Australian Public Assessment Report for Trabectedin

Proprietary Product Name: Yondelis

Submission No: PM-2009-01976-3-4

Sponsor: Janssen-Cilag Pty Ltd

November 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Outcome:	Withdrawn
Date of Outcome:	24 June 2010
Active ingredient(s):	Trabectedin
Product Name(s):	Yondelis
Sponsor's Name and Address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road North Ryde NSW 2113
Dose form(s):	Powder for injection
Strength(s):	0.05 mg/ml
Container(s):	Type I colourless glass vial with a butyl stopper covered with an aluminium flip-off seal
Pack size(s):	One vial per pack
Proposed Therapeutic use:	The initial requested Indications were for the treatment of patients with relapsed ovarian cancer in combination with pegylated liposomal doxorubicin hydrochloride (PLD) and for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracycline and ifosfamide, or who are unsuited to receive these agents.
Route(s) of administration:	Intravenous injection
Dosage:	For the treatment of soft tissue sarcoma, the recommended starting dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.
	For the treatment of ovarian cancer, Yondelis is used in combination with PLD every three weeks. Yondelis is administered at a dose of 1.1 mg/m^2 as a 3-hour intravenous infusion after PLD 30 mg/m^2, as a 90-minute intravenous infusion.

Product Background

Trabectedin was originally isolated, identified and characterized from the marine tunicate *Ecteinascidia turbinate*. A synthetic route was developed for the commercial process.

Trabectedin belongs to a new cytotoxic class of agents having a unique, complex, and transcription-targeted mechanism of action. Trabectedin binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle. Trabectedin has been shown to exert antiproliferative *in vitro* and *in vivo* activity against a range of human tumour cell lines and experimental tumours, including malignancies such as ovarian cancer, sarcoma, melanoma, breast and non-small cell lung cancer.

The requested indications as stated in the proposed Australian Product Information (PI) are:

1. Yondelis in combination with pegylated liposomal doxorubicin hydrochloride (PLD) is indicated for the treatment of patients with relapsed ovarian cancer.

The proposed treatment with trabectedin is in combination with a pegylated liposomal formulation of doxorubicin hydrochloride, marketed in Australia and other countries as Caelyx, and in the USA, Israel and Japan as Doxil. The formulation contains doxorubicin encapsulated in liposomes having surface-bound methoxypolyethylene glycol groups (pegylated liposomes). This process is known as pegylation and protects the liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time. Doxil/Caelyx is administered by IV injection. It is registered in Australia for the treatment of metastatic breast cancer, of advanced epithelial ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen, AIDS-related Kaposi's sarcoma (KS), and in combination with bortezomib for the treatment of progressive multiple myeloma in a defined patient group.

2. Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracycline and ifosfamide, or who are unsuited to receive these agents.

Regulatory Status

Trabectedin was jointly developed by Pharma Mar S.A. and Johnson & Johnson Pharmaceutical Research & Development, and designated by the European Commission as an Orphan Medicinal Product for the treatment of soft tissue sarcoma and ovarian cancer on May 2001 and October 2003, respectively. Trabectedin was designated by the United States Food and Drug Administration (FDA) as an Orphan Medicinal Product for the treatment of ovarian cancer in March 2005. The TGA gave the application an evaluation priority in May 2009.

Relapsed Ovarian Cancer

Trabectedin was approved in the European Union (EU) on 28 October 2009 for "Patients restricted to platinum sensitive relapsed ovarian cancer". Applications are under review in Canada and Switzerland.

Advanced or Metastatic Soft Tissue Sarcoma (STS)

Trabectedin was approved in the European Union (EU) on 17 September 2007 and in Switzerland on 4 February 2009.

II.   *Quality Findings*

Drug Substance (active ingredient)

In this submission Janssen-Cilag Pty Ltd sought to register trabectedin, a new chemical entity, for use in the treatment of ovarian cancer (in combination with pegylated liposomal doxorubicin hydrochloride).

Trabectedin was originally isolated from a marine tunicate; the drug used is semisynthetic.
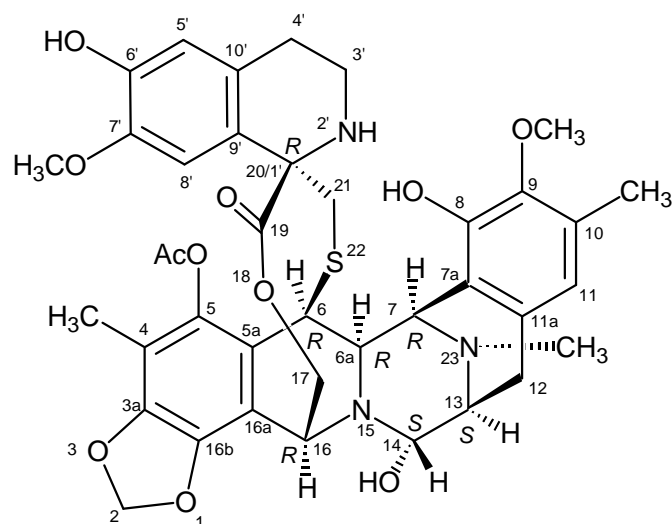
trabectedin

The drug has multiple chiral centres and the pure enantiomer is used. Solubility in water is low (0.01 mg/mL), but higher in acid (up to 1.1 mg/mL) and sufficient to allow administration in aqueous solution. The pKa values are 3, 4.5, 7 and 10.5. The octanol/water partition coefficient has been estimated as log P 1.4 (that is, partitions to octanol). Impurity levels are fairly low (total limited to <1.0%; batches about 0.2%).

Drug Product

The drug product is a lyophilized powder. Each Yondelis vial contains 1 mg of trabectedin with sucrose and a phosphate buffer; there is no overfill. The powder is reconstituted with 20 mL of Water for Injections, then diluted with 500 mL of either glucose or saline for administration by infusion over 3 hours. Some clinical trials used a mannitol, rather than sucrose, based formulation.

The injection is sterilised by filtration. The vials are stoppered and the specifications for a silicone oil lubricant were confirmed. Observed impurity levels are now fairly low (total about 0.6%); proposed limits are wider based largely on early batches (consistent with batches used in toxicology studies). The proposed sucrose formulation is markedly more stable than other formulations; it is stored in a refrigerator. The diluted solutions are compatible with infusion solution bags and lines.

Bioavailability

Yondelis is only intended for intravenous administration. Pharmacokinetic data for the injection were not been reviewed by the quality evaluator.

Advisory Committee Consideration

This application was considered at the 131st meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) on 29 March 2010. The committee made some recommendations for amendments to the PI and queried why dosing recommendations were based on body surface area.

Quality Summary and Conclusions

Some labelling and Product Information issues required finalisation. Otherwise registration was recommended with respect to quality aspects.

III. *Nonclinical Findings*

Introduction

The nonclinical submission was generally adequate, although only limited primary pharmacology studies were conducted by the sponsor and supplemented by literature publications. The repeat-dose toxicity studies suffered from some shortcomings, as detailed under *General toxicity*.

Pharmacology

Primary pharmacodynamics

Trabectedin appears to have a unique mechanism of action, related to the way in which it binds to DNA, and as may be expected it was active *in vitro* against some cell lines that were resistant to other drugs. Additionally, it was frequently shown to increase activity in drug combinations compared to the single agents alone. Submitted studies (sponsor-conducted and from the literature) demonstrated the potent concentration-dependent *in vitro* cytotoxic effects of trabectedin against a range of tumour cell types. However, it was not clearly evident that those indicated for the current application (ovarian carcinomas and soft tissue sarcomas) were much more sensitive than other tumour types. As with other antineoplastic drugs, cell lines could be selected for resistance to trabectedin, and this was associated with over-expression of P-glycoprotein in one study (Erba *et al*., 2000), but not in another study (Shao *et al*., 2003).[1,2]

In the limited studies by the sponsor, the median inhibitory concentration (IC_{50}) values were down to the low nM range (1-10 nM) against some ovarian and soft tissue sarcoma cell types under appropriate experimental conditions, a range that was similar to the expected clinical maximal plasma concentration (C_{max}) values of about 1.6 and 10.4 nM, respectively after 24 hour and 3 hour infusions. However, results were variable and values were well above this range for others; a fibrosarcoma cell line (SW684) was particularly unresponsive. IC_{50} values in the above range or even lower, were reported in the literature, for example 0.23 nM for Ewing's sarcoma cell line TC-71 (Scotlandi *et al*., 2002), 3.7 nM for ovarian carcinoma cell line IA9 (Marchini *et al*., 2005), 1.0 nM in a rhabdosarcoma cell line TE-671 (Meco *et al*., 2003) and values ranging from 0.1-9 nM in 16 of 20 sarcoma cell lines (Moneo *et al*., 2007) and from 0.0002-0.3 nM in 8 soft tissue sarcoma cell lines (Li *et al*., 2001).[3,4,5,6,7] However, with the exception of the study by Marchini *et al*. (2005), in which cells were treated only for one hour, cell exposures to drug were prolonged (4-5 days), and as may be expected cytotoxic effects increased with increasing duration of exposure. Additionally, cytotoxic effects increased after some delay following initial exposure, suggesting that the full effects of trabectedin may take some time to take place.

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[1] Erba E, Bergamaschi D, Bassanol L et al. Isolation and characterization of an IGROV-1 human ovarian cancer cell line made resistant to Ecteinascidin-743 (ET-743). Brit. J. Cancer 2000*;* 82: 1732-1739.

[2] Shao L, Kasanov J, Hornicek FJ, Morii T, Fondren G, Weissbach L. Ecteinascidin-743 drug resistance in sarcoma cells: transcriptional and cellular alterations. Biochem Pharmacol 2003*;* 66: 2381-2395.

[3] Scotlandi K, Perdichizzi S, Manara MC et al. Effectiveness of Ecteinascidin-743 against drug-sensitive and –resistant bone tumour cells. Clin Cancer Res 2002; 8: 3893-3903.

[4] Marchini S, Marrazzo E, Bonomi R et al. Molecular characterisation of two human cancer cell lines selected *in vitro* for their chemotherapeutic drug resistance to ET-743. Eur. J. Cancer 2005; 41: 323-333.

[5] Meco D, Colombo T, Ubezio P et al. Effective combination of ET 743 and doxorubicin in sarcoma: preclinical studies. Cancer Chemother Pharmacol 2003; 52: 131-138.

[6] Moneo V, Serelde BG, Fominaya J et al. Extreme sensitivity to Yondelis® (Trabectedin, ET-743) in low passaged sarcoma cell lines correlates with mutated p53. J Cell Biochem 2007; 100: 339–348.

[7] Li WW, Takahashi N, Jhanwar S et al. Sensitivity of soft tissue sarcoma cell lines to chemotherapeutic agents: identification of Ecteinascidin-743 as a potent cytotoxic agent. Clin Cancer Res 2001; 7: 2908-2911.

Comparisons with other antineoplastic agents *in vitro* suggested that trabectedin was more potent (at least as judged by IC_{50} values), but these are not particularly meaningful, given differences in toxicity between antineoplastic drugs. Possibly the most appropriate study was that by Izbicka *et al*. (1998) in which drugs were compared at concentrations selected on the basis of apparently achievable concentrations in patients, with some evidence for higher responses with trabectedin than six other drugs.[8]

A tissue distribution study in nude mice indicated that trabectedin and/or its metabolites was localised in a transplanted mammary tumour to a similar extent as in normal mammary tissue. There were, however, few submitted studies on the *in vivo* activity of trabectedin, and the one conducted by the sponsor did not use the intended intravenous (IV) route, with intraperitoneal (IP) administration being shown to be active only against IP but not subcutaneous (SC) xenografts. Submitted literature studies did use a more appropriate model (IV administration and SC xenografts), with human ovarian carcinomas being shown to be susceptible with the treatment schedules used (Valoti et al., 1998; Hendricks et al., 1999: some authors in common).[9,10] An acceptable efficacy was achieved with a cisplatin-sensitive cell line at 100 µg/kg (about the maximum tolerated dose) given on a q4dx3 schedule (3 times at 4 day intervals), but 200 µg/kg was both highly efficacious and toxic, eliciting 1/6 deaths. With a cell line only marginally sensitive to cisplatin, acceptable efficacy was achieved only with 200 µg/kg. Intermittent dosing schedules were generally found to be more effective than fractionated daily dose schedules. Thus, higher doses given less frequently were more effective than repeated injections at lower doses.

A few submitted studies (*in vitro* and *in vivo*) investigated the combination of trabectedin with other anticancer drugs, including doxorubicin which is intended to be used in combination with trabectedin for the treatment of relapsed ovarian cancer. *In vitro* data for this combination were variable, with instances of additivity, synergy and less than additivity, depending on experimental conditions (cell line, concentrations tested, sequence of administration of the two drugs, etc). Similarly, results of an *in vivo* study also varied depending of the experimental conditions (cell lines, sequence of administration of the two drugs, etc), but in some cell lines there was evidence of a beneficial effect of combining the two drugs.

Safety and secondary pharmacology

Safety pharmacology studies were generally adequate, with no findings of concern, although effects on gastrointestinal (GI)-tract and renal function were not examined. It would have been desirable, however, to have investigated the latter in view of the (apparently secondary) renal lesions seen in the cynomolgus monkey (see *General Toxicity*). Although IV doses were low relative to those proposed for humans, they were considered to be appropriate. The highest dose used in the rat central nervous system (CNS)/behavioural test (50 µg/kg) is about the maximum tolerated dose (MTD) in the Sprague-Dawley (SD) strain used, although it corresponds to only 0.2 times the human dose on a body surface area basis (0.3 vs 1.5 mg/m^2). The dose tested in the anaesthetised cynomolgus monkey cardiovascular/respiratory study (90 µg/kg = 1.1 mg/m^2 infused over 1 hour) is only slightly lower than a lethal dose in a range-finding single dose toxicity study (116.6 µg/kg; although this was given by bolus injection). This infusion achieved a plasma trabectedin concentration at least up to 10.6 ng/mL (about 14 nM), with no consistent effect of treatment other than tendencies for slightly lower blood pressures. Potassium currents in cells expressing the

[8] Izbicka E, Lawrence R, Raymond E et al. *In vitro* antitumour activity of the novel marine agent, Ecteinascidin-743 (ET-743, NSC-648766) against human tumours explanted from patients. Annals of Oncol 1998; 9: 981-987.

[9] Hendriks HR, Friebig HH, Giavazzi R, Langdon SP, Jimeno JM, Faircloth GT. High antitumour activity of ET473 against human tumour xenografts from melanoma, non-small-cell lung and ovarian cancer. Annals of Oncol 1999; 10: 1233-1240.

[10] Valoti G, Nicoletti MI, Pellegrino A et al. Ecteinascidin-743, a new marine natural product with potent antitumour activity on human ovarian carcinoma xenografts. Clin Cancer Res 1998; 4: 1977-1983.

HERG gene were unaffected by concentrations up to 1 µM *in vitro*, which is well above the expected clinical C_{max} and, additionally, experiments were conducted in protein free medium while trabectedin (and possibly its metabolites) is highly plasma protein bound.

In view of hepatotoxicity which was a feature of the rat toxicity studies (see *General toxicity*), and which occurs in humans, it is noteworthy that human hepatocytes showed greater sensitivity to trabectedin than concurrently tested human sarcoma cell lines following a 24 hour exposure *in vitro*. IC_{50} values for 3 human hepatocyte samples varied widely (1.7, 30.2 and 81.3 nM), as did those for the 2 human sarcoma cell lines investigated (2715 and 357 nM). *In vitro* data similarly showed little or no margin of safety for haematopoietic progenitors and were predictive of myelotoxicity in patients. An IC_{50} value of only 15 nM was obtained with a 1 hour pulse exposure of human CFU-GM to trabectedin followed by 7-14 days in culture (study not referenced). Although tumour cells were not tested concurrently in this study, human tumour cells similarly treated in the CTRC Research Foundation study appeared less sensitive to trabectedin than CFU-GM (13-16% of tumour samples showed ≤50% survival at 10-100 nM). Similarly, a lower IC_{70} value was obtained with human haematopoietic progenitors from cord blood than for most (1 hour treatment) or about half (24 hours treatment) of the human tumour cell lines tested, in a published study (Ghielmini *et al*., 1998).[11]

Pharmacokinetics and relative drug exposures

Plasma trabectedin clearance values were relatively high in rats (about 6-12 L/h/kg) and cynomolgus monkeys (1.4-3.1 L/h/kg) after IV 3 or 24 hour infusion of doses of 50-100 µg/kg, compared with human values of about 0.6-0.7 L/h/kg for a 70 kg person. Infusion administration was not conducted in mice, but corresponding values were high and variable after bolus injection of 200 µg/kg in 2 studies (2.4 and 10.7 L/h/kg), although there were no clearance data for the strain (MF1) used in the limited toxicity studies in this species.

As shown in Table 1, toxicokinetic data for the repeated-dose toxicity studies were incomplete, and where available they showed (with one exception) systemic drug exposures (area under the plasma concentration time curve [AUC]) below that expected in humans.

There were also no toxicokinetic data for early studies (1995/1996) conducted in mice, rats and dogs, with 5 consecutive days of treatment, or for embryofetal toxicity studies in rabbits and rats with daily administration. The high dose used in the latter study (2.5 µg/kg/day x 12 days = 30 µg/kg in total) would have resulted in a cumulative drug exposure well below the human value, based on data for the rat in the above table.

In vitro plasma protein binding data at a concentration (100 ng/mL) that was high relative to C_{max} values achieved in the toxicity studies revealed some species differences, with higher free drug in the rat, cynomolgus monkey and especially rabbit than in the human. However, in view of the known or presumed extensive circulating metabolites (below), adjustment of drug exposure ratios for free drug would not be appropriate. *In vitro* assays with mammalian cells transfected with MDR1 genes and an *in vivo* study in P-gp knockout mice indicated that trabectedin is a substrate of P-glycoprotein (P-gp). P-gp knockout mice dosed with radio-labelled trabectedin had significantly higher total radioactivity levels in the brain (by 13 fold) and testis (by 2 fold) than the wild-type controls. Greater hepatotoxicity was observed in P-gp knockout mice than in the wild type counterparts. Pharmacokinetics, tissue distribution and toxicity of trabectedin may be altered in patients coadministered with a P-gp inhibitor or inducer.

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[11] Ghielmini M, Colli E, Erba E et al. *In vitro* schedule dependency of myelotoxicity and cytotoxicity of ecteinascidin743 (ET-743). Annals Oncol 1998; 9: 989-993.

Table 1: Toxicokinetic data in repeated-dose toxicity studies

Species	Treatment cycles (TC)	Dose (µg/kg) and infusion time	$AUC_{0-\infty}$ (ng.h/mL)[†]	C_{max} (ng/mL)[†]	AUC exposure ratio (ER)[&]
Mouse (MF1)	1-3x at 3 wk intervals	20, 100 (bolus)	-	13.8, 135[#]	-
Rat (female Fischer 344)	3x (5 days)* at 3 wk intervals	2.5, 5, 10 (bolus)	-	-	-
Rat (SD)	3x at 3 wk intervals	2.5(f), 10, 25, 50, 75 (m) (all 3 h)	-, 0.7, 2.2, 8 (all TC3), 6 (TC1)	-, 0.3, 1.1, 1.6, 2.0	-, <0.1, <0.1, 0.1, 0.1
Cyno. monkey	4x at 3 wk intervals	25, 50, 75 (all 3 h)	9.3, 25.4, 28.6	0.8, 4.8, 2.9	0.1, 0.4, 0.4, 0.8
		75 (24 h)	51.6 (all TC1)	1.4	
		120, 75, 100 (all 3 h)	84.0, 34.2, -	5.0, 4.4, 5.6	1.3, 0.5, -, 0.6
		100 (24 h)$	40.1 (all TC4)	1.0	
Cyno. monkey	3x (monthly)§	10, 20, 30 (all 3 h)	3.8, 10.8, 15.9 (all TC3)	0.5, 1.1, 2.6	<0.1, 0.2, 0.2
		70[††] (3 h)	38.1 (TC4)	5.1	0.6
Cyno. monkey	4x at 3 wk intervals	25, 50, 70 (all 24 h)	-	-	-
Cyno. monkey	4-8x at 3 wk intervals	25, 35, 50, 65 (all 3 h)	12.6, 13.1, 24.1, 30.2 (all TC1)	1.9, 2.2, 3.4, 4.5	0.2, 0.2, 0.4, 0.5

[†] includes some values for only one sex and $AUC_{0-168\,h}$
[&] $AUC_{0-\infty}$ relative to a human value of 65 ng.h/mL with a dose of 1.5 mg/m^2
[#] 0 min (immediately post-dosing) *serum* concentrations in males, from a separate pharmacokinetic study
* each TC comprised 5 consecutive days of treatment, [$] ↑ doses for the last TC
[§] each TC comprised 3 treatments at weekly intervals followed by one week recovery
[††] 4 treatments at 3 week intervals, - = no data
Cyno.: cynomolgus

Metabolites

There were few *in vivo* metabolism data, but trabectedin was extensively metabolised in rats as shown by a very low plasma drug/radioactivity AUC ratio and low biliary excretion of parent drug compared with radioactivity after [14C]trabectedin administration. Low plasma drug/radioactivity ratios were also seen in mice (FVB strain), and humans in which parent drug represented <1% of recovered radioactivity and identified metabolites (ET-729, an N-demethylated derivative, and ET-731, an N-demethylated-14-dehydroxylated metabolite) and known degradants (ET-745, a 14-dehydroxylated derivative, and ET-759A, a carbonyl derivative) were present in excreta. The sponsor's *Clinical Summary* notes, however, that most human metabolites have not been identified, due in part to low concentrations, low faecal extraction recoveries and complex metabolite profile, and this would also apply to the experimental species. ET-729 is pharmacologically active and more toxic than trabectedin in rats. *In vitro* experiments with liver microsomal preparations and 12,000 g supernatants showed that ET-729 was generated by all species examined (mouse, rat, rabbit, dog, cynomolgus monkey, human), but it was below the level of quantification (LOQ) (0.1 ng/mL) in human plasma (sponsor's *Clinical Summary*). The N-demethylated derivative, ET-729, and oxidative product, ET-759A, were also identified in rat bile, but there were no *in vivo* data for other species other than the finding of ET-729 in mouse plasma after trabectedin administration. This may have been generated from trabectedin but it was an impurity (0.2%) in the drug batch used which complicated interpretation of the results. Additionally, similar metabolite profiles were seen in human and cynomolgus monkey samples *in vitro*, and in particular both contained a composite

human metabolite (designated 16), not seen in the other species. This suggests that the cynomolgus monkey is probably the most appropriate species for toxicity testing, but proper inter-species comparisons of systemic metabolite exposures were precluded by the paucity of *in vivo* data.

