensitive).

Figure 4 **Plot of Kaplan Meier Estimates of Survival: Patients with a TFI Less than or equal to 90 or greater than 90 Days (Total IV Topotecan (SCLC) Population)**



Patients who were sensitive to prior chemotherapy achieved a median survival time of 30.3 weeks (95% CI 27.6, 33.4) compared with 19.9 weeks (95% CI 16.0, 22.6) for those who were refractory to prior chemotherapy.

A further category was introduced *post-hoc* at the request of CHMP in order to answer the question "is the therapeutic effect preserved in patients with a very long TFI?" This additional category sub-divided patients with sensitive SCLC into those with TFI 90 – 180 days or TFI >180 days. Outcomes for patients with resistant disease are also shown. These data are shown in the Kaplan – Meier plot in Figure 5 and in Table 10.

Figure 5 **Plot of Kaplan Meier Estimates of Survival: Patients with a TFI less than 90, 90 - 180 or greater than 180 Days (Total IV Topotecan (SCLC) Population)**

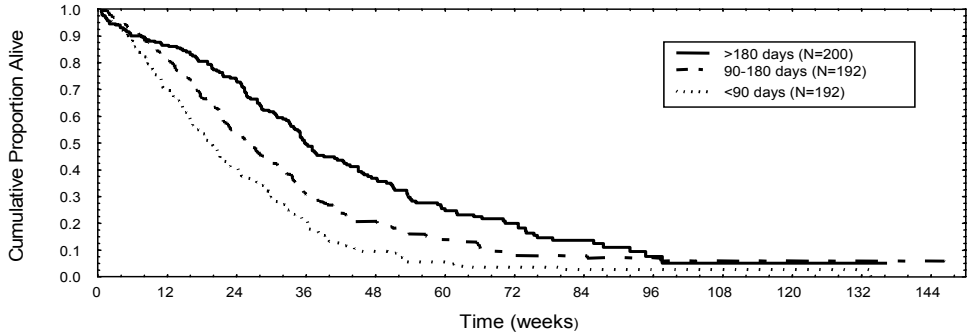


Table 10 **Overall Survival and One Year Survival Rate by Treatment-Free Interval Following First-Line Treatment (Total IV Topotecan (SCLC) Population)**

	Progression Free Interval (N = 584[a])		
Survival	**<90 days N=192**	**90-180 days N=192**	**>180 days N=200**
Overall			
Median (weeks)	19.9	25.7	35.7
(95% CI)	(16.3, 22.4)	(22.4, 29.6)	(33.3, 42.6)
One Year (%)	8.3	18.0	32.3
(95% CI)	(4.3, 12.3)	(12.3, 23.8)	(25.4, 39.3)

a 47 patients were excluded from the analysis due to a missing or invalid date of end of first line therapy

Performance Score

Total IV Topotecan (SCLC) Population: Summary of survival by PS

	Performance status 0 or 1	**Performance status >1**	**ITT Population**
	n=514	n=116	n=631
Median Survival	31 wks	16 wks	27 wks
95% C.I.	28 – 33	11.6 – 19.7	25.4 – 29.6
1 yr Survival rate	23%	8%	20%
95% C.I.	18.7 – 26.3	3.0 – 13.3	16.5 – 23.1

The overall survival according to PS is of similar range to the survival benefit seen in the topotecan-treated patients on Study 478. The survival of PS 2 patients is substantially improved compared to the expectation for the untreated patient as demonstrated by Study 478 in the patients who receive active symptom control alone.

Discussion Clinical Efficacy

Based on the results of Study 478, it is concluded that oral topotecan has a beneficial effect as compared with best supportive care/ASC in a resistant population of SCLC patients. This group had a progression free interval of at least 45 days and the patients were judged by their doctor not to be eligible for further more intensive (i.e. IV) chemotherapy. In a situation where the comparator was ASC it is most likely that the patients included in study 478 had a very poor prognosis. Today, second line chemotherapy is commonly used in patients who can tolerate such treatment.

The median survival prolongation achieved with oral topotecan of 12 weeks is considered clinically valuable. The statistical significance of the difference between the survival curves (p=0.0104) is considered as sufficient for the superiority conclusion. Taking the results in consideration together with previous results with topotecan in relapsed SCLC (study 090) it is beyond doubt that the drug is efficacious in this setting. It has also now been clearly shown for the first time in a randomised study that chemotherapy has a place second line in the treatment of SCLC, and also in the group of patients with the worst prognosis.

A separate analysis of the patients with a poor performance status (PS>1) was presented in the 478 Study report. Median (95% CI) survival was 7.7 (5.3-13.1) and 20.9 (13.4-26.9) weeks in the ASC alone and topotecan treated groups, respectively (N=42, p=0.0146). Thus, it was made plausible that those patients also benefit from topotecan therapy.

Patients who received platinum/etoposide followed by CAV as first line treatment seem to have better overall survival than other groups. However, the number of patients is too small to draw any further conclusions. Nevertheless, there is a benefit for the patient irrespectively of the previous therapy.

Study 396 is showing similarity regarding efficacy between the IV regimen proposed for use in relapsed SCLC and the oral regimen used for topotecan administration in Study 478.

The pooled data further substantiated the clinical evidence of activity of IV topotecan in relapsed SCLC with this administration form. This cannot be regarded as proof of activity by itself but in the light of historical comparison it supports a positive conclusion regarding efficacy. The outcome of the analysis by sensitivity facilitates comparisons of subsets of patients. As expected, these analyses clearly demonstrate that patients with a long TFI have a greater survival than those patients with a short TFI.