Cytochrome P450 (CYP) 3A4 was the main CYP enzyme involved in *in vitro* metabolism at a clinically relevant trabectedin concentration (13 nM), although other CYP enzymes were also involved in the metabolism of trabectedin at high concentrations *in vitro*. Trabectedin at up to 50 nM had little effect on the activity of different CYP isoforms. The effects of CYP inhibitors or inducers on trabectedin metabolism were not studied in animal species. A published *in vitro* study with the Hep G2 cell line showed increased cytotoxicity of trabectedin by co-incubation with 3A4, 2E1, 2C9 and 2C19, suggesting pharmacokinetic interactions with CYP inhibitors in patients (Brandon *et al.* 2005).[12]

Toxicology

General toxicity

High doses used in the repeated-dose toxicity studies did not achieve high systemic drug exposures, as tabulated above, but were generally limited by toxicity, which is not unusual for cytotoxic anti-cancer agents. Toxicity was most obviously evident as premature deaths (died or killed moribund), often resulting in small numbers of survivors and/or amended study plans and doses, for example in the longest duration cynomolgus monkey study where the number of doses had to be reduced due to mortalities and an additional group was added. The exception was the mouse (MF1) for which three single treatments of 100 µg/kg at 3 week intervals was relatively well tolerated, in contrast to the main species used (rat, cynomolgus monkey). The major tissue toxicities in these main species variably affected the liver/bile duct (with elevated plasma bilirubin, bile acids and aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase activities), bone marrow (usually with associated leukopenia and anaemia, often severe), lymphoid tissues (lymphoid depletion) and sometimes the GI-tract. It was noticeable that female rats were more sensitive to trabectedin than males, for example in terms of mortality and elevated transaminases, a difference also apparent in single-dose studies. Although not entirely clear, this may reflect differences in hepatic metabolism and biliary excretion, with lower biliary and faecal recovery of drug-related material in females being seen in excretion studies. Additionally, a higher biliary recovery of the active metabolite ET-729 was reported for female rats (1.05% of a 250 µg/kg dose vs 0.19% for males, probably over 120 minutes) in a published study (Reid *et al.*, 2002).[13]

GI-tract lesions are commonly observed with anti-cancer cytotoxic agents, and findings (often in premature deaths) included ileum, caecum and colon crypt cell necrosis/epithelial dysplasia, stomach single cell necrosis, duodenal/stomach ulcerations/erosions, necrotic typhlitis and widespread GI-tract inflammation/haemorrhage. However, the latter (in cynomolgus monkeys) was associated with bacterial colonisation, indicative of immunosuppression, and this may also have been the cause of typhlitis in a different study in the same species. GI-tract changes were also noted in the rat single-dose toxicity studies, that is, colon glandular dilation, epithelial hyperplasia and inflammation, or stomach ulceration and widespread epithelial atrophy (stomach, small intestine, caecum, colon), as well as in mice.

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[12] Brandon EFA, Meijerman I, Klijn JS et al. *In vitro* cytotoxicty of ET-743 (trabectedin, Yondelis), a marine anti-cancer drug, in the Hep G2 cell line: influence of Cytochrome P450 and phase II inhibition, and Cytochrome P450 induction. Anticancer Drugs 2005; 16: 935-943.

[13] Reid JM, Kuffel MJ, Ruben SL et al. Rat and human liver cytochrome P-450 isoform metabolism of Ecteinascidin 743 does not predict gender-dependent toxicity in humans. Clin Cancer Res 2002; 8: 2952-2962.

Myelosuppression is an expected effect of cytotoxic agents, and was a consistent finding in the single- and repeated-dose toxicity studies, although related instances of infection were not common, and were restricted to the case in monkeys noted above, in which bacterial colonies were disseminated widely. The intended patient population will be treated concurrently (ovarian cancer) or will most likely have been previously treated (soft tissue sarcoma) with doxorubicin, which itself is myelosuppressive and associated with leukopenia (Adriamycin product information). In this context, there were no full toxicity studies of trabectedin in combination with or after other drugs, including corticosteroids (see below) or doxorubicin. Neutropenia and thrombocytopenia commonly occurred during the clinical trials (sponsor's *Clinical Overview*).

Hepatotoxicity was mainly evident in rats, with lesions variably including focal/multi-focal necrosis, single cell necrosis, apoptosis, increased hepatocytic mitosis, cytomegaly and portal fibrosis, together with bile duct cell necrosis, hyperplasia and proliferation or peribiliary fibrosis. It is noteworthy in this context that recovery of drug-related material was primarily from the faeces in rats as in humans, and substantial biliary excretion was shown to occur in rats. There were no excretion data for cynomolgus monkeys but presumably this also applies to this species, and the reason for such a species difference for liver toxicity is not clear. Potential hepatobiliary toxicity is a known side effect of trabectedin treatment in humans, with the proposed product information noting that hyperbilirubinaemia and transient elevations in ALT, AST and alkaline phosphatase have been observed. In contrast to the toxicity studies, clinical treatment is intended to include corticosteroid premedication (proposed PI) which appeared to decrease the frequency and severity of transaminase elevations (sponsor's *Clinical Overview*). Dexamethasone has been reported to show hepatoprotective effects in rat hepatocytes *in vitro*, for example a 1 µM concentration reduced lactate dehydrogenase (LDH) release elicited by 50-100 nM trabectedin by about 70% in a 24 hour assay (Lee *et al*., 2008).[14] Additionally, hepatotoxicity (elevated alkaline phosphatase, AST and bilirubin, haemorrhagic hepatocytic necrosis, bile duct cell degeneration/hyperplasia) elicited by 40 µg/kg trabectedin in female Wistar rats was attenuated by pre-treatment with 5-20 mg/kg oral (PO) dexamethasone (Donald *et al*., 2003).[15] Importantly it was shown that dexamethasone did not influence the antitumour activity of trabectedin.

Although there were few indications of hepatotoxicity in the repeated-dose cynomolgus monkey studies (elevated alkaline phosphatase was seen in one study), liver weights tended to be increased and hepatocytic hypertrophy was a finding in another study. Increased transaminases were seen in a limited scope single-dose study (n=1 or 2 females/dose), and hepatocytic necrosis was also noted, although only in a premature death, with a relatively high dose of 116.6 µg/kg. Signs of hepatotoxicity were also noted in mice and especially the dog, although the latter species was used only for five consecutive day treatment regimens.

There were no indications of renal toxicity in rats (or mice and dogs), but this was a consistent finding in the cynomolgus monkey studies, and changes were sometimes graded as marked or severe although plasma urea and creatinine were generally unaffected. Findings, generally unilateral, included renal tubular dilated/flattened epithelia, basophilia or degeneration/necrosis and interstitial or peritubular fibrosis, and showed involvement of the ipsilateral ureter and urinary bladder in one study. These were considered by the report authors in two studies to be secondary to

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[14] Lee JK., Leslie EM, Zamek-Gliszczynski MJ, Brouwer KLR. Modulation of trabectedin (ET-743) hepatobiliary disposition by multidrug resistance-associated proteins (Mrps) may prevent hepatotoxicity. Toxicol Appl Pharmacol 2008; 228: 17-23.

[15] Donald S, Verschoyle RD, Greaves P et al. Complete protection by high-dose dexamethasone against hepatotoxicity of the novel antitumour drug Yondelis (ET-743) in the rat. Cancer Res 2003; 63: 5902-5908.

often pronounced thrombotic, inflammatory and necrotic reactions at the infusion site (generally the femoral vein). However, the attribution of renal toxicity to injection site reactions was uncertain, and a potential for direct nephrotoxicity cannot be excluded and the proposed PI includes a note to this effect. Infusion site reactions, often marked, also occurred in the rat study without significant renal toxicity.

Other toxicities of unknown significance included occasional pancreatic findings (degranulation, zymogen accumulation, single cell necrosis) and retinal oedema. The latter was noted at ophthalmic examination only in one cynomolgus monkey study with a single male and female being affected (respectively treated with 25 and 35 µg/kg/infusion), but there were no corresponding histological findings. The ophthalmologist noted that this may possibly represent a sign of retinal toxicity, but there were no further details as to its nature or distribution other than it was focal. Unfortunately, interpretation of the results of this study was not straightforward because of high mortalities and a resulting amended study plan with different groups receiving different treatment durations. Consequently it was difficult to determine properly any effect of dose, but it is noteworthy that the female initially showed a unilateral change which was bilateral at a later examination time. Transient widespread swelling was also noted in this study which complicates any interpretation of the retinal finding. It is proposed that a European Union (EU) Risk Management Plan will be adopted in Australia, which includes monitoring of potential pancreatic and retinal changes.

Overall, repeated-dose studies in cynomolgus monkeys, the main species investigated, suffered from a number of deficiencies. One study in which animals variably received 4-8 treatments at 3 week intervals, appeared to be a replacement for another study which was shortened to 4 (from the scheduled 8) treatments at the same intervals because of local infusion site intolerance and early deaths. The small number of survivors and the presence of pronounced infusion site reactions made determination of primary drug-related changes sometimes difficult in both studies. However, taken together with the results of two range-finding studies (both of which included 4 treatments at 3 week intervals), these studies were considered to be adequate to indicate potential toxicity in this species. Only one of the rat studies used infusions at 3 weekly intervals, although this was limited to 3 treatments and was designated as a range-finding study. The proposed PI notes that for the soft tissue sarcoma indication there were no pre-defined limits to the number of cycles administered and that treatment continued while clinical benefit was noted. The pivotal clinical trials for both indications appeared to be >1 year suggesting that repeat-dose toxicity studies should be up to 6 months duration according to a superseded EU guideline.[16] This was clearly not the case for rats, and only applied to the low-dose (25 µg/kg/infusion) in cynomolgus monkeys. A more recent International Council on Harmonisation (ICH) guideline, adopted by the EU and the TGA, applicable to patients with advanced disease and limited therapeutic options suggests that toxicity studies of three months duration would be sufficient.[17]

Studies generally included necropsies at different times after treatment, with variable evidence of reversibility in the one rat study using the proposed treatment regimen. Although injection site lesions and hepatic changes, as well as many clinical pathology changes, were still evident after the 3 week recovery (that is, the dosing interval) bone marrow cellularity had normalised. It was difficult to determine reversibility in cynomolgus monkeys because of the small numbers examined.

[16] EMEA, Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on the pre-clinical evaluation of anticancer medicinal products (CPMP/SWP/997/96).
[17] EMEA, ICH Topic S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, November 2009. Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008).

Genotoxicity and carcinogenicity

Trabectedin was genotoxic in the three assays used (bacterial reverse gene mutation and chromosome aberration tests *in vitro* and an *in vivo* mouse micronucleus test), a result that may be expected for a cytotoxic compound which binds to DNA. No carcinogenicity studies were conducted, which is acceptable given the intended indications and limited life expectancy of the proposed patient population.

Reproductive toxicity

Embryofetal development studies were conducted in rats and rabbits, with daily IV administration, but fertility and early embryo development and pre-postnatal studies were lacking which is acceptable given the proposed indication for trabectedin.

Doses were selected on the basis of range-finding studies, and there were no specific effects on embryofetal development, with only slightly reduced fetal weights being seen with 0.5 µg/kg/day (significant only for females) and 2.5 µg/kg/day in rats, which was associated with lower maternal weight gain and food consumption with the higher dose. There were no toxicokinetic data but as noted above (*Pharmacokinetics and relative drug exposures*), the high dose used in the rat study (2.5 µg/kg/day x 12 days = 30 µg/kg in total) would have resulted in a cumulative drug exposure well below the human value. A slightly higher dose of 3 µg/kg/day in the pilot study resulted in an excessive reduction in maternal weight gain (by 35%), while maternal deaths occurred at 10-30 µg/kg/day. Besides a lack of toxicokinetic data for the rabbit study, pharmacokinetic plasma data were not available for this species, although the high dose of 2 µg/kg/day (28 µg/kg in total) probably could not be increased appreciably as a late (gestation day 28) maternal death occurred with 3 µg/kg/day in the pilot study.

Local tolerance

Trabectedin is highly irritant and showed often marked histological reactions at the infusion sites in animal studies. Findings included thrombophlebitis, perivascular haemorrhages and collagen degradation, ulceration and degeneration/necrosis of SC muscle. Paravenous administration was shown to result in enhanced reactions. Local reactions have apparently been occasionally observed in clinical trials (sponsor's *Clinical Summary of Safety*); the proposed PI notes that administration via central venous access is strongly recommended and that potentially severe local reactions may develop using a peripheral venous line.

Nonclinical Summary and Conclusions

Trabectedin is a cytotoxic anti-neoplastic agent which exhibits an unusual DNA binding pattern. It is intended for the treatment of relapsed ovarian cancer, in combination with doxorubicin, and advanced soft tissue sarcoma after failure of anthracyclines and ifosamide or when these agents cannot be used. Respective IV doses are 1.1 mg/m^2 (3 hour infusion) and 1.5 mg/m^2 (24 hour infusion).

Primary pharmacology studies were mainly literature publications. Trabectedin binds to the minor groove of DNA, bending the DNA towards the major groove, affecting several transcription factors, (in particular, NF-Y) and DNA repair pathways and perturbing the cell cycle.

The antiproliferative activity of trabectedin *in vitro* was demonstrated in a range of tumour cells (established cell lines and freshly isolated), with highly variable IC$_{50}$ values being obtained in a number of studies. Values were often, but not always, <10 nM with ovarian carcinoma and sarcoma cell types, and there was some evidence for poor efficacy against fibrosarcomas. The N-desmethyl metabolite of trabectedin was also active. Human tumour cell lines selected for resistance to other antineoplastic drugs were often sensitive to trabectedin. Limited *in vivo* studies demonstrated antiproliferative activity in xenografts in nude mice, but even in sensitive cell types, high doses (close to toxic) were required to achieve good efficacy. Effects of combining

trabectedin and doxorubicin varied with experimental conditions, but significant benefits were sometimes observed.

Safety pharmacology studies *in vivo* (CNS/behavioural in rats, cardiovascular/respiratory in cynomolgus monkeys) did not reveal adverse effects of IV treatment with appropriate but relatively low doses. Trabectedin was also inactive in an *in vitro* hERG inhibition test at clinically relevant concentrations. Secondary pharmacodynamic studies showed that trabectedin was toxic towards human hepatocytes and haematopoietic precursors (CFU-GM enumerated) *in vitro*. Respective IC_{50} values were 1.7-81 nM (24 hour exposure) and 15 nM (1 hour exposure) for 3 individual samples.

Plasma trabectedin clearance values were relatively high in rats (about 6-12 L/h/kg) and cynomolgus monkeys (1.4-3.1 L/h/kg) after single IV infusion of doses of 50-100 µg/kg. Plasma protein binding, assessed *in vitro*, was high in all species tested (including humans) but with some species variation (90.0-98.9% at 100 ng/mL). Trabectedin was shown to be a substrate for p-glycoprotein *in vitro*, and *in vivo* in *mdr1a1b* knockout mice.

Low plasma drug/radioactivity ratios in rodents and humans were indicative of extensive [^{14}C]Trabectedin metabolism, but there were few *in vivo* data due in part to the low doses which could be administered. *In vitro* data showed several metabolites were generated by mouse, rat, rabbit, dog, cynomolgus monkey and human liver samples (microsomal preparations and 12,000 g supernatants). All species generated the N-desmethyl derivative, but a composite oxidation/O-demethylation peak was seen only with cynomolgus monkeys and human samples. CYP3A4 was involved in *in vitro* metabolism at a clinically relevant trabectedin concentration (13 nM), and a higher concentration (50 nM) had little effect on the activity of different CYP isoforms. Radioactivity was recovered primarily from the faeces in mice and rats, as in humans, and biliary excretion was shown to occur in rats. There were no excretion data for other species.

Maximum tolerated doses were low in single-dose IV toxicity studies in rodents (e.g. 100 µg/kg for MF1 mice, 50-75 µg/kg in SD rats) and cynomolgus monkeys (87 µg/kg in a single female cynomolgus monkey). Studies included clinical pathology and histological examinations, with findings that were similar to those in the repeat-dose studies. These included bone marrow depletion, reductions in red and white blood cells, lymphoid depletion in thymus, spleen and lymph nodes, hepatotoxicity characterised by increases in serum transaminases and hepatocellular necrosis, and inflammation at the injection site. Cholangitis and increased serum bilirubin and alkaline phosphatase were observed in rats. Gastrointestinal toxicity, characterised by changes to the epithelium of the stomach and the small and large intestine (epithelial cell necrosis, ulceration, hyperplasia and atrophy) was observed in rodents.

Repeated-dose toxicity studies (all with IV administration) were mainly conducted in rats and cynomolgus monkeys, with additional studies in mice and dogs, using a variety of treatment schedules. Drug exposures based on plasma AUC were generally lower than that expected in humans with the recommended doses. Of 4 rat studies, only one study employed infusion administration (3 hours) and this was limited to 3 treatments at 3 week intervals, with the high doses used (75 µg/kg in males, 50 µg/kg in females) being lethal. The two full cynomolgus monkey studies using high doses of 65-70 µg/kg by 3 hour or 24 hour infusion were amended and/or shortened to 4-8 treatments at 3 week intervals because of high mortalities. There were no toxicity studies of trabectedin in combination with other drugs.

Toxicity mainly affected the liver and bile duct (primarily in rats), bone marrow (myelodepression) and sometimes the GI-tract. Associated clinical pathology changes included elevated serum enzyme activities (transaminases, γ-glutamyltransferase and alkaline phosphatase), bilirubin and bile acids, reduced albumin, leukopenia and anaemia. Histological liver findings included hepatocytic necrosis (multifocal, focal, single cell) and bile duct necrosis, hyperplasia/proliferation and peribiliary fibrosis. Several GI-tract lesions were observed but some may have been related to

infections secondary to immunosuppression (inflammation/haemorrhage and typhlitis in two different cynomolgus monkey studies).

Renal toxicity (generally unilateral) was a feature of the cynomolgus monkey studies, and was considered by the study authors to be secondary to local infusion site reactions which were often marked; however renal toxicity of trabectedin cannot be excluded. There were no indications that the kidney was a target organ in rats, or in mice and dogs. Retinal oedema was noted at ophthalmic examination in two cynomolgus monkeys in one study, but a relationship to treatment was uncertain.

Trabectedin was positive in the three genotoxicity tests conducted, a bacterial reverse gene mutation assay, an assay for chromosome aberrations *in vitro* and an *in vivo* micronucleus test in mice. No carcinogenicity studies were conducted, which is acceptable given the proposed indication.

Embryofetal development studies were conducted in rats and rabbits, with daily IV administration during the period of organogenesis. No specific effects of treatment were seen but cumulative doses (28-30 µg/kg in total) were low relative to the proposed human unit dose. Fertility and early embryonic development and pre-/post-natal studies were not carried out and are not required.

Doses that could be used in the toxicity studies were limited by excessive toxicity and mortalities, and drug exposures based on plasma AUC were generally below that expected during therapy with the recommended dose. This is, however, often the case with cytotoxic anti-neoplastic drugs and should not preclude approval of registration. Although individual repeated-dose studies in cynomolgus monkeys were not ideal, taken together they were adequate to indicate potential toxicity in this species. Results, combined with those in rats, revealed major toxicities occurred in the liver, bone marrow, GI-tract and infusion site. Overall, there were no nonclinical objections to this application for registration, although it should be noted that there were no toxicity studies with trabectedin in combination with other drugs (for example, doxorubicin).

Issues likely to be addressable from the clinical data

The extent to which the intended tumour types may be expected to respond to the recommended trabectedin doses could not be determined from the limited nonclinical data. Efficacy will therefore have to be determined from the clinical trials.

Except for the GI-tract, the above toxicities are specifically mentioned in the proposed product information and the extent to which these are acceptable given the proposed indications will depend on evaluation of the clinical data and their inclusion in a proposed Risk Management Plan.

Renal toxicity was prominent in cynomolgus monkeys, but not rats, and was considered by the study authors to be secondary to infusion site reactions which were often marked and involved surrounding tissues. However, while this is a probable cause, it would be difficult to exclude a potential for direct nephrotoxicity, and this should receive attention by the clinical evaluator. This also applies to retinal oedema, which was noted at ophthalmic examination in one cynomolgus monkey study following 6-8 cycles of treatment. While this finding appeared to be incidental or secondary to other toxicity, the ophthalmologist noted that it may possibly represent a sign of retinal toxicity, although there were no corresponding histological findings. It is noted that both of these observations are included in the proposed Risk Management Plan.

IV. Clinical Findings

Introduction

Clinical Pharmacology

The data presented on clinical pharmacology was complex, consisting of all the pharmacodynamic (PD) and clinical pharmacokinetic (PK) results available to date in adult cancer patients enrolled in clinical trials with trabectedin and its combination. Nine trials for ovarian cancer used the

combination of Doxil and trabectedin proposed in the application. The remaining trials were common to both indications and a number were used in the assessment of the population pharmacokinetics of trabectedin.

An integrated summary by the sponsor of the pharmacology of trabectedin, mainly based on the population pharmacokinetic analyses, and entitled *Key Clinical Pharmacology Findings* was presented in the sponsor's *Summary of Clinical Pharmacology Studies*.

Trial designations used ET for trabectedin, then A for a Phase 1 trial and B for a Phase 2 trial, then a number to show the order of the study in the year they were planned, and lastly the year the trial began. The first trials were in 1995-6.

Clinical Studies on Efficacy and Safety

Studies were presented separately for the indication of relapsed ovarian cancer (ROC) and soft tissue sarcoma (STS). This evaluation keeps this separation for evaluation of efficacy and safety.

Studies in Relapsed Ovarian Cancer

Efficacy

The clinical development program supporting the efficacy of trabectedin in the treatment of ROC included one pivotal, Phase 3 study (ET743-OVA-301) and 3 single-agent, Phase 2 studies (ET-B-026-03, ET-B-009-99, and ET743-INT-11). In addition, to provide support for the recommended dose regimen of trabectedin when used as a combination agent in the treatment of ROC, data from a Phase 1 study (ET743-USA-11) in multiple tumour types including ovarian cancer were also included in this document. These studies are summarised in Table 2.