Clinical Safety

The current Summary of Product Characteristics (SPC) for Hycamtin has been maintained by regular Periodic Safety Update Reports, and the total safety database now represents a cumulative exposure in excess of 229,349 patients with SCLC, ovarian and a variety of other cancers that have been treated with topotecan since launch to November 2004.

This part of the AR will focus on safety aspects of relevance for the proposed new indication; relapsed SCLC. It is considered of relevance to make sure that:

- the safety profile for topotecan in general does not differ from that in relapsed ovarian cancer (currently approved indication);
- IV and oral topotecan do not differ in terms of safety;
- certain subpopulations of patients do not show increased toxicity (mainly impact of gender, age, disease and performance status).

Therefore, safety data from the randomised studies in SCLC, the comparisons between SCLC and ovarian cancer patients and comparisons between relevant subpopulations of SCLC patients will be referred to below.

Patient exposure

Oral topotecan was delivered at or above the planned starting dose in 87% and 92% of courses in Study 478 and Study 396 respectively (Table 11).

Table 11 Extent of Oral topotecan exposure by dose: Studies 478 and 396

Dose mg/m^2/day (range)		478 Oral topotecan +ASC Pts / Courses	396 Oral topotecan Pts / Courses
1.5	(1.5-1.8)	7/8	17/36
1.9	(1.9-2.0)	13/29	46/111
2.3	(2.2-2.3)	70/202	151/297
2.7	(2.7-2.8)	13/22	54/113
3.1	(2.95-3.1)	5/17	24/65
3.3*	(3.3-3.5)	0	2/5

* Dose higher than protocol permitted maximum

For the Total IV topotecan (SCLC) population IV topotecan was delivered at or above the planned starting dose in 76% of courses. The IV dose was escalated in 6% of courses and reduced in 24% of courses in accordance with the same dose management criteria described in each relapsed SCLC protocol (Table 12).

Table 12 Extent of IV topotecan exposure by dose: Individual SCLC Studies: Total IV topotecan (SCLC) population

IV topotecan (patients/courses)								
Dose mg/m^2/day (range)		**396**	**065**	**090**	**014 EORTC**	**014SB (092)**	**053**	**Total IV topotecan (SCLC) population**
0.5	(0.50-0.67)	0	0	0	1/2	0	0	1/2
0.75	(0.675-0.87)	0	½	2/2	1/4	0	0	4/8
1.0	(0.875-1.17)	18/45	5/10	14/31	8/18	4/4	14/49	63/157
1.25	(1.175-1.37)	50/139	20/46	31/69	20/55	22/44	44/110	187/463
1.5	**(1.375-1.67)**	**151/429**	**54/138**	**107/338**	**101/353**	**119/311**	**99/241**	**631/1810**
1.75	(1.675-1.87)	28/70	5/5	1/6	1/1	0	6/21	41/103
2.0	(1.875-2.17)	13/31	3/9	0	0	0	1/5	17/45
2.25	(2.175-2.37)	0	1/1	0	0	1/1*	0	2/2
>2.37		0	1/2	0	0	0		1/2
Total		151/714	54/213	107/446	101/433	119/360	99/426	631/2592

* Inspection of one CRF (Study 014SB) suggests a transcription error for a dose of 1.5 mg/m^2/day.

For the Total IV topotecan (SCLC) population 63% of patients received ≥ 3 courses of treatment and the median number of courses administered was 4 (range 1-22).

In the Total IV topotecan (Ovarian) population, a total of 523 patients received 2991 courses of topotecan treatment, at doses ranging from 0.5 to 2.5 mg/m^2/day. The extent of exposure by dose, is shown in Table 13. As in the Total IV topotecan (SCLC) population, the majority of courses (73%) were at the planned starting dose of 1.5 mg/m^2/day.

Table 13 Extent of IV topotecan Exposure by Dose: Total IV topotecan (Ovarian) population

	Patients/courses
Dose mg/m^2/day (range)	**Total IV topotecan (Ovarian) population**
0.5 (0.50-0.67)	0
0.75 (0.675-0.87)	3/13
1.0 (0.875-1.17)	49/158
1.25 (1.175-1.37)	137/500
1.5 (1.375-1.67)	**522/2173**
1.75 (1.675-1.87)	32/93
2.0 (1.875-2.17)	13/47
2.25 (2.175-2.37)	2/5
>2.37	½
Total	523/2991

In the Total IV topotecan (Ovarian) population, 46 patients had more than 10 courses of treatment and two received 33 courses, with a mean cumulative dose of 229 mg/m^2. Overall median dose intensity was 2.31 mg/m^2/week. This is similar to the overall median dose intensity of 2.29 mg/m^2/week achieved in the Total IV topotecan (SCLC) population. In the Total IV topotecan (Ovarian) population, the median number of courses was five and the median cumulative topotecan dose was 37.5 mg/m^2.

Adverse events

Non-haematological AEs

In the Total IV topotecan (SCLC) population, 595 (94%) patients experienced non-haematological AEs, regardless of Grade or relationship to treatment; 338 (54%) patients experienced Grade 3/4 toxicities. The numbers of patients experiencing AEs in the Total IV topotecan (Ovarian) population were similar: 517 (99%) patients experienced non-haematological AEs, regardless of Grade or relationship to treatment; 268 (51%) patients experienced Grade 3/4 toxicities.

In both populations, nausea, alopecia and vomiting were the most frequently occurring AEs followed in the Total IV topotecan (SCLC) population by asthenia, dyspnoea and fatigue and in the Total IV topotecan (Ovarian) population by diarrhoea, constipation and fatigue. It should be noted that with the exception of asthenia and dyspnoea, the incidences of each of these most frequent events were smaller in the Total IV topotecan (SCLC) population than in the Total IV topotecan (Ovarian) population. The incidences of asthenia and dyspnoea were only slightly higher in the Total IV topotecan (SCLC) population than in the Total IV topotecan (Ovarian) population, despite dyspnoea being a recognized symptom of SCLC.

In the Total IV topotecan (SCLC) population, the most frequently occurring Grade 3/4 AEs were dyspnoea, asthenia and fatigue; in the Total IV topotecan (Ovarian) population, the most frequently occurring Grade 3/4 AEs were nausea, vomiting, sepsis and abdominal pain.

Tables 14 and 15 below illustrate non-haematological toxicity with IV topotecan in relapsed SCLC and ovarian cancer, respectively.

In Study 478, the most frequent AEs in the oral topotecan plus ASC group were nausea, vomiting and diarrhoea and the most frequent Grade 3/4 toxicity was diarrhoea. The most frequent AEs in the ASC alone group were disease progression, dyspnoea and cough and the most frequent Grade 3/4 toxicity was disease progression.

In Study 396 a total of 138 patients (90.2%) in the oral topotecan group and 136 patients (90.1%) in the IV topotecan group had non-haematological AEs, of any relationship to study treatment. In general the treatments were similar with respect to the incidence of individual AEs and the most commonly occurring events in both groups were nausea, fatigue and alopecia, together with diarrhoea

in the oral treatment group and dyspnoea in the IV treatment group. These events were mainly of mild or moderate severity.

Table 14 Incidence of Non-haematological AEs (n %) by worst CTC Grade: Incidence for all cases at least 10% and for Grades 3 and 4 more than 1.5%: Total IV topotecan (SCLC) population

Preferred Term	CTC Grade				Totals* for G3 & G4	Totals** for all Grades
	1	2	3	4		(N= 631)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with AEs	500 (79)	476 (75)	286 (45)	135 (21)	338 (54)	595 (94)
Nausea	168 (27)	96 (15)	27 (4)	1 (<1)	28 (4)	294 (47)
Alopecia	99 (16)	113 (18)	7 (1)	-	7 (1)	226 (36)
Vomiting	100 (16)	70 (11)	15 (2)	1 (<1)	16 (3)	188 (30)
Asthenia	44 (7)	68 (11)	39 (6)	9 (1)	48 (8)	161 (26)
Dyspnoea	25 (4)	57 (9)	51 (8)	***22 (3)	73 (12)	155 (25)
Fatigue	48 (8)	72 (11)	29 (5)	2 (<1)	31 (5)	151 (24)
Fever	48 (8)	60 (10)	9 (1)	10 (2)	19 (3)	127 (20)
Constipation	67 (11)	53 (8)	5 (1)	0	5 (1)	125 (20)
Diarrhoea	72 (11)	41 (7)	3 (1)	6 (1)	9 (1)	124 (20)
Anorexia	50 (8)	55 (9)	13 (2)	2 (<1)	15 (2)	120 (19)
Coughing	69 (11)	39 (6)	7 (1)	1 (<1)	8 (1)	116 (18)
Headache	55 (9)	26 (4)	6 (1)	0	6 (1)	87 (14)
Chest pain	35 (6)	31 (5)	11 (2)	2 (<1)	13 (2)	79 (13)
Abdominal pain	29 (5)	30 (5)	12 (2)	4 (1)	16 (3)	75 (12)
Stomatitis	33 (5)	34 (5)	4 (1)	1 (<1)	5 (1)	75 (12)
Back pain	31 (5)	34 (5)	8 (1)	0	8 (1)	73 (12)
Epistaxis	53 (8)	9 (1)	1 (<1)	3 (1)	4 (1)	66 (11)
Pain	24 (4)	25 (4)	13 (2)	4 (1)	17 (3)	66 (11)
Pneumonia	1 (<1)	10 (2)	15 (2)	***8 (1)	23 (4)	34 (5)
Hyponatremia	7 (1)	7 (1)	7 (1)	5 (1)	12 (2)	26 (4)
Sepsis	1 (<1)	0	3 (1)	19 (3)	22 (4)	23 (4)
Convulsions	0	3 (<1)	3 (1)	7 (1)	10 (2)	13 (2)
Respiratory insufficiency	0	1 (<1)	3 (1)	7 (1)	10 (2)	11 (2)

* Totals include events of Grade 5 reported in Study 065
** Totals include events of unknown Grade and Grade 5
*** Includes one case of dyspnoea and one case of pneumonia classed as Grade 5

Table 15 Incidence of Non-haematological AEs by worst CTC Grade: Incidence for all cases at least 10% and for Grades 3 and 4 more than 1.5%: Total IV topotecan (Ovarian) population