The pivotal trial ET743-OVA-301 compared two treatments, Doxil alone and Doxil in combination with trabectedin. The activity of trabectedin alone, as a single agent in ROC was not part of the pivotal trial. However three phase 2 trials submitted in the application examined the activity of trabectedin as a single agent in ROC. A less direct indication of the activity of trabectedin in this disease would be if the combination of trabectedin with Doxil were more effective than Doxil alone. The Phase 1 study ET743-USA-11 did not include efficacy in its objectives, and was designed to determine the maximum tolerated dose (MTD) of trabectedin in combination with pegylated liposomal doxorubicin (a Doxil equivalent).

Safety

The safety profile of trabectedin plus Doxil for this proposed indication was based on safety findings in 663 subjects with ROC who were treated in the randomized pivotal Phase 3 Study ET743-OVA-301 of the trabectedin + Doxil combination in comparison to Doxil monotherapy. Results were also presented for trabectedin treatment alone, treatment not proposed for registration in Australia, but which allow comparison with the safety of the combination. These studies included three Phase 2 non-controlled studies (Studies ET743-INT-11, ET-B-026-03, and ET-B-009-99). As well, the application included 16 completed Phase 2 studies of trabectedin as a single agent in various solid tumour types, and 18 completed Phase 1 studies, including a dose escalation study supporting the dosing regimen and dosing schedule for the trabectedin + Doxil combination (Study ET743-USA-11).

Table 2: Clinical studies included for evaluation of efficacy

Study	Design and Study Population	Study Treatment(s), Starting Dose, and Regimen	Subjects Evaluated		
Phase 3					
ET743-OVA-301	Randomized, open-label, pivotal study in subjects with relapsed epithelial ovarian, epithelial fallopian tube, or primary peritoneal cancer	Trabectedin 1.1 mg/m^2 q3wk 3-h + DOXIL 30 mg/m^2 q3wk 1.5-h vs DOXIL 50 mg/m^2 q4wk 1.5-h	672 337 trabectedin + DOXIL 335 DOXIL monotherapy		
Phase 2					
ET-B-026-03	Randomized, open-label, study of 2 dose regimens in subjects with potentially platinum-sensitive, recurrent, advanced epithelial ovarian carcinoma	Trabectedin 1.5 mg/m^2 q3wk 24-h Trabectedin 1.3 mg/m^2 q3wk 3-h	54 53		
ET-B-009-99	Open-label, single arm study in subjects with advanced epithelial ovarian carcinoma	Trabectedin 1.3 mg/m^2 q3wk 3-h Trabectedin 1.5 mg/m^2 q3wk 3-h Trabectedin 1.65 mg/m^2 q3wk 3-h	41/59*		
ET743-INT-11	Open-label, single arm study in subjects with epithelial ovarian, fallopian tube, or primary peritoneal cancer	Trabectedin 0.58 mg/m^2 qwk 3-h	147		
Phase 1			Ovarian	Other	All
ET743-USA-11	Open-label study evaluating 6 dose levels of trabectedin in combination with DOXIL in subjects with a malignancy refractory to standard therapy or for which an anthracycline-based regimen was appropriate	Trabectedin 0.4 - 1.3 mg/m^2 q3wk 3-h + DOXIL 30 mg/m^2 q3wk 1- to 2- h	4	32	36
Total			971	32	1003

qwk= weekly dosing ; q3wk= every 3 week dosing
*Fifty-nine subjects were enrolled & treated. However, among the 59 subjects, 18 subjects received 1.5 mg/m^2 or 1.65 mg/m^2 as their starting dose and 41 subjects received 1.3 mg/m^2 as the starting dose. Subjects in the 2 highest dose groups (1.5 mg/m^2 or 1.65 mg/m^2) were excluded from the integrated efficacy analysis.

Studies in Soft Tissue Sarcoma

Efficacy

In the original Marketing Authorization Application (MAA) in the EU, efficacy data was taken from a protocol-specified interim analysis of the pivotal Study ET743-STS-201 at a predefined clinical cutoff date of 31 May 2005. In the present application, these data have been updated to reflect the final analysis of time to progression for Study ET743-STS-201 with a clinical cutoff date of 31 May 2006, a year later. The results of the pivotal study are presented in this report, followed by the results of the 3 initial, supportive Phase II studies conducted in patients with STS.

Safety

Safety data were provided from the three initial Phase 2 studies of trabectedin in 183 subjects with advanced STS) previously treated with chemotherapy. These studies had been the basis of the initial MAA with trabectedin. As well, further safety data were obtained from 19 clinical studies,

including the Phase 2 randomized study (ET743-STS-201, the pivotal study in support of the safety and efficacy of trabectedin). The cut-off date for the integrated safety analysis was 30 April 2007.

Another 3356 patients were not included in the sponsor's *Integrated Safety Database* because they were treated in compassionate use programs (2132), because they were treated in studies ongoing at the cutoff (316 Phase 3, 33 Phase 2 and 184 Phase 1), or because they were treated in completed Phase 1 (489) or Phase 2 (202) studies at doses different from those in the *Integrated Safety Database* or in regimens that combined trabectedin with other chemotherapeutic agents.

The evaluation plan was to review the early Phase 1 trials; those examining intrinsic factors such as hepatic dysfunction; those examining extrinsic factors such as dexamethasone which interacts with the enzymes metabolising trabectedin; population PD/PK analyses of trabectedin as a single agent and in combination with Doxil, and of Doxil also, including effects on neutrophils and the serum concentration of liver enzymes; and the results of the PK sections of other Phase 2 and 3 trials that were mainly performed for efficacy and safety.

Pharmacology

The code name for trabectedin (Ecteinascidin) in early studies was ET-743.

Trials that included pharmacological studies

Studies using human biomaterials

Study ET-729: Determination of the Presence of Metabolite ET-729 (N-desmethyl ET-743) in Plasma from Patients Receiving ET-743 Intravenously

This study was to determine whether ET-729 occurred in human plasma in subjects receiving intravenous (IV) trabectedin. It did not.

Study ET-743-FIN-140: Determination of ET-743 concentrations in urine from patients entered in studies ET-A-001-95, ET-A-003-95 and PMA-002-95

Less than 1% of the administered dose was excreted as trabectedin over the first 24-hour period after the start of a 1- or 3-hour infusion or the first 48-hour period after the start of a 24-hour infusion, so urinary excretion of unchanged drug played a very minor role in the overall elimination of trabectedin.

Human PK Studies

PK and initial tolerability studies

ET-A-001-95 (1 hour): Phase 1 Clinical and Pharmacokinetic Study to Determine the Safety of Ecteinascidin-743 (Trabectedin) Administered as a Single Intravenous Infusion Over 60 Minutes Every 21 Days in Patients With Solid Tumours

The objectives of the study were to determine the maximum tolerated dose (MTD) of trabectedin when administered as a single infusion over 60 minutes and to propose a safe dose for Phase 2 trials. The MTD was reached at 1100 μg/m^2, and a dose of 1000 μg/m^2 was proposed as a safe dose for Phase 2 evaluation in this schedule.

PK findings at different dose levels showed that maximum concentrations of trabectedin in plasma (Cmax) were typically observed immediately prior to the end of the infusion. The concentrations declined in a multi-exponential manner upon cessation of the IV infusion. Initially, a marked and rapid decline in plasma concentrations was observed which was followed by more prolonged distribution and terminal phases. In general, an increase in mean plasma Cmax and AUC values was observed with an increase in the daily dose administered. Trabectedin exhibited a high plasma clearance (CL) with mean values ranging from 43.4 to 98.2 L/hour across the range of doses administered. The mean values of volume of distribution (Vss) ranged from 950 to 1642 L. The

terminal half-life in plasma was relatively long with mean values ranging from 18.7 to 35.5 hours. Intersubject variability in the plasma C_{max} and AUC values of trabectedin ranged from 9 to 62 % (expressed as coefficient of variation).

Evaluator's comment

The results are to be treated with some caution because the sampling time was short (up to 24 hours after stopping the infusion) and because inter-patient variability was high

ET-A-001-95 (3 hour): Phase 1 Clinical and Pharmacokinetic Study to Determine the Safety of Ecteinascidin-743 (Trabectedin) Administered as a Single Intravenous Infusion Over 3 hours every 21 Days in Patients with Solid Tumours

The study had the same objectives as the previous trial. Extending the infusion duration from 1 to 3 hours resulted in a higher MTD and recommended dose for Phase 2 (1800 and 1650 µg/m², compared to 1100 and 1000 µg/m² in the 1-hour dosing schedule) without affecting the toxicity profile. Anti-tumour activity was observed in both schedules. Therefore, the recommended dose and schedule for trabectedin in Phase 2 studies was to be 1650 µg/m² in 3-hours, preferably through a central catheter.

Trabectedin exhibited a high plasma clearance with mean values from 51.0 to 103.9 L/h across the range of doses administered. The mean values of volume of distribution (Vss) ranged from 587 to 2178 L. The terminal half-life in plasma was relatively long with mean values ranging from 12.3 to 46.2 hours. Intersubject variability in the plasma C_{max} and AUC values of trabectedin ranged from 14 to 86% (expressed as coefficient of variation).

Evaluator's comment

The same concerns as above apply, possibly leading to overestimates of clearance values and underestimates of distribution volume and terminal half-life.

ET-A-002-95: Phase 1 Pharmacokinetic Study to Determine the Safety of Trabectedin (Ecteinascidin-743 (ET-743) Administered as a Continuous Intravenous Infusion Over 24 Hours Every 21 Days in Patients with Solid Tumours

The objectives of this dose-escalating, open-label, single-arm Phase I study were to determine the MTD of ET-743 (trabectedin) when administered as a continuous IV infusion over 24 hours every 21 days; and to propose a safe recommended dose for Phase 2 evaluation. Secondary objectives included a study of the pharmacokinetics of trabectedin in humans at different dose levels.

The MTD of trabectedin administered as a 24-hour continuous infusion was found to be 1,800 µg/m², with prolonged or complicated severe thrombocytopenia and neutropenia as dose-limiting toxicities. Haematological and hepatic toxicities were reversible and had no dose cumulative characteristics. Characteristic transient liver function abnormalities were not dose limiting but were prevalent and often of a severe degree (Grade 3-4) at both the recommended dose and MTD. In these cases, they were associated with concomitant hematologic toxicities. The recommended dose for Phase 2 studies was 1,500 µg/m² in patients with low or moderate pretreatment and without liver function biochemical abnormalities. Patients with minor baseline liver function abnormalities had a higher likelihood of severe hematologic toxicities and dose limiting toxicities requiring dose adjustments or delays.

Maximum concentrations of trabectedin in plasma (C_{max}) were typically observed immediately prior to the end of the infusion. The concentrations declined in a multi exponential manner upon cessation of the IV infusion. Initially, a marked and rapid decline in plasma concentrations was observed which was followed by more prolonged distribution and terminal phases. In general, an increase in mean plasma C_{max} and AUC values was observed with an increase in the daily dose administered. Trabectedin exhibited a high plasma clearance with mean values ranging from 41.4 to

110.5 L/h across the range of doses administered. The mean values of volume of distribution (V) ranged from 629 to 8369 L. The terminal half-life of trabectedin in plasma varied greatly with mean values ranging from 8.88 to 126.0 hours. The wide range of mean CL, V, and half-life values is attributable, in part, by the inability to accurately estimate the terminal phase at the lower dose levels where plasma concentrations of trabectedin reached the limit of quantitation (LOQ) shortly after terminating the IV infusion. Intersubject variability in the plasma C_{max} and AUC values of trabectedin ranged from 6 to 84 % (expressed as coefficient of variation).

Evaluator's comment

The recommended dose of trabectedin as a single agent administered over 24 hours is the same as that used in one of the two arm of the pivotal trial for STS (ET743-STS-201). The toxicities noted above were also found in that Phase 3 trial.

The study had the same problem of a short sampling time as in the previous studies (up to 24 hours after stopping the infusion), so that caution again is needed in accepting the values found. A very large difference was noted in mean values of the volume of distribution (629 to 8369 L).

ET-A-003-95: Phase 1 Clinical and Pharmacokinetic Study to Determine the Safety of Ecteinascidin-743 (ET-743) Administered as a Daily Times Five Intravenous Infusion Every 21 Days in Patients with Solid Tumours

The objective of this dose-escalating, open-label, non-randomized, single-center Phase 1 study was to determine the MTD of ET-743 (trabectedin) when administered as a daily times 5 IV dose, every 21 days, to propose a safe dose for Phase 2 evaluation, and, among other things, to study the human pharmacokinetics of trabectedin at the different dose levels.

The MTD of trabectedin administered as a 60-minute continuous infusion was 1900 μg/m². Grade 4 neutropenia, Grade 3-4 thrombocytopenia, Grade 4 rhabdomyolysis and Grade 3 thrombophlebitis were dose-limiting toxicities. Haematological and hepatic toxicities were reversible and had no dose cumulative characteristics. Characteristic transient liver function abnormalities were not dose-limiting but were prevalent. The recommended dose for Phase 2 studies is 1625 μg/m² in pretreated patients with and without liver function biochemical abnormalities.

Trabectedin exhibited a high plasma clearance with mean values ranging from 78.1 to 223.2 L/h across the range of doses administered on Day 1 of Cycle 1. The mean values of volume of distribution (V) ranged from 539 to 3243 L. The terminal half-life of trabectedin in plasma varied greatly with mean values ranging from 2.60 to 19.5 hours. Intersubject variability in the plasma C_{max} and AUC values of trabectedin during Day 1 ranged from 24 to 96 % (expressed as coefficient of variation). For most dose levels, the mean plasma area under the plasma concentration time curves to 24 hours (AUC_{24h}) values on Day 5 were higher than those on Day 1, whereas no clear trend was observed for C_{max}.

Evaluator's comment

The dose and schedule recommended in this study were not used in either the pivotal study in ROC (ET743-OVA-301) or in that for STS (ET743-STS-201). Of note is the occurrence in one patient of Grade 4 rhabdomyolysis, a severe and serious adverse event seen also in later trials. The event here was classed as possibly related to the study drug administered at the highest dose in the study, 1.9mg/m².

The report states that "The wide range of mean CL, V, and half-life values is attributable to the inability to accurately estimate the terminal phase at the lower dose levels where plasma concentrations of trabectedin reached the limit of quantitation shortly after terminating the IV infusion."

ET-A-004-97: Phase I Clinical and Pharmacokinetic Study of Ecteinascidin-743 (trabectedin) Administered as a 72 Hours Continuous Intravenous Infusion Every 21 Days to Patients with Advanced Solid Tumours.

The objective of this dose-escalating open-label single-arm Phase 1 study was to determine the MTD of ET-743 and to characterize the plasma pharmacokinetics of ET-743. Secondary objectives included identifying the dose-limiting toxicities of ET-743.

The MTD was 1200 μg/m² (level IV) and the recommended dose for phase II trials is 1050 μg/m² (level III). The dose limiting toxicities were neutropenia, thrombocytopenia, renal failure and rhabdomyolysis and reversible transaminitis. All dose-limiting toxicities (DLTs) were at dose level IV.

The PK results showed there is non-linearity, as shown by the over-proportional increase in AUC from the recommended dose to the MTD. The report suggested that this may have led to overexposure of patients to the study drug and to the toxicities that defined 1.2 mg/m² as the MTD. Terminal half-life was long, with median values in the range 37.4-75.9 h depending on the dose level. Distribution was wide with volumes of distribution in excess of the body fluids volume.

Evaluator's comment

The dosing schedule in this study was not used in the pivotal trials for the two indications requested in this application. The study reported one case of Grade 3-4 rhabdomyolysis from the 9 patients who received the highest dose of trabectedin.

The range of values in this study was not as great as in previous studies so the values may be more reliable, although no coefficient of variability (CV) was given.

ET-A-005-99 (1-hour): Phase I and Pharmacokinetic Study of ET-743 Administered as 1-hour Infusion Weekly for 3 Consecutive Weeks every 4 Weeks to Patients with Advanced Cancer

The objective of this dose-escalating, open label, non-randomized, phase I study was, among other things, to determine the MTD and both principal and dose-limiting toxicities (DLTs) of ET-743 administered intravenously (IV) (1-hour infusion) weekly for 3 consecutive weeks every 4 weeks, and to characterize the pharmacokinetics of ET-743 on this schedule of administration.

The MTD for this weekly 1-hour ET-743 schedule was dose level IV (700 μg/m²) and the DLTs related to this weekly schedule were severe neutropenia and acute, transient increase in the blood levels of transaminases, creatine phosphokinase (CPK), LDH, severe rhabdomyolysis and severe fatigue. Dose level III (610 μg/m²) was declared the recommended dose (RD) for phase II clinical trials on ET-743 administered with the studied 1-hour weekly schedule.

The pharmacokinetics of ET-743 was characterized in this study by:

• A high clearance, with mean (standard deviation [SD]) values of 67.7 (38.5) L/h over the dose ranges 460 to 920 μg/m².

• A long terminal half-life, with mean (SD) value of 71.4 (58.3) hours

• A large volume of distribution with mean (SD) value of 2769 (1651) L for Vss [volume of distribution at steady state]; and of 4898 (2524) L for Vz [volume of distribution calculated from the terminal phase].

• For dose proportionality, the results were inconclusive for the three parameters evaluated: C_{max}, area under the plasma concentration time curve to the last measurable time point (AUC_{last}) and area under the plasma concentration time curve from time zero to infinity (AUC_∞). The report stated that these results were likely due to the high variability of the PK parameters and the narrow dose range of this study, but that from the visual inspection of the dose-linearity graphs, there appeared not to be major deviations from linearity.

Evaluator's comment

The schedule of a 1-hour infusion of trabectedin was not used in the pivotal trials in the present application. Again rhabdomyolysis is noted as a drug-related effect at a higher dose.

Dose-proportionality was suggested, but not conclusively shown by these data. The high variability of individual results was noted.

ET-A-005-99 (3-hour): Phase I and Pharmacokinetic Study of ET-743 Administered as a 3-hours Infusion Weekly for 3 Consecutive Weeks every 4 Weeks to Patients with Advanced Cancer

The objective of this dose-escalating, open label, non-randomized, phase I study was among other things to determine the MTD, and both principal and dose-limiting toxicities (DLTs) of ET-743 administered IV (3-hour infusion) weekly for 3 consecutive weeks every 4 weeks, and to characterize the pharmacokinetics of ET-743 on this schedule of administration.

The MTD for this weekly ET-743 schedule was established as 0.65 mg/m^2 and the dose recommended as a safe starting dose for further study was 0.58mg/m^2.

AUC and C$_{max}$ tended to increase in proportion to the dose, suggestive of linear pharmacokinetic behavior, although there was substantial interpatient variability, particularly in the expanded cohort evaluated at the 580 μg/m^2 dose level. There was no trend or significant difference between the mean CL values determined during the first cycle of therapy at each dose level evaluated. The mean ± SD CL for the first dose of ET-743 calculated for the entire group of 25 patients was 34.8 ± 15.7 l/h/m^2. The mean CL of ET-743 in 13 patients treated during the second cycle of therapy, 41.5 l/h/m^2, was almost 20% greater than the value for the first cycle, although the difference was not statistically significant ($P = 0.10$). The relationship between the CL values in individual patients during the first and second cycles of therapy showed a moderate correlation between the values ($r = 0.51$) with a positive intercept (28.9 l/h/m^2) that differed significantly from the origin ($P = 0.003$), implying that the greater CL of the drug during Cycle 2 may not be an artifact. However, there were no significant differences in any of the other pharmacokinetic parameters between the first and second cycles of therapy, whether evaluated for all patients, or only those for whom data was available for both cycles.

Evaluator's comment

The schedule and recommended dose were those used in one of the two arms of the pivotal trial for STS (ET743-STS-201).

The PK analysis was compromised in this study by "logistical problems" that required the use during the study of a different analytical method to measure trabectedin, which did not correlate with the previous method. A number of measurements at longer sampling time were not used so that the true biological half-life "might have been significantly underestimated by the sampling schedule employed in this study".

PK studies on Intrinsic Factors

ET-A-006-00: Phase I Clinical and Pharmacological Trial for ET-743 in 3 Hour Infusion in Patients with Advanced Cancer and Alteration of Hepatic Function

The study was an open-label, multicenter, non-randomized, stratified, dose-escalating Phase I clinical and pharmacokinetic trial. Treatment consisted of trabectedin administered as a 3-hour IV infusion repeated every 3 weeks (one cycle = 3 weeks). Patients were stratified within three Strata according to their baseline liver dysfunction (tested ≤ three days previous to study inclusion; for all Strata, bilirubin, AST and ALT were < 2.5 x upper limit of normal (ULN), and albumin was > 2.5 g/dl):

Stratum I - alkaline phosphatase (AP) ULN to ≤ 1.5 x ULN;

Stratum II - AP 1.5 x to $\leq$ 2.5 x ULN;
Stratum III - AP > 2.5 x ULN.

The starting trabectedin doses were 1.1 mg/m^2 (Stratum I), 0.9 mg/m^2 (Stratum II) and 0.75 mg/m^2 (Stratum III) with a maximum of two dose reductions per patient allowed in each Stratum.

The objectives were to determine the MTD for trabectedin, to establish the recommended dose for phase II studies (RD) according to the degree of hepatic involvement, to determine the corresponding safety and toxicity profiles, to establish the influence of hepatic damage and the methods for evaluating it on the pharmacokinetic (PK) and pharmacodynamic profile for trabectedin when administered using this regimen, to study the correlation between the toxicity profile and pharmacokinetics, to determine the efficacy of trabectedin at the RD, measured in terms of response rate (RR). In this section, the first objectives are reviewed.

The MTD and RD for Stratum I was 1.3 mg/m^2. One DLT was found in the first six patients treated. However, as this is the usual dose administered with this trabectedin 3-hour every week schedule in patients with solid tumours, further dose escalation was not recommended. Recruitment was stopped in the other two Strata, Stratum II and III. These two Strata had to enrol patients with moderate to severe AP increases as reflection of a greater liver impairment. This implied eligibility criteria more restrictive than those usually followed in cancer trials. These restrictive criteria, together with the fact that this phase I trial was conducted at two sites only, made it difficult to enrol enough number of patients within an adequate timeframe. Therefore, after five years from the trial beginning, the sponsor agreed with the investigators that the premature closure of these two Strata without having achieved the MTD; thus, information on the RD for these two Strata was not provided.