Preferred Term	CTC Grade				Totals* for G3 & G4	Totals** for all Grades
	1	2	3	***4		(N= 523)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with AEs	478 (91)	468 (90)	226 (43)	119 (23)	268 (51)	517 (99)
Nausea	214 (41)	126 (24)	43 (8)	2 (<1)	45 (9)	386 (74)
Alopecia	87 (17)	225 (43)	8 (2)	-	8 (2)	321 (61)
Vomiting	134 (26)	113 (22)	25 (5)	11 (2)	36 (7)	284 (54)
Diarrhoea	114 (22)	65 (13)	21 (4)	7 (1)	28 (5)	208 (40)
Constipation	117 (22)	69 (13)	11 (2)	3 (1)	14 (3)	201 (38)
Fatigue	94 (18)	83 (16)	23 (4)	1 (<1)	24 (5)	201 (38)
Abdominal pain	80 (15)	61 (12)	22 (4)	***7 (1)	29 (6)	170 (33)
Fever	58 (11)	94 (18)	11 (2)	2 (<1)	13 (2)	167 (32)
Stomatitis	62 (12)	49 (9)	5 (1)	2 (<1)	7 (1)	121 (23)
Headache	67 (13)	30 (6)	7 (1)	1 (<1)	8 (2)	106 (20)
Dyspnoea	43 (8)	40 (8)	15 (3)	***5 (1)	20 (4)	105 (20)
Asthenia	35 (7)	41 (8)	12 (2)	4 (1)	16 (3)	92 (18)
Anorexia	48 (9)	36 (7)	7 (1)	0	7 (1)	91 (17)
Urinary Tract Infection	6 (1)	55 (11)	9 (2)	2 (<1)	11 (2)	72 (14)
Coughing	49 (9)	12 (2)	4 (1)	0	4 (1)	65 (12)
Pain	34 (7)	20 (4)	9 (2)	2 (<1)	11 (2)	65 (12)
Hypokalemia	37 (7)	21 (4)	3 (1)	1 (<1)	4 (1)	62 (12)
Rash	32 (6)	29 (6)	1 (<1)	0	1 (<1)	62 (12)
Back pain	31 (6)	25 (5)	3 (1)	1 (<1)	4 (1)	60 (12)
Alkaline phosphatase increased	47 (9)	11 (2)	1 (<1)	0	1 (<1)	59 (11)
Dyspepsia	40 (8)	18 (3)	0	0	0	58 (11)
Anxiety	29 (6)	22 (4)	2 (<1)	1 (<1)	3 (1)	54 (10)
Haematuria	41 (8)	10 (2)	0	***2 (<1)	2 (<1)	53 (10)
Malaise	18 (3)	20 (4)	6 (1)	2 (<1)	8 (2)	46 (9)
Infection	6 (1)	12 (2)	16 (3)	6 (1)	22 (4)	40 (8)
Intestinal Obstruction	0	15 (3)	13 (3)	11 (2)	24 (5)	39 (8)
Sepsis	1 (<1)	2 (<1)	10 (2)	***19 (4)	29 (6)	32 (6)
Bilirubinemia	2 (<1)	4 (1)	9 (2)	4 (1)	13 (2)	19 (4)
Thrombo-phlebitis deep	0	1 (<1)	10 (2)	0	10 (2)	12 (2)
Embolism Pulmonary	0	0	1 (<1)	8 (2)	9 (2)	9 (2)

* Totals include events of Grade 5
** Totals include events of unknown Grade and Grade 5
*** Includes one case of abdominal pain, two cases of dyspnoea, one case of haematuria and three cases of sepsis classed as Grade 5

Haematological AEs

For both oral and IV topotecan, the principle haematological AE was bone marrow suppression, mainly neutropenia. The overall incidence of haematological toxicities in study 396 by course (reflecting dose adjustment) and by grade is shown in Table 16.

Table 16 Number (%) of Haematological Toxicities (including Neutropenia) by course: Oral topotecan vs. IV topotecan (Study 396, ITT Population)

Haematological Toxicity	N	Worst Toxicity Grade			
		1	2	3	4
Oral Topotecan					
Leucopenia	622	141 (22.7)	185 (29.7)	144 (23.2)	43 (6.9)
Neutropenia	618	90 (14.6)	123 (19.9)	133 (21.5)	108 (17.5)
Thrombocytopenia	622	203 (32.6)	82 (13.2)	79 (12.7)	60 (9.6)
Anaemia	622	277 (44.5)	253 (40.7)	43 (6.9)	9 (1.4)
IV Topotecan					
Leucopenia	704	87 (12.4)	213 (30.3)	284 (40.3)	63 (8.9)
Neutropenia	700	52 (7.4)	106 (15.1)	264 (37.7)	211 (30.1)
Thrombocytopenia	703	295 (42.0)	107 (15.2)	81 (11.5)	46 (6.5)
Anaemia	703	273 (38.8)	331 (47.1)	68 (9.7)	4 (0.6)

n = number of courses with laboratory data

The incidences of anaemia and thrombocytopenia associated with oral and IV topotecan were similar. The incidence of Grade 3/4 neutropenia per patient was lower in patients receiving oral topotecan (73.2%) compared with IV topotecan (87.7%). However, the complications associated with neutropenia were more similar. Table 17 shows the incidence of complications per patient and per course.