The Strata defined in this study did not result in any statistically significant differences in the trabectedin PK parameters. Clearance (CL) for Strata I, II and III was 48.4, 65.5 and 38.9 L/h, respectively, for those patients with enough samples for defining the terminal elimination phase. Half-life (t½) and volume of distribution at steady-state (Vss) showed a decrease from Stratum I to III, although the differences did not reach statistical significance. The relationship between isolated liver function tests (bilirubin, transaminases, AP, GGT and prothrombin time) at baseline and trabectedin PK parameters were inconclusive. A possible explanation given was that, except for AP, the ranges of values in these liver function tests were very narrow.

Evaluator's comment

This trial was relevant to the present application in identifying the increased hepatotoxicity resulting when trabectedin was administered to patients with moderate to severe increased AP concentrations (proposed PI). It was noted that the drug dose of patients in Stratum I in the study was 1.3mg/m^2, given as a 3-hour infusion weekly for 3 weeks in a 3 week treatment cycle, whereas the requested dose and schedule for trabectedin to treat STS in the one arm of the pivotal trial was 0.58mg/m^2 given as a 3-hr infusion weekly for 3 weeks in a 4 week treatment cycle.

ET-A-013-01: Mass Balance Study of ET-743 Administered as a 3- or 24-Hour Intravenous Infusion to Patients with Advanced Cancer

The objectives of this open-label, non-randomized study were to obtain the mass-balance of ET-743 in adult patients with solid tumours; to identify the metabolites of ET-743 formed in adult patients with solid tumours; to determine, if possible, the concentration of as many ET-743 metabolites as feasible in body fluids; to assess on an opportunistic basis, if possible, if the genotypes of the patients for CYP2D6, CYP2C9, CYP2C19, CYP3A4 and UGT1A1 are related to major differences in the disposition of ET-743.

[^{14}C]-ET-743 was given IV as a 24-hour or 3-hour infusion. All patients received 1100 µg of ET-743 in the first cycle. Doses of 1500 µg/m^2 or 1300 µg/m^2 were administered in subsequent cycles

for patients receiving the 24-hour and 3-hour infusions, respectively. Doses were scheduled to be received every 3 weeks

Plasma and whole blood concentrations of [^{14}C]trabectedin-related radioactivity were comparable. Only 7% of the [^{14}C]trabectedin related compounds in plasma were accounted for by trabectedin, indicating the importance of metabolism in trabectedin elimination. [^{14}C]Trabectedin was metabolised to several radiolabelled metabolites all of which eluted on HPLC before the parent compound. Results indicated the presence of a glucuronide metabolite in urine. Metabolites detected in faeces under varying but neutral experimental conditions were: trabectedin, ET-745, ET-731, and ETM-217, while ET-729, ET-759A, and ETM-259 were detected only after extraction under acidic conditions. Trabectedin and ET-745, ETM-259, ET-759A, and ETM-204 were detected in urine.

Trabectedin and total radioactivity display a large volume of distribution of about 2000 L and 240 L respectively. On average, 57.6% and 5.8% of the administered dose, measured in terms of radioactivity, was recovered in the feces and the urine, respectively. The overall recovery of radioactivity averaged 61.4% (3-hour administration schedule). The excretion of unchanged trabectedin is very low both in faeces, and in urine (<1% of dose).

The report suggested that the recovery of only about two-thirds of the radioactivity administered may be due to the extensive tissue distribution and retention and long half-life of trabectedin. The latter has been reported for other antineoplastic agents that irreversibly bind to DNA.

Evaluator's comments

The dose and schedule of trabectedin requested in this application to treat ROC is 1.1 mg/m^2 as a 3 hour infusion, given with Doxil, every 3 weeks; and as a single agent to treat STS at a dose of 1.5 mg/m^2 given as a 24 hour infusion 3-weekly.

PK Studies on Extrinsic Factors

ET-B-010-99 Phase II clinical trial of ET-743 as second or third line treatment in patients with advanced stage and/or metastatic soft tissue sarcoma

ET-743 is metabolized by human liver microsomal enzymes, the most important of which is CYP3A4, with participation of CYP2E1, CYP2C9 and perhaps CYP4A1 and CYP2D6. As metabolism by CYP enzymes is a frequent cause of drug-drug interactions, ET-743 clearance could be decreased by inhibitors of the CYP enzymes involved in its metabolism and increased by inducers of the same enzymes. ET-743 has a high liver extraction ratio (>50%) and so would be relatively insensitive to interactions mediated by enzyme induction.

This multicenter Phase II study was designed to study the impact of dexamethasone prophylaxis on the safety and PK of trabectedin. In the first stage of patient enrolment, the trial was placebo-controlled, double blind and randomized. However following an assessment of the impact of the dexamethasone treatment after 28 patients were treated, the trial became open-labelled.

A second amendment to the protocol was made following an interim safety analysis assessment in 23 evaluable patients, into the impact of the dexamethasone prophylaxis, wherein it was concluded that administration of ET-743 without dexamethasone increased the risk of having a serious adverse event and increased the risk of treatment-related death. Three treatment-related deaths had been observed, all during cycles with placebo; two patients died following febrile neutropenia, while a third suffered cardiac and renal failure. This amendment altered the design of the study such that all subsequent patients received dexamethasone treatment, and the study became open-label, having previously been a randomized double blind study.

The pharmacological objective was to assess the pharmacokinetic parameters of ET-743, administered at a dose of 1300 μg/m^2 in a 3 hour IV infusion every 3 weeks, with the prophylactic

administration of dexamethasone. The initial pretreatment regimen of dexamethasone consisted of 4 mg twice daily, administered for 4 days starting 1 day before trabectedin at the beginning of each treatment cycle. Trabectedin was administered at initial doses of 1.3 to 1.65 mg/m^2, given as a 3 hour infusion every 3 weeks. Dexamethasone or placebo was given in a double-blind, crossover fashion at the beginning of Cycles 1 and 2.

Results showed that the plasma clearance of trabectedin was 28.2% higher and the terminal half-life was 21.3% lower with concomitant dexamethasone therapy relative to placebo. The clinical significance of these observations is not known given that the mean differences fall within the degree of intersubject variability in the pharmacokinetic parameters of trabectedin.

Evaluator's comment

The problem of data analysis arising from the lack of bioequivalence in the patient groups from the changes in the protocol design was not resolved, so that the conclusions remain tentative.

Although the results given should be interpreted cautiously, results from the population pharmacokinetic analyses (see below) showed a similar result - that the plasma clearance of trabectedin was 19.2% higher in subjects who received any concomitant dexamethasone administration relative to those who did not (p=0.068).

All subjects enrolled in the pivotal studies received a substantially different regimen of dexamethasone (a single IV dose given before administration of trabectedin). Although dexamethasone in theory could reduce the efficacy of trabectedin, its safety benefits as shown in this study justified its use, which would not affect a comparison of the two arms in the pivotal trials since all patients received prophylactic injections of dexamethasone.

Population Pharmacokinetics

The population pharmacokinetics of trabectedin were studied in the following different patient populations - as a single agent in patients with solid tumours, mainly STS; in combination with Doxil in patients with ovarian cancer; in patients with liver toxicity; and in patients with trabectedin-induced neutropenia.

Population PK of trabectedin used as monotherapy

The study report described the population PK of trabectedin (ET-743) following administration at a variety of dosing schedules and infusion rates in subjects with cancer, many with STS, and the influence of select patient demographic characteristics, laboratory values, and concurrent dexamethasone use on the between- and within-patient variability in pharmacokinetic parameters. The resultant model was used to estimate individual pharmacokinetic parameters for further analyses in model-based simulations and for the assessment of dose proportionality.

The studies included data from eight clinical studies (three Phase 1 studies and five Phase 2 studies). Base model development was performed on this Index dataset. Subsequently, the model was evaluated with Test Dataset 1, which included four studies (one Phase 1 study and three Phase 2 studies). When data from Study ET-743-STS-201 and Study ET-B-009 became available, these two studies were included in Test Dataset 2 and the model was re-evaluated. In the studies included in this analysis, trabectedin was administered as a single chemotherapeutic agent at doses that ranged from 24 to 1800 μg/m^2 administered as 1-, 3-, and 24-hour infusions every 21 days; 1- or 3-hour infusions on Day 1, 8, 15, every 28 days; or 1-hour infusion daily for 5 consecutive days in cycles consisting of 21 days. Finally, all datasets were integrated (Index, Test 1, and Test 2) and parameters for the model were re-estimated. The re-estimated parameters from this final population pharmacokinetic model were presented in the report.

A four-compartment pharmacokinetic model with linear elimination was the final model employed. The α, β, and γ half-lives were estimated to be approximately 0.1 hours, 7 hours, and 180 hours,

respectively. The between-patient variability in CL was 51 % CV, which is similar to the values previously reported for trabectedin.

The variability in the pharmacokinetics of trabectedin appeared to be moderate to large. Between-subject variability for clearance, central volume of distribution, the rate constant for the exchange between compartment 1 and compartment 2 (K_{12}), and the rate constant for the exchange between compartment 3 and compartment 1 (K_{31}) were estimated to be in the range of 28 to 51 %CV. Within-subject variability for clearance, central volume of distribution, and K_{12} were estimated to be in a narrower range, from 28 to 30 %CV. A mixture model for residual variability (RV residual variability: σ2) was used to distinguish between patients whose data were well described by the model (Subpopulation 1, n = 382) versus others less well described (Subpopulation 2, n = 221). The RV of the two subpopulations was substantially different. While for 63.4% of subjects the RV was 18%, the RV for the remaining subjects was 53%.

Patient covariates including age, body weight, body surface area, lean body mass, ideal body weight, creatinine clearance, ALP, AST, ALT, LDH, liver metastases, study, albumin, and total protein were not related to plasma pharmacokinetics of trabectedin. Simulated plasma concentration-time profiles of trabectedin in males and females exhibited minimal and clinically insignificant differences when dosed on the basis of body surface area.

In patients receiving dexamethasone, trabectedin area under the plasma concentration versus time curve was approximately 12% lower for Cycle 1 and 15% lower for Cycle 2, relative to patients who did not receive dexamethasone. The clinical relevance of this phenomenon was assessed in light of the variability in the systemic clearance and the effect on the efficacy and toxicity.

A small difference in population clearance values for patients with STS (37.7±16.8 L/h) and patients with other types of cancer (41.6±18.2 L/h) was observed but not statistically significant. This difference was unlikely to be clinically relevant, given the degree of variability in trabectedin systemic clearance.

The differences found in plasma concentrations of trabectedin between the first 2 cycles of a variety of schedules were less than 10%. Trabectedin elimination was linear, and its pharmacokinetic disposition is dose-proportional within the clinically relevant dose range.

Population Pharmacokinetics of Trabectedin (ET-743) and Liposomal Doxorubicin in Subjects with Ovarian Cancer

In this analysis, a population PK model was developed to characterize the plasma PK of trabectedin when coadministered with liposomal doxorubicin (Doxil). A different model was developed to characterize the plasma pharmacokinetics of total (liposomal and free) doxorubicin after Doxil was administered with and without trabectedin to parallel groups of patients.

The objectives of this analysis were:

(1) to update the plasma PK parameters of trabectedin after concomitant administration of Doxil based on a recently completed Phase 3 trial ET743-OVA301 in ovarian cancer patients;
(2) to quantify the effect of Doxil on trabectedin PK;
(3) to model the plasma PK of Doxil with and without concomitant trabectedin administration and compare parameter values with the those reported in literature when Doxil was given as a single agent.

The data used were those from the PK section of the pivotal Phase 3 study on ovarian cancer, ET743-OVA-301. Next, data previously used in STS and other patients (see above) was added to refine the model, and finally data from trial ET743-INT-11 (see below for details of this study).

In the covariate analysis, only the effect of co-administration of Doxil on trabectedin pharmacokinetics was explored because a full covariate search had been performed during the

previous population PK analysis. The influence of previously identified covariates (for example, dexamethasone coadministration on trabectedin clearance and sex on trabectedin central volume of distribution) was re-assessed after adding the ET743-OVA301 study. Plasma clearance of trabectedin was increased by 19% in patients who received any concomitant dexamethasone administration relative to those who did not. Central distribution volume increased by 19% for males compared to females, findings consistent with those in the historical population PK model.

Results were presented as a "visual descriptive check plot" and a numerical predictive check. To visualize a possible effect of Doxil on trabectedin, model-based simulations were performed using re-sampled posthoc parameters of 1000 subjects of the final combined dataset.

When the model was used to predict PK parameters of trabectedin of patients in the pivotal ovarian trial, ET743-OVA-301, a difference was found from those of monotherapy with trabectedin. The study report states "The results show that trabectedin coadministered with Doxil results in a clearance of 25.2 L/h compared to 36.7 L/h if trabectedin is taken alone (a decrease of approximately 31%). The central volume of distribution in the combination therapy amounts to 11.3 L compared to 13.9 L, and K_{12} is estimated at 2.34/h compared to 3.94/h. These observed decreases in trabectedin PK parameter values for the combination therapy are more pronounced than expected and not consistent with the findings in the Phase 1 study ET743-USA-11. Although this effect is significant, it should be stressed that this effect could be caused to a large degree by the unexpectedly high degree of variability in the concentration-time profiles observed during and immediately after the cessation of the infusion."

In this comparison, the plasma concentrations of trabectedin, as predicted by the population PK models, were shown for female patients treated with trabectedin alone (from the combined database) and for patients from the pivotal ovarian trial, who received the combination of trabectedin and Doxil. In the 24-hour plots, subjects receiving the combination of Doxil- and trabectedin as a 3 hour infusion have a significantly higher exposure compared to monotherapy subjects who received trabectedin as a 24 hour infusion. This trend remained up to 10 hours after the end of the 3 hour infusion. The median exposures indicated by the bold lines show that the upper limit of the 90% prediction interval of the trabectedin therapy is similar to the median of the combination therapy. The high degree of random variability seen during the infusion appeared to contribute to the very high trabectedin concentrations observed during the first 3 hours. However, after the first 24 hours, similar exposures were observed.

To check a possible relationship to toxicity, the AUC and C_{max} values were calculated in each case, and correlated with neutropenia and ALT concentrations. Those patients who seem to have very high, unexpected concentrations of trabectedin (>25,000 pg/mL) were almost equally distributed over the toxicity group with Grades 0-1-2, and the group with Grades 3-4. The findings were similar for AUC and C_{max} and for both neutropenia and ALT.

A one-compartment model was developed, tested and modified for a population PK model of Doxil alone and when administered with trabectedin. The results showed that clearance decreased only minimally, from 25.9 mL/h (inter-individual variation [IIV] 29%) to 22.37 mL/h (IIV 12%], when Doxil was coadministered with trabectedin. The report stated that the pharmacokinetic parameter estimates of Doxil were within the ranges observed in a published paper.[18]

When the various covariates were tested using the final model, patients with a high body surface area (BSA) received a higher absolute dose of Doxil and seemed to have a disproportionately higher clearance and volume of distribution. This was reflected in a power close to one for the covariate BSA on clearance and volume of distribution.

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[18] Gabizon A, Shmeeda H Barenholz Y, Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. Clinical Pharmacokinetics. 2003; 42: 419-36.

<u>Evaluator's comments</u>

This increase in exposure to trabectedin predicted by the model in ovarian cancer patients when treated with the combination of trabectedin and Doxil raises the question of the clinical significance of the finding. Although the report stated that the difference was not associated with increased toxicity of trabectedin given with Doxil in the pivotal study, this was not correct, as shown later in this evaluation (see Safety). A number of these increased toxicities could, by their nature, be attributed to trabectedin. The sponsor argued that the finding was not clinically significant because the study quoted above (ET743-USA-11, see below) found the contrary, namely that there was no effect on trabectedin PK parameters by coadministration of Doxil, based on a non-compartmental analysis in this single trial, and that the high degree of variability in the individual values used in the population PK model could account for the result. Against these arguments, however, was the increased toxicity of the combination in the pivotal trial that could be explained by the results of the population PK model used showing increased exposure to trabectedin when coadministered with Doxil. As well, the directions of the changes in the parameters observed were internally consistent, with a reduction in clearance associated with an increase in the central volume of distribution. It is noted that the final model used had been validated using other data that also had a high variability.

In this case, there is acceptable evidence that the unexpectedly high concentrations of trabectedin during and following the 3-hour infusion of the two drugs were not associated with increased neutropenia or liver toxicity. However a correlation of reduced clearance and an increased central volume of distribution with neutropenia and ALT was not mentioned in the study.

In addition, the report states "The clinical relevance of this effect is expected to be minimal for the Doxil dose given in the combination therapy with trabectedin. The residual variability in the model is relatively small (17%)." This statement was not explained, so that patients with a high BSA receiving a higher dose of Doxil should be considered to have a higher clearance of drug, with uncertain clinical outcomes.

<u>Population Pharmacokinetics and Pharmacodynamic Analysis of Trabectedin-Induced Neutropenia in Subjects with Cancer</u>

The primary objectives of the population pharmacokinetic and pharmacodynamic (PKPD) analysis of neutropenia after trabectedin administration were three-fold:

1) to develop a semi-mechanistical model that described the time course of the absolute neutrophil counts (ANC) in subjects with cancer receiving trabectedin and to quantify the between subject variability;
2) to estimate the pharmacodynamic (system and drug related) parameters in STS patients;
3) to evaluate the potential impact of patients' demographic characteristics and other covariates on pharmacodynamic parameters. In addition, simulation techniques were employed to assess the impact of the dosing regimen on the incidence of the Grade 3 and 4 neutropenia.

A population PKPD analysis of trabectedin was performed based on the data from 13 clinical studies. In these studies, subjects diagnosed with cancer were treated with IV trabectedin as monotherapy at doses that ranged from 0.03 to 1.8 mg/m^2, administered as one of six different dosing schedules: 1, 3 and 24 hours infusion every 21days; 1 or 3 hours infusion on day 1, 8, 15 every 28 days; and 1 hour infusion daily for 5 consecutive days every 21 days. In total, 12340 absolute neutrophils counts (ANC) from 704 cancer subjects, including 310 with diagnosis of STS in Phase 2 studies, were used for the population PKPD analysis.

An open, 4-compartment disposition model as described above was used to describe the pharmacokinetics of trabectedin. As well, a 5-compartment transit model was developed to describe the granulopoiesis process. The key conclusions are as follows:

• A modified Friberg model was used and found suitable to describe the absolute neutrophil counts after the IV administration of six different dosing regimens of trabectedin to cancer subjects, included subjects with diagnosis of STS.

• The modeling results confirmed the absence of cumulative neutropenia toxicity associated with trabectedin in the subjects who received 3 or more cycles of therapy on any of the treatment schedules evaluated

• The depth and duration of neutropenia are dependent on dose level and trabectedin AUC as seen by comparing 1.5 mg/m^2 24 hour infusion with regimens providing lower overall doses (1.3 mg/m^2 3 hour infusion and 0.58 mg/m^2 3 hour infusion). This relationship is non-linear, therefore a proportional change in trabectedin dose or exposure will lead to a more than proportional reduction in the ANC at nadir.

• Time course of neutropenia was also dependent on the frequency of dosing. Larger, infrequent dosing regimens (for example, every 3 weeks [q3wk]) resulted in higher peaks and lower nadir of drug concentrations in the effect compartment. These fluctuations are translated to the ANC with larger, infrequent dosing regimens leading to more severe neutropenia. Different durations of infusion had negligible effect on severity of neutropenia, with little difference between profiles. These findings suggested that neutropenia is not C$_{max}$ dependent.

• The majority of patient related covariates, including age, total protein, serum albumin, performance status, concomitant administration of dexamethasone and study type had no discernable impact on the PKPD model parameters.

• The PKPD model parameters of trabectedin were similar in subjects with diagnosis of STS and subjects with other solid tumours.

• Although the effect of sex on k_{e0} and body weight on EC_{50} was statistically significant, the magnitude of the effect was not clinically relevant. This finding was confirmed by the simulations, which indicated a negligible influence of sex and body weight on the time course of ANC when trabectedin dosing is normalized by body surface area.

Evaluator's comment

The results are important, in that a greater fall in ANC occurred than predicted proportionally from a dose increase of trabectedin. Also the last conclusion above needs comment, because of the statistically significant effect of body weight on the fall in ANC. The effect is of concern because body weight is used to determine the BMI, a covariate that was found in the previous population PK study to be associated with greater toxicity of trabectedin. Both these effects were judged not to be clinically relevant because of the inter-patient variability in one case and the small effect seen in the other case. However the question should remain open, until disproved by confirmatory studies with less variable data.

Population Pharmacokinetics and Pharmacodynamic Analysis of Liver Toxicity following Administration of Trabectedin (ET-743) in Subjects with Cancer

PK/PD Analysis of ALT Toxicity

Transient reversible and non-cumulative transaminitis with a short latency period has been observed following administration of trabectedin. Although the liver toxicity of trabectedin has been intensively studied, the exact mechanism of liver toxicity has not yet been identified. However, the reproducibility, exposure dependency, high incidence and short latency period of trabectedin-induced transaminitis suggest it is an intrinsic hepatotoxic drug. Therefore, release of ALT and AST from the hepatocyte cytoplasm to serum is indicative of hepatocyte injury. Transient hepatotoxicity has been shown for other anticancer agents such as methotrexate, docetaxel, and gemcitabine. To

date, the temporal relationship between elevation in liver enzymes and drug exposure has not been fully elucidated.

Since a correlation exists between the elevation of ALT and AST concentrations in serum and trabectedin administration, this analysis utilized ALT as a representative measure of hepatocyte leakage to characterize the relationship between trabectedin exposure and the time course of transaminase elevation. The apparent development of tolerance to the elevation in ALT concentrations following subsequent cycles of drug administration was also investigated. The effect of subject covariates was also assessed in order to describe the variability in serum ALT concentration after trabectedin administration. Through simulations, the impact of significant subject covariates, such as concomitant administration of dexamethasone, was determined. Simulations were also performed to assess the effectiveness of the current dose reduction strategy for trabectedin in a Phase 2 clinical trial in sarcoma subjects.

Data from thirteen clinical studies (711 subjects in four Phase 1 and nine Phase 2 studies) were available for the PK/PD analysis of liver toxicity following trabectedin administration. Base model development to describe the time course of ALT elevation in relation to trabectedin plasma concentrations and covariate analysis was performed using the index dataset, composed of twelve Phase 1 and 2 trials where trabectedin was administered as a single agent including doses ranging from 24 to 1800 μg/m^2 administered as 1-, 3-, or 24-hour IV infusions every 21 days (q3wk); 1 and 3 hours infusion on Day 1, 8, 15 every 28 days (qwk x 3); or 1 hour infusion daily for 5 consecutive days every 21 days. Model predictability was performed using a test dataset composed of the Study ET-743-STS-201, in subjects with STS. The final PK/PD model was estimated and refined using the Combined Dataset from the thirteen trials.

The conclusions were as follows:

PK/PD Modeling of ALT

• An adaptive precursor-dependent PK/PD model adequately characterized the temporal relationship between trabectedin pharmacokinetics and transient ALT elevation. It accounted for the development of apparent tolerance to transaminitis following subsequent cycles of trabectedin administration across dosing schedules and infusion durations.

• Dexamethasone use results in a 60% reduction in ALT elevation.

• The hepatoprotective effects of dexamethasone are, at least in part, attributable to the pharmacodynamic properties of this compound. The described PK/PD analysis provides justification for the beneficial concomitant administration of dexamethasone when treating cancer subjects with trabectedin.

• Other subject covariates (including body weight, age, sex, study, as an indicator of infusion length, liver metastases, and ECOG/PS score) had no additional predictive value once dexamethasone use was incorporated into the trabectedin PK/PD model for ALT.[19]

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[19] ECOG Performance Status (PS). The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

ALT Model-Based Simulations

• All dosing regimens evaluated in the simulations exhibited transient elevations in the ALT profile following trabectedin administration.

• Co-administration of dexamethasone resulted in significantly lower ALT peak concentrations.

• The majority of the maximum ALT concentrations occur within 24 hours following trabectedin administration, suggesting a rapid onset of trabectedin effect on hepatocytes.

• Although trabectedin dosing regimens of 1.5 mg/m^2 q3wk infused over 24 hours result in higher peak ALT concentrations compared to the 0.58 mg/m^2 qwk x 3 regimen infused over 3 hours, total ALT elevation (that is, AUC) over 3 weeks is comparable between the two regimens suggesting that the total extent of liver toxicity is not different between a qwk x 3 and q3wk dosing schedule.

• Although the infusion length differed between the 1.3 mg/m^2 (3 hours) and 1.5 mg/m^2 (24 hours) regimens, the ALT versus time profiles for trabectedin were similar. Thus, infusion length does not substantially influence transaminitis.

• Simulations indicated that the current dose reduction strategy helps minimize the incidence and magnitude of ALT elevation. The current dose reduction algorithm is advantageous in managing transaminitis thus allowing subjects to tolerate this side effect and continue therapy.

Bilirubin Toxicity

• The incidence of bilirubin toxicity Grade ≥ 2 was low, yet was dependent upon treatment schedule, sex, and trabectedin AUC and C_{max}.

• A subject on the q3wk regimen has approximately a 2.8-fold higher probability of elevated total bilirubin Grade ≥ 2 than a subject on the same dose administered once weekly for three weeks. In addition, a male subject has approximately an 89% higher probability of experiencing elevated bilirubin levels than a female.

• The results of the exposure-safety assessment of bilirubin toxicity Grade ≥ 2 suggest that bilirubin elevation is related to trabectedin exposure. Dose reduction may improve the tolerability of trabectedin in subjects who develop total bilirubin toxicity Grade ≥ 2. However, in general, an exposure-guided dose adjustment for trabectedin to limit total bilirubin toxicity in subjects with cancer is not warranted.

Evaluator's comment

The analysis was useful in separating the effects of trabectedin on serum transaminase concentrations and on bilirubin toxicity. The former appears to be dose related, but the total ALT elevation was independent of dosing schedule and infusion time. The latter was related to the dose, treatment schedule, and the exposure to trabectedin, as shown by the AUC and C_{max} values.

Individual Phase 2 and Phase 3 trials that provided PK data and results

A number of trials included patients with ovarian cancer and STS in whom sampling for PK studies was done. Those that provided evaluable data are summarised below.

Phase 2 Study ET-B-026-03

In this Phase II open label, multicentered, randomized study, ET-743 was given either over 24 hours or 3 hour infusion in women with histologically proven, potentially platinum-sensitive, recurrent advanced epithelial ovarian carcinoma. The primary objective was to determine the optimal dosing regimen of trabectedin either as a 24-hour (1.5 mg/m^2) or 3-hour (1.3 mg/m^2) infusion, and a secondary objective to evaluate the PK parameters of trabectedin.

Full pharmacokinetic profiles (up to 6 to 8 days after the end of the 24-hour and 3-hour infusions) of trabectedin were collected during Cycle 1. A total of 20 patients per study arm were to be evaluated for PK using standard non-compartmental methods

Eighteen patients, 11 in the Arm A (24-hour) and 7 in the Arm B (3-hour), had PK evaluation during Cycle 1. The mean plasma concentrations of trabectedin were much higher for the 3 hour as compared to 24 hour infusion. The minor differences observed in the mean CL, Vss, and the terminal half-life values between the regimens were within the degree of inter-subject variability and are not likely to be clinically significance.

Phase 2 Study ET743-INT-11

In this multicenter, single-arm, open-label, non-comparative, Phase 2 study, subjects with platinum-sensitive and platinum-resistant advanced ovarian cancer were treated with trabectedin, administered as a 3-hour infusion at the starting dose of 0.58 mg/m^2 every week for 3 weeks (on Days 1, 8, and 15) of a 4-week cycle. One of the secondary objectives was to determine peak trabectedin concentration 10 minutes before the end of the infusion on Days 1, 8, and 15 during Cycle 1.

The mean concentrations of trabectedin on Days 1, 8, and 15 during Cycle 1 were between 3.04 and 3.22 ng/mL. Variability of concentrations between subjects ranged from 45% to 57 %CV on each day. The plasma concentrations reported in this study were within the range observed in subjects previously treated on the same dosing regimen in another study, Study ET-743-INT-3 (see below).

Phase 1 Study ET743-USA-11

This was a Phase 1, single-center, open-label, uncontrolled, dose-finding evaluation of escalating dose levels of trabectedin. The primary objective was to determine the MTD of trabectedin when administered in combination with Doxil (doxorubicin HCl liposome injection). One secondary objective was to study possible interactions between trabectedin and pegylated liposomal doxorubicin (Doxil).

The planned dose escalation groups for trabectedin were 0.4, 0.6, 0.75, 0.9, 1.1, and 1.3 mg/m^2. Trabectedin was administered in combination with Doxil 30 mg/m^2 every 21 days to subjects with advanced malignancies.

Results: 1.Doxil: The population analysis included concentration-time data from 30 subjects. Pegylated liposomal doxorubicin showed a long terminal half-life (74 hours), a slow clearance (0.037 L/h), and a small volume of distribution (3.9 L). No evidence of changes was found in pegylated liposomal doxorubicin clearance within the range of trabectedin doses studied. The clearance and distribution volume estimates for pegylated liposomal doxorubicin when coadministered with trabectedin in the present study were comparable with previously reported values.

2. Trabectedin: Plasma concentrations of trabectedin generally increased with an increase in the dose administered. Maximum concentrations of trabectedin in plasma were typically observed either during or immediately prior to the end of the infusion for all dose-level cohorts (31 subjects in total). Concentrations then declined in a multi-exponential manner upon cessation of the IV infusion, with a marked and rapid decline seen initially followed by a more prolonged distribution and terminal phases. For the 3 highest dose-level cohorts, the range of mean clearance values of trabectedin was narrow, ranging from 40.8 L/h to 48.4 L/h. Mean values for volume of distribution ranged from 2395 to 3093 L. These results are consistent with those reported previously. The mean clearance values for the 0.4 mg/m^2 and 0.6 mg/m^2 cohorts were higher (74.5 L/h and 70.9 L/h, respectively), whereas the mean values for volume of distribution were lower (744 L and 1595 L, respectively) relative to the 3 higher dose groups. The plasma concentrations of trabectedin were consistently measurable at 168 hours after the end of the infusion following doses of 0.9 mg/m^2 and

greater. Thus, the terminal phase of the plasma concentration-time profiles for the higher dose groups (mean, 75.6 hours to 93.0 hours) was estimated with a greater degree of accuracy, relative to the lower dose groups (mean 19.6 hours and 43.1 hours, respectively). This accounts for the inconsistency in the estimates of plasma clearance and distribution volume noted above. Pharmacokinetic parameter values of trabectedin in the present study were similar to those reported previously when trabectedin was given as a single agent.

Evaluator's comment

The variability in this study was moderate for trabectedin PK (for the 1.3mg/m^2 dose, the CV was 22.2% for CL, 13.3% for Vss, and 9.9% for t½), and the results internally consistent. The results in this study appear reliable, and those with higher doses are relevant to the present application.

Phase 2 Study ET743-INT-3

This open-label, randomized, Phase 2, non-comparative, multicenter study evaluated the efficacy and safety of two dosing regimens of trabectedin as third-line therapy for subjects with locally advanced or metastatic breast cancer who had been previously treated with both anthracyclines and taxanes. One of the secondary objectives was to evaluate and compare the PK profile of trabectedin during Cycles 1 and 2 of therapy. Subjects assigned to Treatment Arm A (trabectedin, 3/4 weeks) received trabectedin as a 3-hour infusion, at the dose of 0.58 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle. Subjects assigned to Treatment Arm B (trabectedin, 1/3 weeks) received trabectedin as a 3-hour infusion, at the dose of 1.3 mg/m^2 on Day 1 of a 21-day cycle.

PK parameters were evaluated for trabectedin at the more relevant dose (for the present application) of 1.3mg/m^2. Trabectedin exhibited a relatively high plasma clearance. The mean value was 40 L/hr for subjects in the trabectedin, 1/3 weeks treatment arm. Given that the blood/plasma ratio of trabectedin is 0.89 in humans, the mean blood clearance of trabectedin was approximately 49 L/hr. This is approximately 0.6 times that of human hepatic blood flow (≈80 L/hr). The volume of distribution of trabectedin for subjects in the trabectedin, 1/3 weeks treatment arm was greater than 4000 L, and higher than the volume of total body water (≈42 L). Apparently, trabectedin distributes extensively to peripheral tissues. Overall, the values of PK parameters in this study were within the range observed when trabectedin was administered as a 3-hour IV infusion and 24-hour IV infusion at various doses in previous studies

The pharmacokinetic parameters of trabectedin for each treatment arm were compared. The apparent differences in the systemic clearance and volume of distribution at steady state values between the 2 treatment arms are likely due to the limitations in estimating the terminal half-life (and AUC_∞) for subjects in the trabectedin, 3/4 weeks treatment arm. Most PK samples in this lower dose treatment were below the limit of quantification of the analytical assay after 48 hours. Thus, CL values were likely overestimated, and Vss values were likely underestimated for subjects in the trabectedin, 3/4 weeks treatment arm. A more accurate estimation of the $t_{\frac{1}{2}term}$ (and AUC_∞) was obtained at the higher dose in the trabectedin, 1/3 weeks treatment arm, where the plasma concentration of trabectedin could be measured at 168 hours after dosing. The mean plasma C_{max} and AUC_{48h} values of trabectedin after the first administered dose of 0.58 mg/m^2 and 1.3 mg/m^2 were dose-proportional. Notably, neither parameter was affected by the different sampling interval employed for each treatment arm. These latter results suggest the pharmacokinetics of trabectedin are comparable for each regimen. The 90% confidence intervals (CI) for the ratios of geometric mean of dose-adjusted AUC_∞, AUC_{last}, and C_{max} from Cycle 2 versus Cycle 1 for each treatment arm were calculated. On average, plasma concentrations were 7.6% lower to 25.7% higher in Cycle 2 than Cycle 1 for subjects in the trabectedin, 3/4 weeks treatment arm. For those in the trabectedin, 1/3 weeks treatment arm, plasma concentrations were 7.2% to 30.5% higher in Cycle 2 than Cycle 1.

The report stated that differences in parameter values between Cycle 2 and Cycle 1 were likely clinically insignificant because they were within the degree of intersubject variability. In addition, pharmacokinetic parameters, CL, Vss, and $t_{\frac{1}{2}term}$ were not statistically significantly different at a 5% level of significance when Cycles 1 and 2 for each treatment arm were compared.

Phase 2 Study ET743-STS-201

This pivotal randomized, multicenter, open-label study of trabectedin, administered by two different schedules (weekly [qwk] for 3 of 4 weeks versus once every 3 weeks [q3wk]) enrolled patients with locally advanced or metastatic liposarcoma or leiomyosarcoma, following treatment with an anthracycline and ifosfamide. The results showed an approximately dose-proportional increase in the mean truncated AUC values was observed after administration of trabectedin at a dose of 1.5 mg/m^2 (AUC$_{48h}$, 31.6 ng.h/mL) relative the 0.58 mg/m^2 dose (AUC$_{48h}$, 13.4 ng.h/mL)

On average, Cmax values of trabectedin were 10% and 19% higher for the q3wk, 24-hour and the qweek, 3-hour dosage groups, respectively. No accumulation was observed based on plasma AUC values for the q3wk, 24-hour dosage group. AUC of Cycle 2 was 17% higher than AUC of Cycle 1 for the qweek, 3-hour group. This degree of accumulation fell within the intersubject variability in the pharmacokinetic parameters of trabectedin observed in this study (range: 15% to 60% for Cmax and AUC$_\infty$, expressed as %CV).

Evaluator's Overview of Pharmacology

The above studies provided much pharmacological data under differing clinical circumstances about trabectedin as a single agent and in combination with Doxil. On the whole, the various results were consistent, although the way in which the population PK models were adjusted and manipulated to produce an acceptable output is sometimes disturbing, especially when the original outcomes of the models were unfavourable or difficult to explain. On the other hand, the models did predict PD/PK behaviour with a small number of exceptions in most studies, and since the numbers used were so much larger than in individual studies, variability should have been reduced, and the results more generally reliable. However the CV remained high, about 50% for CL values.

In the application, the PK results were integrated in the sponsor's *Clinical Summary*, with similar results presented in both the ROC section and in the STS section, except that the latter did not include Doxil, since this was not used in combination with trabectedin for STS.

Review of the Integrated Summary of Pharmacokinetic Properties of Trabectedin

PK Parameters of Trabectedin

The TGA evaluator prepared two tables that compared the most important PK parameters, total body clearance (CL), volume of distribution (V or Vss or Vz), and terminal half-life in those studies that had more reliable data, with those from the population PK studies.

Not included were the early Phase I studies ET-A-001-95, ET-A-002-95, and ET-A-003-95, from 1996, which limited the sampling time to 24 hours. As the terminal half-life was later shown to be about 170 hours, the PK parameters in those studies were under- or over-estimated. Studies ET-A-004-97 and ET-A-005-99 used dosing schedules different to those requested and were not included.

The first calculations showed that the values for CL from both population PK analyses were the same (31 L/h), whereas the values from the individual studies in the table were greater, ranging from 34.8 to 65.5 L/h (mean* 45L/h; median* 41.4L/h). These latter values are within the range of variability of the 31 L/h, (CV 51%), on its upper side and close to it on the lower side. The volumes of distribution from the population PK models were higher (5210 to 6040 L) than in the individual

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* Data from Study ET743-USA-11, CL 40.8-48.4L/h, not included.

studies (3718 to 4981 L), again with high variability. Terminal half-lives in the latter ranged from 95.9 hours to 148 hours, shorter that those in the population PK population, 151 to 171 hours.

Other Pharmacology Properties of Trabectedin

Dose-proportionality

Some early studies such as ET-A-004-97 and ET-A-005-99 were unable to demonstrate conclusively dose-proportionality between trabectedin dose and related PK parameters, while others such as ET743-INT-3 did. The results from the population PK analyses supported this relationship.

The *Integrated Summary in Pharmacokinetics* states the results of the population PK analyses "are in agreement with post-hoc analyses that used non-compartmental pharmacokinetic parameter values". Not mentioned also was the result of the population analyses of neutrophil toxicity that found the toxicity of trabectedin in reducing the ANC was disproportional to dose.

Effect of Body Weight and BSA

The *Integrated Summary*, in Effects of Intrinsic Factors, Body Size, does not comment on those results of the population PK analysis that found a statistically significant effect of body weight on EC_{50} for neutropenia in the model, probably because the analysis concluded it was not clinically significant. However it may have contributed to the disproportionate ANC toxicity seen in the same analysis with an increased dose of trabectedin, based as it is on BSA.

Also of note is that BSA significantly affected the PK parameters of Doxil as shown by the population PK analysis as described above.

Drug-Drug Interaction

The population PK analysis of data from patients received the combination of trabectedin and Doxil compared to those from other studies receiving trabectedin alone, showed that the plasma clearance of trabectedin was reduced by about 30% with co-administration of Doxil, as was the volume of the central compartment. The *Integrated Summary* refers to this result and notes that it was not confirmed in individual studies. The evaluator argued that it has significance and may be an explanation of the increased toxicity seen with the combination.

The population PK analysis of trabectedin PKs and increases in liver enzymes was useful in distinguishing the effects on liver enzymes and on serum bilirubin and of confirming the protective effect of dexamethasone, and partly explaining its mode of action.

Evaluator's Conclusions about the Integrated Summary of Pharmacokinetics

The *Summary* is generally correct, minimising aspects that suggest difficulties with the use of the drugs, as expected. Most of the information is not critical to the safe practical use of trabectedin in the clinic, and the population PK analyses usefully point to further studies to be done and directions to follow.

Efficacy

Relapsed Ovarian Cancer

Introduction

The pivotal trial was entitled "An Open-Label, Multicenter, Randomized, Phase 3 Study Comparing the Combination of Yondelis with Doxil/Caelyx or Doxil/Caelyx Alone in Subjects with Advanced Relapsed Ovarian Cancer". The study was initiated on the 20 April 2005, and the clinical cutoff was the 15 May 2008. At this time, the number of patients who died had not reached the number required for a final analysis of overall survival. Interim analyses were done and repeated as described later. The study and any amendments were reviewed by an Independent Ethics

Committee or Institutional Review Board. The study was conducted according to the ethical principles of the Declaration of Helsinki, consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. Informed consent was obtained within 14 days before the subject's first dose.

The primary objective of this study was to compare the Progression Free Survival (PFS) after treatment with either the combination of trabectedin plus Doxil/Caelyx or Doxil/Caelyx monotherapy of patients with ovarian cancer.

Secondary objectives were to compare overall survival (OS) between the two treatment arms; to compare the overall objective response rate (ORR) between the two treatment arms; to compare the safety profiles between the two treatment arms; and to characterize the PK of trabectedin and Doxil/Caelyx.

Tertiary objectives were to evaluate patients' quality of life (QOL) and the pharmacoeconomics of the combination; and to exploratory pharmacogenomic profiles and the relationship between circulating tumour cells (CTCs), and the response to therapy, disease progression, and OS.

The study was an open-label, multicenter, randomized, controlled Phase 3 study comparing the combination of Doxil/Caelyx, 30 mg/m^2, administered as a 90-minute IV infusion followed by trabectedin, 1.1 mg/m^2, as a 3-hour IV infusion, every 3 weeks, with Doxil/Caelyx alone at a dose of 50 mg/m^2, administered as a 90-minute IV infusion every 4 weeks. Subjects who had been treated previously for advanced ovarian cancer, and for whom a first-line platinum-based chemotherapy regimen had failed were enrolled in this study. At the time of randomization, subjects were to be stratified on the basis of platinum sensitivity of disease (sensitive or resistant) and baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0 to 1 or 2). However the number of subjects with an ECOG performance status score of 2 was limited in this study, therefore, the ECOG stratification factor was excluded in the stratified log rank test.

The final analysis of overall survival (OS) was to be done when 520 death events had occurred. In the present application, 300 deaths in total had occurred. In response to a related question, the sponsor provided an updated analysis of OS as requested by the FDA. This update (to 31 May 2009) was based on 419 deaths, 81% of those required for the final analysis.

Approximately 650 subjects were to be randomly assigned to one of the treatment arms over 2 years. The analysis of the primary endpoint, PFS, was to be conducted after at least 415 events (disease progression or death) were observed. An interim analysis of safety was to be performed when approximately 100 subjects were randomly assigned.

Accrual was to be monitored to ensure that the number of subjects enrolled in the group with platinum-resistant disease did not exceed 50% of the study population. An Independent Data Monitoring Committee (IDMC) reviewed efficacy and safety data on an ongoing basis and made recommendations to the sponsor regarding study conduct. In addition, a study steering committee composed of study investigators periodically reviewed other issues related to study conduct and offered advice as needed.

A patient's treatment was continued until disease progression occurred or until the patient experienced a confirmed complete response (CR) for at least 2 cycles. It was expected that all patients would continue treatment for approximately 3 to 6 cycles, unless disease progression occurred. Subjects were to be followed for disease progression, the start of new therapy (if applicable), and for survival every 8 weeks during the study and after study treatment was

permanently discontinued for the first 2 years and then every 3 months thereafter. This study would be designated as complete when 520 deaths were observed.

Evaluator's comment

The use of trabectedin in combination with another agent in the pivotal trial was justified by the conclusion that trabectedin showed activity in ROC in the three Phase 2 trials included in this application. Doxil/Caelyx itself is accepted as effective second-line therapy for this disease, and so is ethically acceptable as the comparator arm. Given the possibility of increased efficacy of the combination of Doxil/Caelyx and trabectedin, the test arm is also acceptable.

The primary objective had been overall survival (OS), but was changed and is discussed in a following section on Protocol Amendments.

Selection of patients

Evaluator's comment

Patients who relapsed or progressed within 6 months of first platinum treatment were not eligible. Those relapsing or progressing after the last platinum treatment of 6 cycles were eligible and were classified as platinum-resistant if the relapse/progression was less than 6 months after the last platinum treatment, and platinum-sensitive if longer than 6 months.

The trial from its start on 20 April 2005 randomised 440 patients with both measurable and non-measurable disease. This inclusion criterion was changed on 19 December 2006, 20 months after the trial began, at the FDA's request to include only patients with measurable disease, who were then enrolled until the clinical cut-off of 15 May 2008 when 672 patients in total had been randomised. Analyses of the primary endpoint of Progression Free Survival (PFS) were based on two populations - those with measurable disease, and all patients randomised, and the results before and after the change to the criterion compared. This produced a large number of analyses. However, as shown later, the number of patients in each arm with non-measurable disease was small (24 and 8).