Table 17 Consequences of neutropenia for Oral vs. IV topotecan - Number (%) of patients/courses with Fever, Infection or Sepsis (Study 396, ITT Population)

	Oral Topotecan		IV Topotecan	
	Patients	Courses	Patients	Courses
Consequence	**(n=153)**	**(n=627)**	**(n=151)**	**(n=714)**
Fever ≥ G 2 or FN[1]	8 (5.2)	10 (1.6)	19 (12.6)	25 (3.5)
FN*	4 (2.6)	5 (0.8)	8 (5.3)	8 (1.1)
Fever ≥ G 2 or FN[1] proximate to G 4 neutropenia	7 (4.6)	7 (1.1)	11 (7.3)	13 (1.8)
Infection ≥ G 2[2]	32 (20.9)	47 (7.5)	30 (19.9)	53 (7.4)
Infection ≥ G 2[2] proximate to G 4 neutropenia	15 (9.8)	18 (2.9)	12 (7.9)	15 (2.1)
Sepsis	4 (2.6)	4 (0.6)	5 (3.3)	5 (0.7)
Systemic antibiotic	63 (41.2)	101 (16.1)	85 (56.3)	142 (19.9)
Systemic iv antibiotic	22 (14.4)	23 (3.7)	35 (23.2)	38 (5.3)
IV antibiotic with ≥ G 2 fever/FN/infection proximate to G 4 neutropenia or sepsis	13 (8.5)	13 (2.1)	17 (11.3)	18 (2.5)

FN – febrile neutropenia; G – Grade
Proximate to G 4 neutropenia = within 2 days of G 4 neutropenia
excluding infection and sepsis
excluding sepsis

The haematological toxicities in patients with SCLC and patients with ovarian cancer are presented in Table 18.

Table 18 Haematological Toxicity by Worst CTC Grade: SCLC Compared with Ovarian Cancer (Total IV topotecan (SCLC) and (ovarian) populations)

	SCLC		Ovarian	
	Patients n (%)	**Courses n (%)**	**Patients n (%)**	**Courses n (%)**
Total patients/courses	**631**	**2592**	**523**	**2991**
Neutropenia				
Grade 1	6 (1)	161 (6)	2 (<1)	154 (5)
Grade 2	29 (5)	370 (15)	6 (1)	322 (11)
Grade 3	123 (20)	891 (35)	75 (15)	831 (28)
Grade 4	441 (72)	916 (36)	426 (82)	1224 (42)
Total	599 (97)	2338 (92)	509 (98)	2531 (86)
Patients/courses with data	617	2541	517	2933
Leucopenia				
Grade 1	18 (3)	264 (10)	7 (1)	322 (11)
Grade 2	88 (14)	709 (28)	55 (11)	792 (27)
Grade 3	318 (51)	1158 (45)	283 (55)	1235 (42)
Grade 4	187 (30)	290 (11)	171 (33)	307 (10)
Total	611 (99)	2421 (95)	516 (100)	2656 (90)
Patients/courses with data	620	2558	517	2958
Thrombocytopenia				
Grade 1	144 (23)	997 (39)	145 (28)	1171 (40)
Grade 2	117 (19)	467 (18)	109 (21)	504 (17)
Grade 3	174 (28)	412 (16)	112 (22)	407 (14)
Grade 4	157 (25)	234 (9)	124 (24)	212 (7)
Total	592 (95)	2110 (83)	490 (95)	2294 (78)
Patients/courses with data	620	2557	518	2959
Anaemia				
Grade 1	97 (16)	912 (36)	23 (4)	690 (23)
Grade 2	312 (50)	1264 (50)	276 (53)	1766 (60)
Grade 3	185 (30)	294 (12)	188 (36)	404 (14)
Grade 4	18 (3)	20 (1)	29 (6)	32 (1)
Total	612 (99)	2490 (97)	516 (100)	2892 (98)
Patients/courses with data	620	2556	518	2959

Serious adverse events and deaths

SAEs and deaths in the randomised phase III studies 478 and 396 are presented in a tabulated form (Tables 19-22).

Table 19 Incidence and Occurrence of SAEs (n %); Incidence for All Cases of at least 2%: Study 478

Preferred Term	**Oral topotecan + ASC**		**ASC alone**	
	Patients (n=70)	Occurrences	Patients (n=67)	Occurrences
	n (%)	N	n (%)	N
At least one serious AE	18 (25.7)	36	18 (26.9)	19
Disease progression	5 (7.1)	5	11 (16.4)	11
Thrombocytopenia	5 (7.1)	5	0	0
Leucopenia	3 (4.3)	3	0	0
Neutropenia	3 (4.3)	3	0	0
Pulmonary embolism	2 (2.9)	2	1 (1.5)	1
Neutropenic sepsis	2 (2.9)	2	0	0
Diarrhoea	2 (2.9)	2	0	0

Table 20 Incidence and Occurrence of SAEs (n %); Incidence for All Cases of at least 2%: Study 396

Preferred Term	Oral topotecan		IV topotecan	
	Patients (n=153)	Occurrences	Patients (n=151)	Occurrences
	n (%)	N	n (%)	N
Granulocytopenia	13 (8.5)	14	10 (6.6)	12
Thrombocytopenia	12 (7.8)	12	7 (4.6)	9
Anaemia	6 (3.9)	7	5 (3.3)	5
Febrile neutropenia	5 (3.3)	5	10 (6.6)	10
Fever	4 (2.6)	4	13 (8.6)	13
Sepsis	4 (2.6)	4	5 (3.3)	5
Dehydration	4 (2.6)	5	1 (0.7)	1
Dyspnoea	3 (2.0)	3	5 (3.3)	6
Pneumonia	3 (2.0)	3	3 (2.0)	3
Leucopenia	3 (2.0)	3	2 (1.3)	2
Therapeutic response increased*	3 (2.0)	5	1 (0.7)	2
Vomiting	3 (2.0)	4	1 (0.7)	1
Diarrhoea	3 (2.0)	3	1 (0.7)	1
Marrow depression	1 (0.7)	1	3 (2.0)	3
Asthenia	0	0	4 (2.6)	4
* Overdose of topotecan.				