Efficacy Measurements

Efficacy was assessed by determination of the PFS, OS, and overall response rate (ORR).

Assessment was done at screening, and every 8 weeks during the treatment period and after subjects stopped treatment. Measurable disease and the response criteria used in this protocol are those defined in the RECIST guidelines and were based on radiological assessment only. [20]
Objective Response Rates, Overall Responsive Rates, and Best Overall Response Rates were also assessed as secondary endpoints.

Evaluator's comment

Objective response was determined for both target and non-target individual lesions, and described a patient's response, as when results were reported as Objective Response Rates. Overall response was determined by considering the target and non-target lesions, and whether any new lesions had occurred. Overall response included only Complete Response (CR) and Partial Response (PR), whereas Best Overall Response considered other factors such as the duration of the objective response, and could include Stable Disease (SD), Progressive Disease (PD) and Not Evaluable (NE).

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[20] RECIST: The Response Evaluation Criteria in Solid Tumours (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response using X-ray, CT and MRI.

Statistical aspects

The patient populations analysed for efficacy were the "all-randomised", "all-measurable", and "all-evaluable"; for safety the "all-treated". Others were the PK analysis set, and the pharmacogenomic set. The variables of secondary efficacy also included a definition of response or progression based on the concentrations of CA-125.[21]

"All Randomized Subjects" analysis set was defined as all subjects who are randomized to this study, independent of whether they received study drug or not.

"All Measurable Subjects" analysis set was defined as all randomized subjects who have measurable disease at baseline as assessed by the independent review (any of the independent radiologist reviewers). Measurable disease is defined as having at least one lesion measured with diameter of ≥20 mm using conventional techniques or of ≥10 mm using a spiral CT scan.

"All Evaluable Subjects" analysis set was defined as all measureable subjects who received at least one dose of Yondelis or Doxil/Caelyx, and for whom at least one post-baseline response evaluation is available before the start of subsequent therapy for ovarian cancer, as assessed by the independent radiological review.

"All Treated Subjects" analysis set was defined as all randomized subjects who receive at least one dose of Doxil/Caelyx or Yondelis. Subjects who receive dexamethasone as pre-medication but do not receive Doxil/Caelyx nor Yondelis were not be included in "All Treated Subject" analysis set.

Primary Efficacy Endpoint

The primary efficacy analysis was the PFS of the patients with measurable disease, assessed by independent radiologists. Table 3 provides a summary of the key PFS analyses and identifies the corresponding methodology.

Table 3: Summary of key PFS analyses and related methodologies

Analysis Set	Data Source	Method of Analysis
All-Measurable Subjects	Independent radiologist evaluations	Unstratified log-rank (primary) Stratified log-rank Cox proportional hazard
All-Measurable Subjects	Investigator tumor evaluations	Unstratified log-rank
All-Randomized Subjects	Independent oncologist evaluations	Unstratified log-rank
All-Randomized Subjects	All investigator data	Unstratified log-rank

The number of events, subjects censored, the estimate of medians and 95% confidence intervals (CIs) for the medians were summarized.

Progression-free survival rates were estimated using the Kaplan-Meier method at 6 months and 1 year. Additional analyses were to compare PFS between treatment arms by a 1-sided log-rank test, stratified by performance status (ECOG performance status score 0 or 1 versus 2) and platinum sensitivity (platinum-sensitive versus platinum-resistant).

Also a Cox proportional hazards model was used to compare 2 treatment arms as a secondary analysis. Prognostic factors included the following baseline information as covariates: baseline

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[21] CA-125 (cancer antigen 125 or carbohydrate antigen 125) is a protein that in humans is encoded by the *MUC16* gene. MUC16 is a member of the mucin family glycoproteins. CA-125 has found application as a tumour marker or biomarker that may be elevated in the blood of some patients with specific types of cancers.

ECOG performance status score (0 or 1 or 2), platinum sensitivity (platinum-sensitive or platinum-resistant), race (white or non–white), baseline CA-125 (<2 times ULN or ≥2 times ULN), baseline age (<65 or ≥65), baseline liver or lung involvement (yes or no), and prior taxane use (yes or no). From the Cox proportional hazards regression, Hazard Ratio (HR) estimates and their 95% CIs were estimated for treatment and for the prognostic factors.

The sample size of 650 randomised patients, and the assumptions used to estimate it are described above.

Evaluator's comment

The original protocol, before it was amended, calculated the same sample size, 650, based on an assumption of a median OS of 62.7 weeks for the Doxil/Caelyx group of patients, and 83.4 weeks for the Doxil/Caelyx plus trabectedin combination with 520 deaths. The amended protocol calculated the sample size as the same, 650, based on an assumed median PFS of 16 weeks with Doxil/Caelyx treatment, and 22 weeks with Doxil/Caelyx plus trabectedin.

Protocol Amendments

The initial protocol that was approved on 11 January 2005 underwent three amendments on the following dates: 9 March 2005, when no subjects were enrolled; 24 October 2005, when 28 subjects were randomized; and 19 December 2006, when 440 subjects were randomized. The major revisions for the 3 amendments are shown below:

Amendment INT-1: identified substantial changes that included the following:

– dexamethasone could be substituted with its equivalent;

– multigated acquisition (MUGA) scan and 2-dimensional (2-D) echocardiograms were not required unless the subject had a history of cardiac conditions or there was suspicion of a cardiac condition.

– Allowing only those subjects with recurrence or progression of more than 6 months after the beginning (first dose) of the initial line of platinum-based chemotherapy for ovarian cancer.

– Revised tumour assessment text following the United States FDA request to have CA-125 measurements at the same time as tumour assessments. Also, CA-125 elevation alone did not necessarily trigger an unscheduled tumour assessment.

Amendment INT-2: identified multiple minor changes to improve clarity and several substantial changes. This amendment had substantial changes that included the following key items:

– Changed the wording of the tertiary objectives;

– Added text to clarify some of the inclusion and exclusion criteria;

– Provided clarification regarding the following: cardiovascular safety; recalculation of body surface area (BSA); the methods and schedule of tumour assessments; the timing for CA-125 results; signs or symptoms deemed related to the disease; the PK process and sampling method; and when and what efficacy assessments were obtained during the follow-up phase after treatment termination.

Amendment-INT-3: identified additional substantial changes to the protocol. All appropriate sections of the protocol were revised. Following the approval of Amendment-INT-3, minor editorial changes were made without the need to further amend the protocol. The major changes were as follows:

– Changed from 2 primary efficacy endpoints, OS and PFS, to a single primary endpoint, PFS. This change occurred after discussion with the FDA and the European Committee for Medicinal

Products for Human Use. Overall survival became a secondary endpoint; the sample size was unchanged;

– Expanded the inclusion criteria to include subjects with epithelial fallopian tube carcinoma;

– Changed the inclusion criteria prospectively so only subjects with measurable disease would be enrolled; measurable disease was based on the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (Attachment 6 of the protocol) using radiologic assessments only;

– Modified the exclusion criteria to clarify that subjects with less than 4 weeks from radiation or experimental therapy, less than 2 weeks from last dose of hormonal therapy, or less than 3 weeks from prior chemotherapy or biological therapy, would be excluded;

– Clarified that all subjects must have a MUGA scan or 2-D echocardiogram at baseline and after the permanent discontinuation of study treatment.

– Revised Continuation of Treatment Criteria to specify that treatment could be allowed up to 72 hours (3-working days) outside the 3-week treatment period if a response/benefit was documented over at least 6 cycles of therapy;

– Clarified that an isolated CA-125 measurement should not be considered as the sole evidence of disease progression, and all clinical signs or symptoms as identified in the protocol were to be considered. Subjects should have radiologic documentation of disease progression before study withdrawal;

– Clarified the continued assessment by a CT scan every 8 weeks after permanent discontinuation of study treatment for subjects who had a complete response; and

– Clarified what procedures were to be performed after subjects have permanently discontinued from study treatment.

Evaluator's comment

 The most significant changes to the protocol were in the third amendment, which changed the primary efficacy endpoints, and to include only patients with measurable disease. These changes were made late in the trial, 20 months after the start, and after 440 of the 650 patients had been randomised (see later discussion).

Methods of Analysing Efficacy and Safety

Central Review Assessment

The primary analysis of PFS was based on the central radiology review data provided by radiologists not involved in the study. This was called the independent radiologists' review. Although protocol Amendments 1 and 2 originally allowed subjects with non-measurable disease to be enrolled, the primary analysis was performed only on subjects with measurable disease (All-Measurable Subjects). Overall, 27 subjects had non-measurable disease, 18 in the would be excluded Doxil/Caelyx monotherapy arm, and 9 in the trabectedin + Doxil/Caelyx arm.

In assessing the final PFS, the sponsor combined these data with death information for subjects who did not progress but died, and with the information on the start of subsequent therapy for ovarian cancer to provide the final event date (either progression or death) for PFS.

Additional analyses of PFS were performed by oncologists who did not participate in the study and who assessed the radiologists' assessments. This was called the independent oncologists' review, and also considered "relevant clinical information" in the assessment. A further secondary analysis was based on the investigator's assessment of tumour response, date of progression, and best overall response. Note however that the population analysed in this case was "evaluable" and not "all-randomised", as in the primary analysis.

A subgroup of patients defined by platinum-sensitivity (platinum-sensitive, platinum-resistant) were also analyzed for efficacy.

Patient reported outcomes were assessed using two cancer-specific instruments, Quality of Life (QOL) questionnaires QLQ-C30 and QLQ-OV28, and one generic measure of health for clinical and economic appraisal, EQ-5D.

Statistical Methods

Hypothesis tested: The Doxil/Caelyx plus trabectedin dosing regimen was to be declared better than the Doxil/Caelyx only dosing regimen if the PFS was better with a p-value less than or equal to 2.5%. PFS was to be analysed when approximately 415 PFS events (progression on independent review, or death) were seen.

Overall Survival (OS) was to be compared between treatment arms using an unstratified one-sided log-rank test. The Doxil/Caelyx plus trabectedin dosing regimen was to be declared better than the Doxil/Caelyx only dosing regimen if the OS was better with a p-value less than or equal to the significance level as specified by the "alpha spending function". The overall 2.5% significance level was to be spread over two OS analyses, one, when approximately 415 events on PFS (progression or death) were seen, and one when approximately 520 events on OS (death) were seen. The exact significance levels were to be calculated once the exact number of events was known, based on an "O'Brien-Fleming alpha spending function".

The objective response rate (ORR) was to be compared between treatment arms using an unstratified Fisher's Exact Test at a 5% significance level.

Results

Efficacy results

Nine subjects did not receive the study drug (6 subjects in the Doxil/Caelyx monotherapy arm and 3 in the trabectedin + Doxil/Caelyx arm). The remaining 663 randomized subjects received at least 1 dose of study medication (trabectedin + Doxil/Caelyx, 334; Doxil/Caelyx alone, 329) and comprise the All-Treated Subjects safety analysis population. The commonest cause of treatment discontinuation was disease progression, more frequent in the Doxil/Caelyx only arm (54% compared with 42%). Adverse events were a more frequent cause of discontinuation in the trabectedin plus Doxil/Caelyx arm than in the monotherapy arm (21% vs 12%).

The report stated that the demographic and baseline disease characteristics for subjects were balanced between the two treatment arms. The evaluator noted that the largest difference shown was 11% more patients (n=38) of ECOG status 0 in the combination arm than in the monotherapy arm, which contained 68% and 57% respectively. As a better performance status can improve the clinical outcomes of treatment, this difference favours the efficacy of the combination arm.

The evaluator noted that disease characteristics at baseline were well balanced in the two arms, although a higher percentage of patients in the monotherapy arm had longer times to relapse after initial treatment and after the last treatments with platinum therapy.

Consistent with subject eligibility requirements, all subjects had received platinum-based chemotherapy and most (99%) had undergone surgery for their cancer. Two percent had received prior radiotherapy. Prior systemic cancer therapies were presented in the study report and were similar between the two arms. The most common were platinum compounds (>99%), taxanes (80%), and nitrogen mustard analogues (18%). The most frequently used concomitant treatments in both treatment arms were serotonin antagonists (75%), corticosteroids (47%), propulsives (35%), colony stimulating agents (29%), and anilides (29%). The evaluator noted that differences in the frequency of the same medication in the two arms reflect mainly the treatments given for the drug associated toxicities that sometimes had a different incidence and severity in the two arms, for

example, colony stimulating factors and blood products for the greater hematological toxicity of the combination treatment.

The number of subjects who received subsequent therapy for ovarian cancer was comparable in both treatment arms (72% of patients in the Doxil/Caelyx monotherapy arm and 69% in the trabectedin + Doxil/Caelyx arm). The evaluator noted that the similarity of subsequent treatment is important in the assessment of overall survival as it validates the comparison of the results of OS for each trial arm for those patients who received further treatment after the trial.

The timing of the treatment cycles for combination therapy and monotherapy differed. The combination of Doxil/Caelyx, 30 mg/m^2, administered as a 90-minute IV infusion followed by trabectedin, 1.1 mg/m^2, as a 3-hour IV infusion, were administered every 3 weeks, and the monotherapy treatment with Doxil/Caelyx alone at a dose of 50 mg/m^2, administered as a 90-minute IV infusion every 4 weeks.

A higher percentage of subjects in the combination treatment arm received 7 or more cycles of therapy (37.5% in the trabectedin + Doxil/Caelyx arm compared with 24% in the Doxil/Caelyx monotherapy arm). Fewer than 10% of subjects in either treatment arm received only 1 cycle of treatment. The evaluator noted that dose intensity was presented in two ways, the first as mg/m^2 per cycle as defined in the Statistical Analysis Plan. The other was as mg/m^2 per week. If the first definition is considered, a median dose intensity for trabectedin of 0.907 mg/m^2 was administered compared to the target dose of 1.1 mg/m^2, giving a relative dose intensity of 82.5%. The median dose intensity for Doxil/Caelyx in the combination arm was 24.7 mg/m^2, compared to the target dose of 30mg/m^2, giving a relative dose intensity of 82.7%. In the monotherapy arm, the median dose intensity of Doxil/Caelyx was 46.7mg/m^2 compared to the target dose of 50mg/m^2, giving a relative dose intensity of 92%. These data show that the relative dose intensity of the one drug in the monotherapy arm was higher than each of those in the combination arm. However such a reduction in dose intensity would not be clinically significant when comparing two drugs with one drug treatment.

Regarding the difference noted above in the number of subjects who received 7 cycles, the difference in the duration of the cycles in each is to be considered. Seven cycles in the combination arm were over 21 weeks, and over 28 weeks in the monotherapy arm. The difference noted would be reduced when the number of subjects completing 28 weeks of treatment were compared in each group.

Of the 299 subjects in the Doxil/Caelyx monotherapy arm who received at least 2 treatment cycles, 117 (39%) had a dose reduction. Of the 309 subjects in the trabectedin + Doxil/Caelyx treatment arm who received at least 2 cycles, 132 (43%) had a reduction of trabectedin and 133 (43%) had a dose reduction of Doxil/Caelyx.

The evaluator noted that cycle delays were comparable in the two arms up to the second cycle. After that cycle delays were more common in the combination arm. Among the 608 subjects with at least 2 treatment cycles, cycle delays were less common in the Doxil/Caelyx monotherapy arm (55%) than in the trabectedin + Doxil/Caelyx arm (83%).

Forty seven percent of the subjects in the Doxil/Caelyx monotherapy arm compared with 78% of the subjects in the trabectedin + Doxil/Caelyx arm had a cycle delay due to an adverse event. Drug-related adverse events were the most common reason for cycle delay. Among the subjects who received at least 2 treatment cycles, 133 (44%) subjects in the Doxil/Caelyx monotherapy arm and 226 (73%) subjects in the trabectedin + Doxil/Caelyx arm had at least 1 cycle delay due to a drug-related adverse event. The most common adverse events resulting in cycle reduction in all subjects included hand-foot syndrome (63 [19%] in the Doxil/Caelyx monotherapy arm and 14[4%] in the trabectedin + Doxil/Caelyx arm) and neutropenia (9 [3%] in the Doxil/Caelyx monotherapy arm and 44[13%] in the trabectedin + Doxil/Caelyx arm).

The evaluator noted that these data show more dose delays and dose reductions occurred in the combination arm compared to the monotherapy arm.

Primary Efficacy and Additional Endpoints

In the several efficacy analyses, the patient populations were either the patients with measurable disease, or all patients randomised. The primary endpoint was PFS in patients with measurable disease. The evaluator noted that as measurable disease was the measure assessed by independent radiologists, they would have no role in evaluating non-measurable disease. However both non-measurable and measurable disease were assessed by independent oncologists, presumably to provide an assessment of the response of this population of patients. As well, for no obvious reason, assessments were also done by investigators, perhaps to provide supporting data. Subgroups of patients with different prognostic factors were also analysed in the same way.

When added to the analyses of secondary efficacy, these analyses make this study the most analysed in the evaluator's experience. In spite of this, the primary analysis of efficacy remains that of PFS in all patients with measurable disease, and in those stratified as having platinum- sensitive disease and platinum-resistant disease, and this will receive the main emphasis in this evaluation.

Primary Analysis by Independent Radiologists of the Patient Population with Measurable Disease

Based on the independent radiologist review, 389 PFS events (shown in Table 4 as "Number failed") had been observed (194 in the Doxil/Caelyx monotherapy arm and 195 in the trabectedin + Doxil/Caelyx arm) at the time of data cutoff. Treatment with trabectedin + Doxil/Caelyx resulted in a 21% risk reduction for disease progression or death compared with Doxil/Caelyx monotherapy (HR=0.79; 95% CI: 0.65; 0.96, log-rank test p=0.0190). The median PFS was 5.8 months for the Doxil/Caelyx only arm and 7.3 months for the trabectedin + Doxil/Caelyx arm, and based on the results used to calculate the Hazard Ratios, the proportion of patients with no progression at 6 months were 48.9% (95% CI: 42.5; 55.0) in the monotherapy arm compared with 54.6% (95% CI: 48.5;60.4) in the trabectedin + Doxil/Caelyx arm. At 12 months the figures for the monotherapy arm were 18.5% (95% CI: 12.9;24.9) compared with 25.8% (95% CI: 19.7;32.3) in the trabectedin + Doxil/Caelyx arm (Figure 1).

Table 4: PFS – Study ET743-OVA-301

Descriptive[a]	DOXIL	Trabectedin/DOXIL
Progression free survival (months)		
Number of Assessed	317	328
Number Censored (%)	123 (38.8)	133 (40.5)
Number Failed (%)	194 (61.2)	195 (59.5)
25% Quantile (95% CI)	2.4 (1.9; 3.6)	2.6 (1.9; 3.7)
Median (95% CI)	5.8 (5.5; 7.1)	7.3 (5.9; 7.9)
75% Quantile (95% CI)	10.1 (8.9; 11.6)	12.7 (11.1; 14.8)
4 Months PFS Rate % (95% CI)	58.9 (52.7; 64.5)	67.6 (61.9; 72.6)
6 Months PFS Rate % (95% CI)	48.9 (42.5; 55.0)	54.6 (48.5; 60.4)
12 Months PFS Rate % (95% CI)	18.5 (12.9; 24.9)	25.8 (19.7; 32.3)
Overall P-value[b]	0.0190	
Hazard Ratio (95% CI)(over DOXIL)		0.79 (0.65; 0.96)

[a] Based on Kaplan-Meier product limit estimates.
[b] Log rank test.
The Hazard Ratio is calculated as the hazard in the Trabectedin/DOXIL dosage group, divided by the hazard in the DOXIL dosage group.
teff01a_rpfsir.rtf generated by rpfsir.sas.

Figure 1: Kaplan-Meier Plot for Progression-Free Survival: Independent Radiologist Review
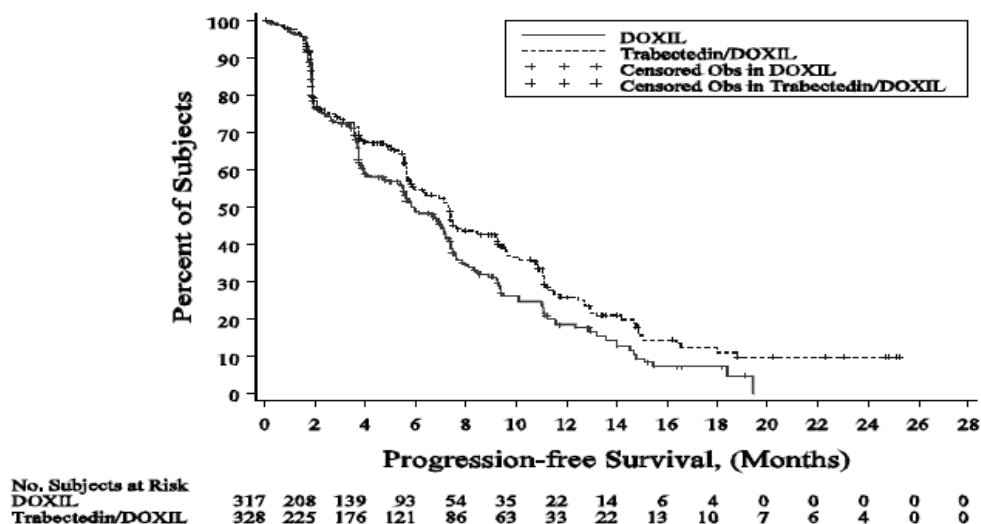
Evaluator's comment

The study has used the analysis of PFS in the measurable population rather than in the ITT population as the primary efficacy endpoint. The above data shows that the PFS interval in these patients was significantly longer as shown by the p-value in the combination therapy arm than in the monotherapy arm. Whether the degree of increase in the PFS as shown by the 95% CI is also clinically significant will be discussed later.

Analysis by Independent Oncologists of the Intention-to Treat (ITT) Patient Population, also referred to as the All-Randomised Patient Population

This population included 28 patients with non-measurable disease in the Doxil/Caelyx arm and 8 in the trabectedin + Doxil/Caelyx arm in addition to those with measurable disease. Based on the independent oncologist review, 432 PFS events had been observed at the time of data cutoff (Table 5), 225 (67.2%) in the Doxil/Caelyx monotherapy arm and 207 (61.6%) in the trabectedin + Doxil/Caelyx arm.