Deaths due to haematological toxicity in the Total IV topotecan (SCLC) population (2.4%) are consistent with rates reported in the Total IV topotecan (ovarian) population (1.5%) and the literature for standard cytotoxic regimens in SCLC (2-5%). In Study 090, deaths due to haematological toxicity were 3.7% for IV topotecan and 1.9% for CAV. Conversely, from Study 396, the figures for IV topotecan versus oral topotecan were 1.3% and 2.6%, respectively. In study 478 deaths due to haematological toxicity on the oral topotecan plus ASC arm were 4.3% (Table 21). In Study 478, the risk of early death associated with oral topotecan was significantly lower than the risk of early death on no active therapy. The risk of death from any cause (including progressive disease) within 30 days of randomisation was 7% for oral topotecan plus ASC and 13% for ASC alone, i.e., patients with relapsed SCLC who do not receive active chemotherapy have nearly twice as great a risk of early death as patients who do receive efficacious chemotherapy.

Table 21 Reported Deaths (n %) by Cause and Time Since Randomisation: Study 478

Cause of Death	Treatment Group	
	Oral topotecan + ASC	ASC
	(N=70)	(N=67)
Death ≤30 Days Since Randomisation	**n (%)**	**n (%)**
Progressive disease	1 (1)	9 (13)
Haematological toxicity	2 (3)	0
Non-haematological toxicity	1 (1)	0
Other reasons	1 (1)	0
Total	5 (7)	9 (13)
Total Deaths	**n (%)**	**n (%)**
Progressive disease	54 (76)	66 (94)
Haematological toxicity	3 (4)	0
Non-haematological toxicity	1 (1)	0
Other reasons	5 (7)	1 (1)
Alive / Missing	8 (11)	3 (4)
Total	63 (89)	67 (96)

Table 22 Reported Deaths (n %) by Cause and Time Since Last Study Medication: Study 478 (oral group only): Study 396

Cause of Death	478	396	
	Oral topotecan	Oral topotecan	IV topotecan
	(n=70)	(n=153)	(n=151)
Death ≤30 Days Since Last Dose	**n (%)**	**n (%)**	**n (%)**
Progressive disease	4 (6)	17 (11)	14 (9)
Haematological toxicity	3 (4)	4 (3)	2 (1)
Non-haematological toxicity	1 (1)	1 (<1)	1 (<1)
Other reasons	3 (4)	2 (1)	2 (1)
Total	11 (16)	24 (16)	19 (13)
Death >30 Days Since Last Dose	**n (%)**	**n (%)**	**n (%)**
Progressive disease*	50 (71)	109 (71)	123 (82)
Other reasons	1 (1)	3 (2)	2 (1)
Alive / Missing	8 (11)	2 (1)	0
Total	51 (73)	114 (75)	125 (83)
* Includes two patients in the oral group (396.114.02006 and 396.114.04681) originally recorded as lost to follow-up less than 30 days after the last dose, but who, on further investigation, were found to have died due to progressive disease more than 30 days after the last dose of topotecan.			

Clinical laboratory evaluations

The incidence of biochemical abnormalities associated with topotecan was generally similar for the Total IV topotecan (SCLC) population and the population with ovarian cancer. In general, non-haematological abnormalities reported were more likely to be associated with the underlying malignancy than with topotecan treatment.

Safety in special populations

Sex: Although the overall incidence of AEs was no different between males and females, generally the incidences of the most frequent AEs were higher in females than in males. Overall there was no increased haematological toxicity associated with the use of topotecan in one gender relative to the other.

Age: Concerning overall incidence of AEs there were no noticeable differences between patients aged 41 to 64 years and those aged 65 years or more. Interpretation of data for the youngest age group is complicated by the small number of patients (n=16). However, the incidence of infectious events and the use of antibiotic treatment was low in the 18-40 years age group. Comparing the age groups 41-64 years and ≥ 65 years, there was a slight tendency towards an increased incidence of the consequences of neutropenia in older patients. Fever or infection ≥Grade 2 proximate to Grade 4 neutropenia were associated with increased use of intravenous antibiotics in the older patients, as was the incidence of sepsis.

Performance status: The incidences by patient of the most frequently occurring (≥15%) non-haematological AEs, regardless of causality, were generally similar for patients who had a baseline PS of 0/1 or 2/3. Differences of note were that patients with a reduced PS had a higher overall incidence of vomiting, asthenia, stomatitis, constipation and epistaxis compared to patients with a PS of 0/1. Grade 3/4 toxicities were more frequent in patients with a reduced PS; this is partly due to the higher incidence of Grade 3/4 dyspnoea in this group, which is one of the common symptoms associated with SCLC.
The proportions of patients with neutropenia, leucopenia, thrombocytopenia or anaemia (all Grades) and Grade 4 neutropenia were similar for the two groups. However, the incidence of Grade 4 thrombocytopenia and Grade 3/4 anaemia was higher in patients with a PS of 2/3 than in those with a

PS status of 0/1. In patients with a reduced PS, the incidence of infection ≥Grade 2 associated with Grade 4 neutropenia was higher than in those with a PS of 0/1 (PS 2/3: 16% of patients in 6% of courses; PS 0/1: 10% of patients in 3% of courses). Similarly, IV antibiotic use associated with infection/fever ≥Grade 2 proximate to Grade 4 neutropenia, or sepsis, was also seen in a greater proportion of patients and courses in the former group (PS 2/3: 19% of patients in 6% of courses; PS 0/1: 10% of patients in 3% of courses).
The incidence of bleeding complications in PS 0/1 patients and PS 2/3 patients was 15% and 23% of patients respectively. Likewise the number of Grade 3/4 bleeding events was higher in patients with a PS of 2/3 than for those with a PS of 0/1, 5/116 (4%) and 8/514 (2%) respectively. The five Grade 3/4 events reported for patients with a PS of 2/3 included one haemoptysis, one epistaxis, one haematemesis, one CVA and one haemorrhage rectum. Four of the five events were reported as related to treatment.
Patients with poor PS tend to have a greater severity of haematological toxicity associated with the use of topotecan than do patients with good PS. This tendency has also been observed in the Total IV topotecan (Ovarian) population and there is a warning to this effect in the current SPC. These risks must be considered in the context of a population known to have a particularly poor survival and are considered to be consistent with the risks associated with adequate management of the disease.