Table 5: PFS– Study ET743-OVA-301

Descriptive[a]	DOXIL	Trabectedin/DOXIL
Progression free survival (months)		
Number of Assessed	335	336
Number Censored (%)	110 (32.8)	129 (38.4)
Number Failed (%)	225 (67.2)	207 (61.6)
25% Quantile (95% CI)	1.9 (1.9; 2.7)	2.5 (1.9; 3.7)
Median (95% CI)	5.6 (4.2; 6.8)	7.4 (6.4; 9.2)
75% Quantile (95% CI)	9.5 (8.4; 11.3)	12.7 (11.1; 14.7)
4 Months PFS Rate % (95% CI)	56.6 (50.8; 62.1)	68.5 (63.0; 73.4)
6 Months PFS Rate % (95% CI)	46.2 (40.2; 52.0)	57.3 (51.3; 62.8)
12 Months PFS Rate % (95% CI)	16.2 (11.3; 21.9)	26.0 (20.2; 32.1)
Overall P-value[b]	0.0008	
Hazard Ratio (95% CI)(over DOXIL)		0.72 (0.60;0.88)

[a] Based on Kaplan-Meier product limit estimates.
[b] Log rank test.
The Hazard Ratio is calculated as the hazard in the Trabectedin/DOXIL dosage group, divided by the hazard in the DOXIL dosage group.

Treatment with trabectedin + Doxil/Caelyx resulted in a 28% risk reduction for disease progression or death compared with Doxil/Caelyx monotherapy (HR=0.72; 95% CI: 0.60; 0.88: p=0.0008). The median PFS was 5.6 months (95% CI: 4.2; 6.8) for the Doxil/Caelyx monotherapy arm and 7.4 months (95% CI: 6.4; 9.2 months) for the trabectedin + Doxil/Caelyx arm. The proportion of patients with no progression at 6mth were 46.2% (95% CI: 40.2; 52) in the monotherapy arm compared with 57.3% (95% CI: 51.3; 62.8) in the trabectedin + Doxil/Caelyx arm. The proportion of progression-free subjects at 12 months in the monotherapy arm was 16.2% (95% CI: 11.3; 21.9) compared with 26% (95% CI: 20.2; 32.1) in the trabectedin + Doxil/Caelyx arm (see Figure 2).

Figure 2: Kaplan-Meier Plot for Progression-Free Survival: Independent Oncologist Review

No. Subjects at Risk														
DOXIL	335	216	148	100	60	40	23	16	8	7	3	2	1	0	0
Trabectedin/DOXIL	336	231	183	135	99	72	40	24	15	11	8	6	4	0	0
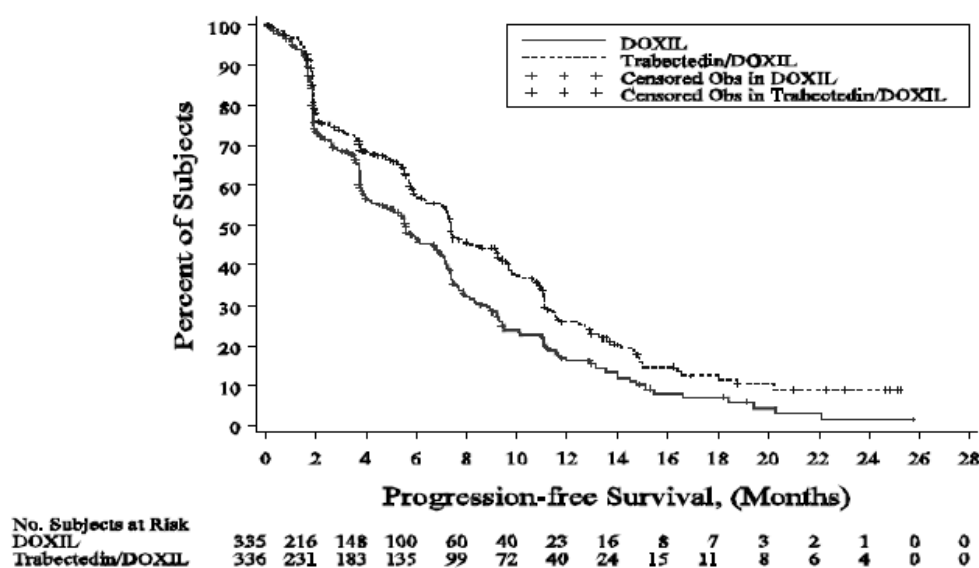
Evaluator's comment

The analysis by the independent oncologists of the PFS for the ITT population, above, gave similar results to those of the previous analysis. Unfortunately the comparison between the results for the population with measurable disease and the ITT population is not precise because the patient populations differed, although the numbers of patients with non-measurable disease in the ITT population (see above) were small.

Analysis by Investigators of the Intention-to Treat (ITT) Patient Population, also referred to as the All-Randomised Patient Population

This analysis gave results consistent with those for the two previous analyses (above) and is not discussed further in this evaluation.

Additional analyses of PFS

Subgroup analyses: The PFS of several subgroups was analyzed to compare the results of the two treatment arms. The sub-groups were defined by the presence of one of the following prognostic factors: baseline ECOG performance status score, platinum-sensitive or platinum-resistant, age group (<65 years or ≥65 years), baseline CA-125 (≥2 times the ULN or <2 times the ULN), prior taxanes use (yes or no), baseline liver/lung (yes or no), race (white or non-white), and histology grade (Grades 1, 2, 3, or unknown), giving 19 subgroups. As above, two different analyses were performed, one of patients with measurable disease by independent radiologists and the second of the ITT population by independent oncologists. A similar subgroup analysis was done for Overall Survival (OS) discussed later.

Evaluator's comment: Both the statistical and clinical significance of the results were difficult to interpret. Regarding statistics, no p-values for the significance of the differences were given. The evaluator considered the point estimates (the risk of relapse) and the 95% CI of the Hazard Ratios calculated from the ratios of the periods of PFS for a subgroup with a particular variable if treated with Doxil/Caelyx plus trabectedin or Doxil/Caelyx alone. When the highest value of the HR from the 95% CI was less than 1, this favoured the combination, as patients treated with the combination were a lower risk of relapse. When the lowest value of the HR from the CI was greater than 1, this favoured the monotherapy arm.

Of the 19 subgroups of patients with measurable disease assessed by independent radiologists, 5 had CIs for the Hazard Ratios with the highest value less than 1, thus favouring combination therapy. The subgroups were patients with platinum-sensitive tumours, those <65 years, those with no prior taxane usage, those with baseline liver/lung involvement, and white patients. Of the 19 subgroups, none had the lowest value of the HR of the CI above 1, so monotherapy was not shown to be better in any subgroup. For the 14 subgroups where the CI included 1, no advantage of either regimen was demonstrated.

In the same type of analysis by independent oncologists of all-randomised patients (the ITT population), 10 subgroups had their highest HR value of the CI less than 1. They were patients with baseline ECOG PS of 0, those with platinum-sensitive tumours, those <65, those with baseline Ca125 concentrations above and those below 2 ULN, those who had prior taxane therapy, those with and without baseline liver/lung disease, white patients and those with Grade 3 histology tumours. Again, no subgroup had a CI interval favouring treatment with monotherapy, while in the remaining 9 subgroups where the CI included 1, no advantage for either regimen was demonstrated.

Overall, all results that showed a difference between treatments favoured the combination arm, and were consistent with the results of the primary efficacy endpoint (above).

Multivariate analysis of PFS using prognostic variables: A number of prognostic variables known to predict clinical outcomes in this disease were used in a multivariate analysis of PFS. The analysis in patients with measurable disease showed that subjects with an ECOG performance status score of 0, platinum sensitivity, no liver or lung involvement, and no prior taxane use (although the 95%CI for the HR for taxane use, 1 to 1.89, contained unity) were at a lower risk of relapse. For patients with both non-measurable and measurable disease, significant variables were those listed plus a CA-125 concentration > 2 x ULN at baseline.

Evaluator's comment: In these analyses, the comparisons made were of PFS between those patients with or without the defined variables in two patient populations. This did not compare the two treatment regimens but confirmed that the variables above did in fact predict a longer period of PFS.

Analysis of PFS by "Platinum-Free Interval" (PFI): The sponsor assigned intervals of 0-6, 6-12, and >12 months to all patients, based on the time from the end of their platinum treatment to relapse, as specified in the protocol. Again two analyses were done on the two patient populations, and the results are shown in Figure 3.

Figure 3: PFS as analysed by platinum-free interval

Hazard Ratio and 95% Confidence Interval
(Study ET743-OVA-301 , PFS, Independent Review, All Measurable or Randomized Subjects)

Reviewer	PFI(month)	Median(month) Mono	Median(month) Combo		HR	95% C.I.	Events/N Mono	Events/N Combo
Indep. Rad.	0-6	3.7	4.7		0.94	(0.68, 1.29)	78/109	74/109
	6-12	5.5	7.4		0.65	(0.45, 0.92)	55/86	69/122
	>12	8.9	11.1		0.7	(0.47, 1.03)	57/117	48/93
Indep. Onc.	0-6	3.7	3.7		0.94	(0.69, 1.26)	90/117	82/115
	6-12	3.8	8.4		0.54	(0.39, 0.76)	68/91	73/123
	>12	9	11.1		0.66	(0.46, 0.97)	63/122	49/94

Favoring DOXIL+Trabectedin   Favoring DOXIL

Hazard Ratio (DOXIL+Trabectedin vs. DOXIL) & 95% C.I. (Log Scale)

Evaluator's comment: The point estimates of the HRs favour the combination. The subgroup with a PFI of 6-12 months, as assessed by both groups of assessors, had a 95% CI that did not include 1, as did the subgroups with a PFI of >12 months evaluated by independent oncologists. However the CI for the PFI subgroup of >12 months as assessed by independent radiologists did include 1, and as this is a primary analysis, is in contradiction to the results for patients with a PFI of 6-12 months, since both groups would be expected to have relatively more drug sensitive disease that the patients with a PFI of 0-6 months.

Secondary Efficacy Endpoints

Overall Survival

As noted above, an analysis of OS was to be done when 415 events - progression or death - had occurred, and the final analysis of OS when 520 events – death - occurred. In the present application, 300 deaths had occurred (155 in the Doxil/Caelyx monotherapy arm and 145 in trabectedin + Doxil/Caelyx arm; 55% censored) when the report was prepared. At the FDA's request, an update to 31 May 2009 when 419 deaths had occurred (215 in the Doxil/Caelyx monotherapy arm and 204 in the trabectedin plus Doxil/Caelyx arm was supplied by the sponsor on the evaluator's request.

The updated data shows the Hazards Ratio (HR) to be 0.85 (95%CI 0.70-1.03, p=0.0920). The mean OS was 19.5 months (95%CI 17.4-22.1) in the monotherapy arm and 22.4 months (95%CI 19.4-25.1) in the combination arm. The Kaplan-Meier plot is shown in Figure 4.

Figure 4: Kaplan-Meier Plot of OS – ET743-OVA-301
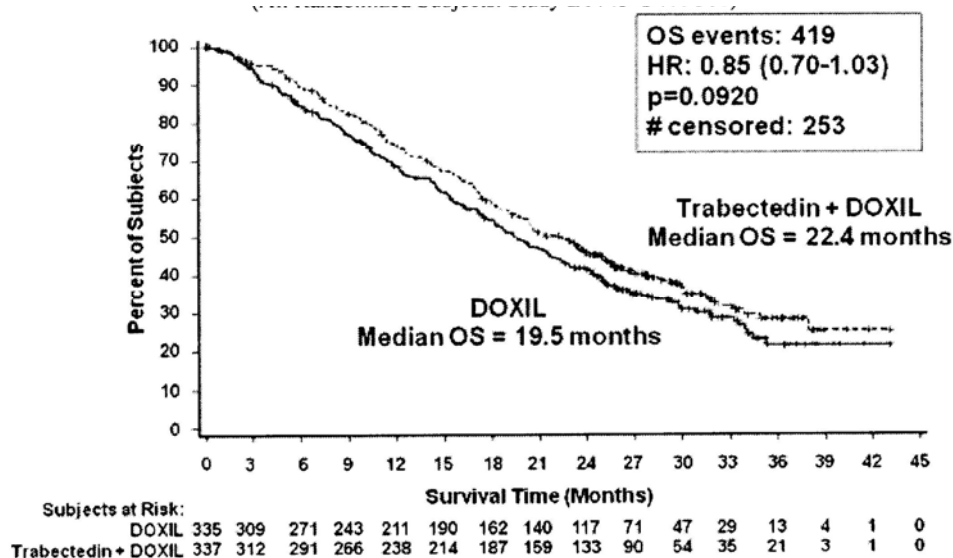
Additional analyses

Multivariate analysis of OS using Prognostic Variables: The results for the updated OS analysis was similar to the earlier analysis in the present application and showed that subjects with an ECOG performance status score of 0, disease with platinum sensitivity, CA-125 <2 times ULN, and no liver or lung involvement, were at a lower risk of death. As noted, this analysis did not compare the two treatment arms.

Subgroup analysis of OS using Prognostic Variables: This analysis was similar to that done for PFS except that all randomised patients were included, a separate analysis of patients with measurable disease was not done, and the two treatment arms compared.

Evaluator's comments: In the absence of p-values, the evaluator used the point estimates and 95% CI for the Hazard Ratios of the periods of OS for patients in each subgroup treated with either combination therapy or monotherapy, as for PFS analyses above. The updated analysis (May 2009) was similar, and was not used here. Of the point estimates for the 19 variables, 17 favoured the combination treatment, and 2 (baseline ECOG PS of 0; age >=65 years), monotherapy. When the upper and lower limits of the CIs are considered, only 2 favoured the combination with an upper value less than 1 (age < 65; CA-125 2 x ULN at baseline). No CI had a lower value greater than 1, favouring monotherapy, so that in the remaining 17 cases where the CI included 1, no difference was demonstrated in OS between the two treatments.

Subgroup analyses of OS using "Platinum-Free Interval": Subgroups with varying intervals to relapse following platinum treatment were analysed for OS, with the results shown in Figure 5.

Figure 5: Platinum free interval for OS – ET743-OVA-301

Hazard Ratio (DOXIL+Trabectedin vs. DOXL) & 95% C.l (Log Scale)
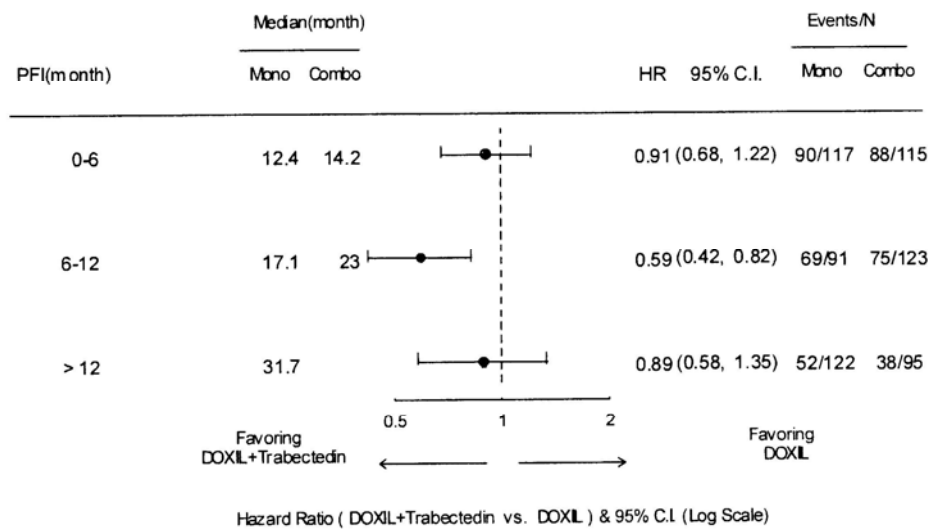
Evaluator's comment: As shown, the CI intervals for two of the three subgroups include unity and are not statistically different. Patients with a PFI of 6 to 12 months appeared to be less at risk of death when treated with combination therapy than with monotherapy. However the clinical interpretation is complicated by the result for patients with intervals longer than 12 months, who would be expected to show the same benefit as those with an interval of 6 to 12 months. The above results, however, show them to be at equal risk with either treatment.

Objective Response Rate (ORR)

The ORR assessed by independent radiologists on the All-Randomized Subjects analysis set for subjects in the trabectedin + Doxil/Caelyx arm was significantly higher (27.6% [95% CI: 22.9;32.7]) than in the Doxil/Caelyx monotherapy arm (18.8% [95% CI: 14.8;23.4]). The odds ratio for overall response was 1.646 (95% CI: 1.144; 2.367: p=0.0080) favoring the trabectedin + Doxil/Caelyx arm. For subjects with platinum-resistant disease, the ORR was 12.2% in the Doxil/Caelyx monotherapy arm and 13.4% in the trabectedin + Doxil/Caelyx arm. For subjects with platinum-sensitive disease, ORR was 22.6% in the Doxil/Caelyx monotherapy arm and 35.3% in the trabectedin + Doxil/Caelyx arm. The results for the assessment of ORR by independent oncologists were similar (30.4% [95%CI 25.5-35.6] in the combination therapy arm and 19.1% [95% CI 15.0-23.7] in the monotherapy arm) with a p value of 0.0009.

The objective response rate was assessed by independent radiologists on the basis of the Platinum-Free Interval (PFI). For the subgroup of subjects with PFI less than 6 months, the objective response rates were 12.0% and 14.8% in the Doxil/Caelyx and trabectedin + Doxil/Caelyx arms, respectively. Though the odds ratio of 1.276 (95% CI: 0.597; 2.728: p=0.5670) favored the trabectedin + Doxil/Caelyx arm, the difference was not statistically significant. For the subgroup of subjects with PFI from 6 months to 12 month, the objective response rates were 15.4% and 33.3% in the Doxil/Caelyx and trabectedin + Doxil/Caelyx arms, respectively. The odds ratio of 2.750 (95% CI: 1.391; 5.438: p=0.0041) was statistically significant in favor of the trabectedin + Doxil/Caelyx arm. For the subgroup of subjects with PFI over 12 months, the objective response rates were 27.9% and 36.8% in the Doxil/Caelyx and trabectedin + Doxil/Caelyx arms, respectively. The difference was not statistically significant.

Evaluator's comment

The ORR is clearly higher with the combination treatment for the All Randomized patient population, and for the subgroup with a PFI from 6 to 12 months. As with PFS and OS, there is again an apparent contradiction in the lack of significant benefit of the combination treatment in the subgroup with a PFI >12 months whereas the subgroup with a PFI of from 6 to 12 months subgroup did show such a benefit.

Best Overall Response Rate

The evaluator noted that these analyses compared the response rates found in the All-Evaluable population and the All-Randomised population. In the former, as expected, there were more non-evaluable patients. In each population, the rates in the combination therapy arm for CR and PR were higher than in the monotherapy arm and lower for SD. When the results of the rates for each were combined, they were as given above for Objective Response Rate (ORR).

Duration of Response

The median duration of response for all responders in each treatment arm as reviewed by independent radiologists was not significantly different, with a p-value for the log rank test of 0.82 – for the monotherapy arm, 7.7 months (range; 6.5 to 9.0) compared with 7.9 months (range; 7.4 to 9.2) for the trabectedin + Doxil/Caelyx arm. The HR was 0.95 (95% CI: 0.62; 1.46).

Evaluator's comment

The assessment by investigators showed a significant difference (p= 0.0318) in favour of the combination (9 months) compared to monotherapy (7.1 months), but is not accepted as the assessment was not independent and differs from that of the independent radiologists.

CA-125 Response and Duration

CA-125 Response: The CR and the PR rates in the Doxil/Caelyx monotherapy arm were 20% and 13% respectively and in the trabectedin + Doxil/Caelyx arm 30% and 18% respectively. No comment was made on the significance of the difference.

Evaluator's comment: The significance of this type of response, which is about twice that assessed by standard methods, is not known.

Duration of CA-125 Response: The difference in the median duration of response in each treatment arm was not significant (p= 0.141). In the monotherapy arm the duration was 7.2 months (95% CI - 7.2; 9.1) and in the combination arm 9.1 months (95%CI -7.6; 9.3).

Quality of life (QOL) assessments

An attempt was made to assess QOL by defining the clinical benefits that may have resulted from treatment based on clinical parameters and patient questionnaires.

Clinical parameters

The evaluator noted that clinical parameters assessed were limited to the response of pleural fluid, ascites and Grade 3-4 abdominal pain. No assessments were made of the effects experienced by patients with other severe and serious adverse events, so this analysis was of limited value.

Patient Questionnaires

Mean change scores across treatment arms were analyzed at every other cycle and for end of treatment. QLQ-C30 and QLQ-OV28 assessed dyspnoea, appetite, constipation, diarrhoea, abdominal/GI symptoms, peripheral neuropathy, other chemotherapy side-effects, global health status, fatigue, pain. Another questionnaire, EQ5D, assessed health status, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Statistical comparisons were made of the two arms, and did not compare the patients' clinical condition at the end of treatment with that at baseline (see comment below). No statistically significant differences between treatment arms were found except for Cycles 3 and 9 in the Fatigue symptom scale, indicating some sporadic worsening of fatigue for subjects randomized to the trabectedin + Doxil/Caelyx arm. In this statistic, no correction was made for the number of analyses done of which there were about 12 for each of the many terms, so it is expected a number would show significance by chance alone.

Evaluator's comment

The high SD for each value makes the results impossible to interpret. Of note is that in the first group the scores for Global Health Status, and for Health State in the second group were reduced in both treatment arms after treatment.

The report noted that in the trabectedin + Doxil/Caelyx arm, 11 of 28 (39%) subjects who had pleural fluid at baseline had complete resolution, compared with 4 of 27 (15%) subjects in the Doxil/Caelyx monotherapy arm. An inconsistent result from the patient questionnaires, however, was that dyspnoea improved to about the same extent in both treatment arms.

The evaluator concluded that any improvement in the patients' QOL has not been convincingly shown for either treatment arm, nor that the q3wk-24 treatment was superior in this respect to the qwk-3hr treatment.

Evaluator's conclusions on efficacy

Analysis by independent radiologists of the primary endpoint, the duration of progression free survival, showed a statistically significant prolongation of 6 weeks, from 5.8 months in the Doxil/Caelyx only arm of the study to 7.3 months in the trabectedin + Doxil/Caelyx arm. Other analyses of PFS were consistent with this result.