The incidence of clinical sequelae of severe neutropenia in patients with a baseline PS of 0/1 or 2/3 is shown by patient and course in Table 23.

Table 23 Number (%) of patients and courses with fever, infection and associated events by Performance Status at Baseline: Total IV topotecan (SCLC) population

Event	PS 0/1		PS 2/3	
	Patients (N=514) n (%)	Courses (N=2188) n (%)	Patients (N= 116) n (%)	Courses (N= 400) n (%)
Fever ≥ CTC Grade 2 or febrile neutropenia*	50 (10)	76 (4)	8 (7)	13 (3)
Infection ≥ CTC Grade 2**	121 (24)	194 (9)	37 (32)	53 (13)
Fever ≥ CTC Grade 2 or febrile neutropenia* proximate to CTC Grade 4 neutropenia	25 (5)	36 (2)	4 (3)	7 (2)
Infection ≥ CTC Grade 2** proximate to CTC Grade 4 neutropenia	50 (10)	71 (3)	19 (16)	22 (6)
Sepsis	15 (3)	17 (1)	8 (7)	9 (2)
Any Systemic Treatment Antibiotic	229 (45)	369 (17)	61 (53)	79 (20)
IV Treatment Antibiotic	95 (19)	114 (5)	35 (30)	36 (9)
IV antibiotic with infection/fever ≥ CTC Grade 2 proximate to CTC Grade 4 neutropenia or sepsis	50 (10)	57 (3)	22 (19)	23 (6)
* Excludes infection and sepsis ** Excludes sepsis; Proximate to Grade 4 neutropenia = within two days of Grade 4 neutropenia One patient with missing performance status was not included				

Study 478: Haematological toxicity by worst CTC Grade: by PS at baseline (ASC + oral topotecan arm only)

	PS 0/1		PS 2/3	
	Patients	Courses	Patients	Courses
Total patients/courses	**51**	**217**	**19**	**61**
	n (%)	**n (%)**	**n (%)**	**N (%)**
Neutropenia				
Grade 1	5 (10)	35 (17)	4 (24)	14 (25)
Grade 2	7 (14)	35 (17)	4 (24)	11 (20)
Grade 3	17 (34)	39 (18)	2 (12)	5 (9)

Grade 4	15 (30)	23 (11)	7 (41)	8 (14)
Patients/courses with data	50	213	17	56
Leucopenia				
Grade 1	6 (12)	55 (26)	2 (11)	12 (20)
Grade 2	20 (40)	53 (25)	6 (32)	15 (25)
Grade 3	12 (24)	23 (11)	5 (26)	8 (14)
Grade 4	8 (16)	8 (4)	3 (16)	3 (5)
Patients/courses with data	50	215	19	59
Thrombocytopenia				
Grade 1	14 (28)	77 (36)	5 (26)	15 (26)
Grade 2	9 (18)	19 (9)	2 (11)	4 (7)
Grade 3	16 (32)	24 (11)	5 (26)	7 (12)
Grade 4	2 (4)	2 (1)	3 (16)	3 (5)
Patients/courses with data	50	215	19	58
Anaemia				
Grade 1	12 (24)	78 (36)	4 (21)	29 (49)
Grade 2	21 (42)	74 (34)	11 (58)	24 (41)
Grade 3	7 (14)	11 (5)	3 (16)	3 (5)
Grade 4	7 (14)	26 (12)	0	0
Patients/courses with data	50	215	19	59

Patients with PS 0/1 appear to have less grade 4 neutropenia than patients with PS 2 (30% vs. 41%). The numbers are very small (seven patients with PS 2), but the trend seems to be clear. Similarly the incidences of severe anaemia and thrombocytopenia (although sub-acute and not generally dose limiting) appear to be slightly higher amongst the PS 2 patients than amongst the PS 0/1 patients.

The effect of Performance Status (PS) and also sensitivity to prior chemotherapy on the risk for early death has been examined. The number of deaths within 30 days of treatment amongst patients in the Total IV topotecan (SCLC) population with a PS of 0/1 or 2/3 at baseline are summarised in Table 24.

Table 24 Deaths within 30 days by Performance Status at Baseline: IV topotecan: Total IV topotecan (SCLC) population

	Performance status 0/1	**Performance status 2/3**
Total no. of patients*	514	116
	n (%)	**n (%)**
Number of deaths	61 (12)	36 (31)
Cause of death		
Progressive disease	40 (8)	26 (22)
Haematological toxicity	10 (2)	5 (4)
Other	11 (2)	5 (4)
* One patient's performance status was unknown		

The number of deaths within 30 days of treatment amongst patients in the Total IV topotecan (SCLC) population who were refractory or sensitive to first line chemotherapy are summarised in Table 25.

Table 25 Deaths within 30 days; Patients Refractory or Sensitive to First Line Chemotherapy: Total IV topotecan (SCLC) population

	Refractory	**Sensitive**
Total no. of patients*	150	480
	n (%)	**n (%)**
Number of deaths	34 (23)	62 (13)
Cause of death		
Progressive disease	23 (15)	42 (9)

Haematological toxicity	3 (2)	12 (3)
Other	8 (5)	8 (2)
* One patient's sensitivity to first line therapy was unknown		

Study 478: Deaths within 30 days of randomisation by cause by PS

Cause of Death	Treatment Group			
	Oral topotecan + ASC		ASC alone	
	PS 0/1	PS 2	PS 0/1	PS 2
	n=52	N=19	n=47	N=23
Death < 30 days Since Randomisation				
Progressive Disease	0	1 (5%)	2 (4%)	7 (30%)
Haematological toxicity	1 (2%)	1 (5%)	0	
Non-haematological toxicity	1 (2%)	0	0	
Other Reasons	1 (2%)	0	0	
Total	3 (6%	2 (11%)	2 (4%)	7 (30%)

Discussion Clinical Safety

The consistency between the safety profiles in patients with relapsed SCLC and ovarian cancer is acknowledged. The dose and posology have not been changed and the eligibility criteria concerning performance status and concomitant disease status are similar between the studies in SCLC and ovarian cancer. Overall, there are no new safety issues for topotecan when used in relapsed SCLC as compared with relapsed ovarian cancer. It has also been shown that there are no major differences regarding safety risks with IV topotecan as compared with oral.

The major AE associated with topotecan in relapsed SCLC was as expected bone marrow suppression. This is manageable with dose adjustments and reversible. Nevertheless, the major risk factor with topotecan treatment is the possibly lethal consequences of bone marrow depression. The overall incidence of haematological toxicity and its consequences did not increase in the elderly but to some extent in patients with poor PS.

There is a trend towards worse tolerability amongst patients of poor PS compared to patients of good PS. The difference is small and difficult to quantify. The demonstrated survival advantage fully justifies the use of IV topotecan in patients of PS 2 as well in patients of PS 0/1.

The incidence of haematological toxicity, especially neutropenia, for IV topotecan is higher when compared to oral topotecan. In Study 396, the incidence of Grade 3/4 neutropenia was 88% on the IV arm and 73% on the oral arm. However, the increased incidence of neutropenia with the IV administration as compared to oral is not translated into a higher incidence of complications such as infectious complications, sepsis and drug related mortality. The SPC includes adequate warnings in this regard.

According to the data presented above the lethal haematological toxicity of topotecan by sensitivity to 1st line chemotherapy is the same. It seems plausible that the degree of sensitivity to the initial therapy does not have an impact on the haematological toxicity. Instead, the toxicity may be related to the haematological profile, bone marrow reserve, and to hepatic/renal capacity.

The ability for a patient to tolerate cytotoxic chemotherapy does not depend on the duration of the response to first-line therapy. The Total IV Topotecan (SCLC) population has demonstrated that a patient's ability to tolerate therapy depends on a full recovery from first-line treatment, adequate bone marrow reserves, renal/hepatic function and performance status (PS) at the time of second-line therapy.

Benefit Risk

The clinical development programme for Hycamtin in relapsed SCLC is extensive and three randomised pivotal studies form the basis of evidence that enables an approval of its use in this indication:

- Study 478 shows that chemotherapy with Hycamtin is beneficial as compared to best supportive care in 2nd line treatment of SCLC that is regarded as resistant (judged by the treating physician). Since a superiority conclusion could be drawn based on a 12-week prolongation of the median overall survival, the proof of clinical benefit from treatment has been established in a randomised comparison for the first time in relapsed SCLC.

- Extrapolation from the results in resistant patients to more sensitive (in the context of having longer progression free interval) is considered justified.

- Study 090 shows that Hycamtin is as good as CAV in 2nd line treatment of patients with a disease regarded as sensitive.

- Study 396 shows that the previously approved IV regimen is similar to the oral regimen used in study 478 regarding efficacy and safety.

In patients with relapsed SCLC, whether of PS 0/1 or of PS >1 a positive benefit has been shown. Topotecan therapy substantially prolongs survival compared to no chemotherapy. The magnitude of this benefit appears to be similar in the two groups. However, there is a trend to slightly worse tolerability amongst patients of poor PS (PS 2) compared to patients of good PS (PS 0/1); but the difference is not quantifiable, the majority of patients complete therapy as planned and the overall burden of therapy is reasonable.

The overall burden of treatment complications according to PS was similar between those patients of poor PS and those of good PS, most likely a result of dose adjustment. Amongst patients of PS 2 there are more haematological and non-haematological adverse experiences, but the tolerability is still acceptable. The SPC includes appropriate warnings in this regard.

All in all, there are no new safety issues for topotecan in relapsed SCLC and the safety profile is consistent with the current SPC, reflecting its use in relapsed ovarian cancer. An EU Risk Management Plan is not considered necessary based on an approval of the application of the new indication, relapsed SCLC. No additional risk minimisation measures are required besides the amendments to the SPC and routine PSURs. The overall benefit/risk is judged as positive for the treatment of patients with relapsed SCLC not suitable for retreatment with their 1st line chemotherapy regimen.

Given the expected benefit in Quality of Life that an oral formulation would provide as compared to the IV formulation, the CHMP were of the view that an application for an oral formulation should be submitted as soon as possible for the same indication. The Applicant has informed the CHMP that they are progressing the development of an oral formulation and has committed to keep the Committee informed of the progress made within agreed timeframes.

CONCLUSION

- On 17 November 2005 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.