For the secondary variables, no statistically significant difference was demonstrated between the two treatments for overall survival (updated - 19.5 compared with 22.4 months). The objective response rate for patients from the All-Randomised population treated with the combination was statistically greater (27.6%) that those treated with monotherapy (18.8%), an 8.8% difference. The median duration of response, assessed by independent radiologists (7.7 and 7.9 months), were similar as were the rates for CA-125 response.

Of the many dozens of analyses done, only two showed a benefit of the combination – an increase of 6 weeks in the PFS and of about 9% in the objective response rate. An increase in OS was suggested in an exploratory analysis of one subgroup of a subgroup (patients with a PFI of from 6 to 12 months), and would be worth further prospective study.

Phase 2 studies of trabectedin as a single agent in the treatment of relapsed ovarian cancer

The three studies ET-B-009-99, ET-B-026-03, and ET 743–INT-11 were completed before the pivotal study and demonstrated efficacy in the treatment of ROC. In this section they were considered together and are referred to as studies 99, 03 and 11 respectively for brevity. Their design and conduct was similar to that of the pivotal trial, except as pointed out below. The trials were of trabectedin as a single agent, and the dose (and in one case the schedule) differed from that in the pivotal trial. The design of the three trials and that of the pivotal trial are shown in Table 2.

The trials had a common objective, to demonstrate efficacy and safety. Their primary endpoint, the objective response rate, differed from that of the pivotal trial, which was the time to progression (TTP). All were non-comparative studies, and chose a significant response rate based on literature reports of the response of ROC to second line chemotherapy as 15% for patients with platinum-refractory disease, and 20% for patients with platinum-sensitive disease. Subsequently it was

decided that the TTP was a better measure of efficacy than the response rate in this disease, so this was used in the pivotal trial (see previously).

Compared to the pivotal trial, which used a 3-hour infusion of trabectedin every 3 weeks, one arm of Study 03 used a 24-hour infusion 3 weekly. However the other arm of this trial used a 3-hour infusion 3 weekly, as did studies 99 and 11. Doses however differed and ranged from 0.58mg/m^2 to 1.65mg/m^2 compared to 1.1mg/m^2 of trabectedin combined with Doxil/Caelyx in the pivotal trial.

The evaluator noted that differences in eligibility from the pivotal study were that patients treated previously with other than platinum drugs were eligible for study 11, and all Phase 2 studies only accepted patients with ECOG PS 0 or 1, while the pivotal study also accepted patients with ECOG PS 2. Requirements for liver function and serum creatinine were also more stringent in the Phase 2 studies than in the pivotal trial.

Patient populations

Defined populations: Study 99 defined and analysed for efficacy two patient populations - a refractory group which included patients with progressive or stable disease while on chemotherapy; patients relapsing following an objective response (CR or PR) to the platinum-taxane chemotherapy while still receiving the same regimen; patients relapsing after an objective response, determined by radiological examination, within 6 months from the discontinuation of previous chemotherapy [Patients with progressive or stable disease were required to have received at least two and four cycles of prior platinum-taxane chemotherapy, respectively], and a relapsing group of patients who had relapsed following an objective response to platinum-taxane chemotherapy with an interval ≥ 6 months between the last dose received and the documentation of relapse.

In study 03, the patients were classified by the time in months from the end of their last platinum based treatment to the date of progression or to the start of trabectedin treatment (>12 months; 6-12 months; <6 months).

In Study 11, the same definition of platinum-sensitive and platinum-resistant were used as in the pivotal study, namely patients who relapse after a treatment-free interval longer than 6 months are considered platinum-sensitive. Patients who have disease progression during first-line chemotherapy or disease recurrence within 6 months after the end of treatment with a platinum-containing regimen are considered platinum-resistant.

Results

Study populations

Number of subjects treated: Ninety-four subjects in the integrated analysis population were treated with the q3wk, 3-h treatment schedule, the same trabectedin schedule as used in the pivotal ET743-OVA-301 study.

Extent of exposure: The median relative dose intensity across all the treatment arms was 85.44% and the median cumulative dose was 5.36 mg/m^2. This value is similar to the median cumulative dose (5.6 mg/m^2) of trabectedin in Study ET743-OVA-301. The median number of cycles for the q3wk; 24-h and the q3wk; 3-h treatment arms was 5.0 and 5.5 respectively, similar to the median of 6 cycles in the trabectedin + Doxil treatment arm of Study ET743-OVA-301. In comparison, the median number of cycles for the qwk; 3-h treatment arm was 3.0 cycles. However, the dose intensities of all 3 treatment arms were very similar: 0.41 mg/m^2 per week for the q3wk; 24-h regimen and 0.37 mg/m^2/week for the qwk and q3wk; 3-h regimens. The trabectedin dose intensity was 0.302 mg/m^2/week in the trabectedin + Doxil treatment arm of Study ET743-OVA-301. The cumulative doses for the q3wk; 3-h and 24-h treatment arms were very similar: 6.50 mg/m^2 and 6.35 mg/m^2 respectively. The cumulative dose for the qwk; 3-h treatment arm was 4.36 mg/m^2 which reflects the lower number of cycles administered with that regimen.

Efficacy

<u>Response rates</u>

Thirty-nine percent of subjects in the q3wk; 24-h treatment arm and 34% of subjects in the q3wk; 3-h treatment arm achieved a CR or PR in these single-agent studies. Subjects in the qwk; 3-h treatment arm had a 16% objective response rate. The ORRs for the two q3wk treatment regimens in the Phase 2 studies of 34% and 39% are numerically higher than the ORR seen in the Phase 3 combination arm of trabectedin + Doxil, 27.6%. This may be a result of inherent differences between Phase 2 studies and a controlled, large, multicenter Phase 3 study.

<u>Progression-free Survival</u>

The results of the single-agent trabectedin studies were consistent with the results from Study ET743-OVA-301 and showed activity in subjects with platinum-sensitive or platinum-resistant disease in all PFI categories. Subjects with platinum-sensitive disease had a median PFS of 6.8 months (95% CI: 5.3; 7.4) for the q3wk;3-h treatment arm, and subjects with platinum-resistant disease an overall median PFS of 2.0 months (95% CI: 1.7;2.8).

Evaluator's conclusions from Phase 2 Studies

The three Phase 2 studies of trabectedin as a single agent in ROC used the objective response rate (ORR) to determine efficacy. This differed from the primary end-point in the pivotal trial, namely, Progression Free Survival (PFS). However PFS was a secondary end-point in the phase 2 trials and ORR in the pivotal trial. Also the design of the Phase 2 trials was similar to that of the pivotal trial, and enough patients in the Phase 2 trials received a similar dose and regime of trabectedin to allow comparison with the pivotal trial.

The ORR for the q3wk-3h regime in the Phase 2 trials was higher (34%) than the 27.6% in the Doxil+trabectedin arm of the pivotal trial. Reasons probably were the well known fact that efficacy observed in Phase 2 trials is often greater than in the subsequent Phase 3 trials. As well, published papers have argued that ORR is less reliable to assess response in this disease than PFS.

Advanced Soft Tissue Sarcoma (STS)

Phase 2 Study ET743-STS-201

The pivotal Phase 2 study, ET743-STS-201 has a long history. The study began as an informal open-label comparison of two dosing regimens of trabectedin, and evolved to the present randomised study comparing the same regimens in patients with advanced or metastatic STS, resistant to or intolerant of anthracycline and ifosfamide therapy. An interim analysis of the study was submitted to the EU, and those data have been updated in the present application.

An early report on the study was included in the present application as well as the final version. The evaluator evaluated the final report but this report refers back to the interim report on a number of subjects, complicating access to the data.

Ethical questions included the use of trabectedin in this group of patients rather than another drug, the use of two comparative arms each using a different schedule of trabectedin, and the lack of a placebo control arm. These questions were addressed by the sponsor when describing modifications of the original study and were found acceptable by the evaluator.

The ethical conduct of the study, the use of Independent Ethics Committees of Institutional Review Boards, the provision of information to patients, and obtaining their informed consent were carried out satisfactorily.

Primary Objective

The primary objective was to compare Time to Progression (TTP) after treatment with trabectedin, administered on two different treatment schedules in patients with liposarcoma or leiomyosarcoma (L-sarcomas) who had been previously treated with an anthracycline and ifosfamide.

Secondary Objectives

Secondary objectives were as follows:

• To estimate the rate and duration of best overall objective response [(ORR, that is, complete (CRs) and partial responses (PRs) of each schedule];

• To compare progression-free survival (PFS) and overall survival (OS) between the two schedules;

• To characterize the safety profile, and

• To estimate the pharmacokinetics of trabectedin.

Study Design

ET743-STS-201 was a Phase 2, open-label, randomized, multicenter study designed to evaluate the efficacy and safety of trabectedin, administered through a central venous line by two different treatment schedules - a 3-hour infusion at the starting dose of 0.58 mg/m^2, every week for three consecutive weeks of a 4-week cycle (qwk 3-h), or 24-hour IV infusion at the starting dose of 1.5 mg/m^2, once every three weeks (q3wk 24-h) to patients with locally advanced or metastatic L-sarcoma whose disease had relapsed or become refractory after treatment with an anthracycline and ifosfamide, given either in combination or in sequence, and who had evidence of disease progression.

The protocol was amended to allow a formal and conclusive evaluation of the primary efficacy endpoint, time to progression (TTP), in both treatment groups, qwk 3-h and q3wk 24-h.

By the random assignment of 260 evaluable patients and the observation of 217 TTP events of either disease progression or death due to progression, the study would have a greater than 90% power to detect a minimum of 60% improvement in median TTP at a 2-sided 5% significance level. Per protocol, a first interim analysis was conducted with 147 events (31 May 2005). Cut-off date for achieving 217 TTP events in the final TTP analysis was scheduled for 31 May 2006.

Evaluator's comment: Of note is the use of TTP as the primary endpoint rather than the more usual Progression Free Survival (PFS). This was justified as noted above. The study report adds, "During the discussions leading to this decision, it was acknowledged that both TTP and PFS were very similar endpoints, the only difference being that PFS also counts death due to any reason as an event and not just deaths due to disease progression. In addition, it was expected that in this particular trial, the rate of deaths not due to progressive disease would be very low and well-balanced between the two study arms, further equating both endpoints in practical terms."

Trabectedin qwk 3-h: patients in this group received trabectedin as a 3-hour infusion at the starting dose of 0.58 mg/m^2 every week for three weeks of a 4-week cycle (Days 1, 8, 15 of a 28-day cycle).

Trabectedin q3wk 24-h: patients in this group received trabectedin as a 24-hour infusion at the starting dose of 1.5 mg/m^2 every three weeks (Day 1 of a 21-day cycle).

Treatment could be continued as long as disease progression was not evident, unacceptable toxicity had not occurred, and the patient did not withdraw informed consent. Treatment was permanently discontinued after the patient received two additional cycles of study treatment after a CR was confirmed. Patients who had disease progression during treatment in the dosage group to which

they had been initially allocated were allowed to cross over to the alternate dosage group, at the discretion of the investigator.

Evaluator's comment: As in all studies that allow crossover of patients to the alternate treatment arm, the contribution of the treatments to overall survival is difficult to determine, and reduces the value of OS as an end-point for comparison.

Efficacy and Safety Variables

Efficacy Measurements

The primary endpoint for efficacy, TTP, was defined as time between randomization and the first documentation of disease progression or death due to progressive disease. Secondary efficacy endpoints were objective response rate (ORR), duration of response, progression-free survival (PFS), and overall survival according to protocol amendment ET743-STS-201 INT-3.

The RECIST guidelines were used to determine ORR. Tumour assessments were performed for all patients up to 30 days before randomization, and every 8 weeks thereafter until disease progression. The timing of assessments was the same for all patients, irrespective of the actual treatment date, to ensure symmetry of progression-based outcomes in the two study arms. Additional tumour assessments could be scheduled, if clinically indicated. Efficacy analyses were conducted primarily based on the independent review of outcomes for all randomly assigned patients. These included the primary efficacy endpoint, TTP, and the secondary efficacy endpoints, ORR, PFS and overall survival. Duration of response was measured in evaluable patients who had an objective response. Sensitivity analyses were conducted in treated patients. Supportive analyses were done on the basis of data obtained from the investigators' assessments.

Statistical aspects: The cut-off for the final TTP analysis (at approximately 217 events) was prospectively defined as 31 May 2006. The results of this protocol-specified analysis are presented in this report. The "all randomized" analysis set comprised all patients who were randomly assigned to one of the two schedules, whether they received trabectedin or not. The "all evaluable" analysis set comprised all randomly assigned patients with a diagnosis of L-sarcomas who received at least one dose of trabectedin, and for whom at least one post-baseline evaluation of response was available. The "all treated" analysis set comprised all patients who received at least one dose of trabectedin (patients who received dexamethasone only were not included). The "confirmed L-sarcoma" analysis set comprised all patients with L-sarcoma as per independent central histopathological review.

For TTP and overall survival, the overall significance level was 5%. The significance for efficacy was claimed if the p-value was less than or equal to the significance level, calculated on the basis of the specified alpha spending function and the observed number of events. Continuous variables were summarized and presented with summary statistics, which included mean, standard deviation, median and range. Categorical variables were summarized in frequency tables. Estimates of TTP and other time-to-event endpoints were calculated by the Kaplan-Meier (K-M) method for each schedule.

Safety measurements

Safety evaluations included adverse events (AEs), clinical laboratory data, the results of physical examination and vital signs findings, and deaths. Adverse events (AEs) were summarized by System Organ Class (SOC) and overall. The Medical Dictionary for Regulatory Activities

(MedDRA) was used to code AEs, and their severity was coded according to the NCI-CTC, Version 2.0.[22]

Results

Efficacy results

<u>Patient disposition</u>

At this cut-off date of 31 May 2006, 291 patients screened for eligibility had been randomly assigned to treatment in one of the two study arms, qwk 3-h and q3wk 24-h (Figure 6). Twenty-one patients were not randomized and one patient was randomized twice before being finally assigned and treated in the qwk 3-h arm.

Figure 6: Disposition of patients – study ET743-STS-201

Patients screened
n=291*

Patients not randomly assigned to treatment: n=21

Patients randomly assigned to a trabectedin schedule
n=270
(All randomized patient analysis set)

Patients randomly assigned to qwk 3-h group
n=134

Patients randomly assigned to q3wk 24-h group
n=136

Treated patients: qwk 3-h group n=130 (All treated patients analysis set)

Randomized patients not treated: qwk 3-h group n=4
Reasons, n:
Screen failure, 2
Disease progression, 1
Patient's choice, 1

Randomized patients not treated: q3wk 24-h group n=6
Reasons, n:
Screen failure, 3
Disease progression, 1
Lost to follow-up, 1
AE/no-drug related, 1

Treated patients: q3wk 24-h group n=130 (All treated patients analysis set)

Patients who permanently discontinued study treatment as per randomization arm: qwk 3-h group n=130
Main reason for discontinuation, n (%):
Disease progression, 93 (71.5%)
Crossover before progression, 14 (10.8%)
Patient choice, 5 (3.8%)
AE/no-drug related, 6 (4.6%)
AE/drug related, 4 (3.1%)
Other, 4 (3.1%)
Death, 3 (2.3%)
Patient ineligible to continue, 1 (0.8%)

Patients who permanently discontinued study treatment as per randomization arm: q3wk 24-h group n=122
Main reason for discontinuation, n (%):
Disease progression, 88 (67.7%)
Patient choice, 17 (13.1%)
AE/drug related, 8 (6.2%)
AE/no-drug related, 3 (2.3%)
Death, 2 (1.5%)
Patient ineligible to continue, 2 (1.5%)
Lost to follow-up, 1 (1.2%)
Other, 1 (0.8%)

Patients ongoing study treatment at cut-off date for final TTP analysis: q3wk 24-h group n=8

Crossover from q3wk 24-h group to qwk 3-h group after disease progression n=6

Crossover from qwk 3-h group to q3wk 24-h group after disease progression n=29

*One patient was screened twice.
SAP Source: Table TSUB01a, TSUB01b, TSUB03a and TSUB03f.

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[22] The National Cancer Institute Common Terminology Criteria (NCI-CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Therefore, the randomized patient population consisted of 270 patients: 134 patients in the qwk 3-h group and 136 patients in the q3wk 24-h group, respectively. Four patients in the qwk 3-h arm and 6 in the q3wk 24-h arm were not treated.

The reasons for discontinuation of treatment are shown in Figure 6. At the cut-off date, 252 of 260 treated patients (96.9%) had ended study treatment: 130 patients in the qwk 3-h group and 122 patients in the q3wk 24-h group. Forty-nine of these 252 patients crossed over to the other schedule: 35 patients after progression of their disease (a choice allowed by protocol and dependent of the investigator's criteria), and 14 patients before progression following the recommendation of the IDMC in August 2005 (all of them from the qwk 3-h group to the q3wk 24-h group). Only eight patients (3.1%; all of them from the q3wk 24-h group) were still ongoing.

Death was reported as cause of treatment discontinuation in five patients (1.92% of 260 treated patients, or 1.85% of 270 randomized patients), three patients in qwk 3-h group and two patients in the q3wk 24-h group. All these five patients died as a consequence of drug-related AEs.

Deviations from Study Design

The frequency of minor and major eligibility deviations was 31.3% and 23.1% in the qwk 3-h arm and 31.6% and 23.5% in the q3wk 24-h arm.

Major protocol deviations occurred in 32 patients (11.8%) with 16 patients (11.9%) in the qwk 3-h and 16 patients (11.8%) in the q3wk 24-h arm. Most protocol deviations consisted of treatment deviations (5.2% of 270 randomized patients), deviations in the assessment of efficacy (3.3%) and patients not withdrawn as per protocol (3.3%), with no relevant differences between treatment arms.

Evaluator's comment: The frequency of violations of the eligibility criteria was high. The study report stated: "Eligibility deviations were detected at the time of accrual, and inclusion was the result of an agreement between the investigator and the sponsor." The sponsor commented on the high frequency and the unusual arrangement with investigators in its response. Of concern was the statement that "In some cases, the eligibility deviations were observed upon retrospective review of the data after completion of the enrollment." The effect seems to be that the patient population treated in the study was not that defined in the eligibility criteria, but one that reflected "the reality of the clinical setting", without affecting the results of the study.

Demographic and other baseline characteristics

The distributions of demographic characteristics were well balanced in the two study groups.

Most patients had metastatic disease (93.0%), and 17 patients had locally advanced disease. Most metastatic lesions were located in the lungs (41.7%), liver (15.7%), abdomen (11.3%), pelvis (9.6%) or thorax (6.9%), and the median number of metastatic sites per patient was 2 in each study arm (range, 1-7, qwk 3-h; range, 1-6, q3wk 24-h). Eighty-six patients (31.9%) had more than two metastatic sites.

A comparison of investigators' and independent pathologists' diagnoses showed that investigators classed all patients' tumours as L-sarcomas, whereas independent pathologists classed 8 tumours (6%) in the qwk 3-h group and 15 (11%) in the q3wk 24-h group as sarcomas of other types. As well, the histological material from 15 (11.2%) and 19 (14%) patients in the qwk 3-h and the q3wk 24-h groups respectively was not available to the independent pathologists for review.

Evaluator's comment: The difference in histology as described introduced an imbalance in the tumour types in the two arms. The real imbalance is unknown due to missing histological material. An estimate of the error rate in diagnosis would be 8.5% from combining the errors in each arm (8 plus 15, out of a patient total of 270). If this was used for the missing materials, it can be estimated that 8.5% of the 15 cases in the qwk 3-h arm and 8.5% of the 19 cases in the q3wk 24-h arm would

be wrongly diagnosed, that is 1 and 2 in the two arms respectively. The totals would then be 9 and 17 cases in the two respective arms that were not of the tumour type intended (L-sarcomas).

The question is whether this difference (8 more patients with a different tumour in one arm compared to the other) would introduce bias in analysis. This is possible if for example the type of tumours wrongly diagnosed and causing the imbalance was either more resistant or more sensitive to the chemotherapy administered, as indicated by the EORTC data.[23] This possibility should be borne in mind because the number of misdiagnosed cases in the q3wk 24-h arm was 8 of 136 patients, of whom only 7 achieved a partial response.

Although patients with more than two prior treatments with chemotherapy were to be excluded (criterion 3) from the study, a total of 34 patients (18 [13.3%] in the qwk 3-h arm and 16[11.8%] in the q3wk 24-h arm) had three or more chemotherapy regimens prior to entry into the study. Most patients (99.3%) had been treated with both anthracyclines and ifosfamide, whereas two patients (0.7%) had been treated with anthracyclines plus other agents, but they had not received prior ifosfamide. The most commonly administered anthracycline was doxorubicin (93.3%). Besides anthracyclines and ifosfamide, gemcitabine (31.9% of randomized patients), docetaxel (24.1%) and dacarbazine (20.4%) were the most common previous anticancer agents delivered to these patients.

The median time intervals from the completion of the last treatment to study randomization were 2.9 and 3.5 for the Qwk 3-h and Q3wk 24-h arms respectively.

Analysis of Efficacy

Results were presented from the planned final analysis of the primary efficacy endpoint, TTP, and each of the secondary efficacy endpoints, ORR, duration of response, PFS, and OS. At the planned cut-off date (31 May 2006), a total of 206 and 216 events of progression were recorded according to the independent review and investigator's assessment, respectively. The "All randomized" analysis set was used for the primary analysis of efficacy. Results of TTP are presented from the independent review (blinded to randomization arm) as primary analysis and from the investigator's assessment as supportive analysis. Additionally, several sensitivity analyses were carried out.

The supportive analyses showed that tumour assessments were mostly done as scheduled by protocol (that is, the median time corresponded to the scheduled time), that symmetry in tumour evaluations was preserved in both study groups and that there were no differences in the rate of clinical PD between treatment arms.

Primary analysis – Time to Progression (TTP)

Independent assessment: The median follow-up for progression was not significantly different in both study arms - 10.8 months (95% CI, 6.0-11.6) and 14.7 months (95% CI, 10.9-22.5) (p=0.0549). A total of 206 events of progression were independently confirmed and form the basis for this final TTP analysis. According to the independent review, the HR showed a 26.6% reduction in the relative risk of progression for patients treated in the q3wk 24-h group (HR=0.734; 95% CI 0.554 - 0.974; p=0.032). The median TTP was 2.3 months (95% CI, 2.0-3.5 months) in the qwk 3-h group and 3.7 months (95% CI, 2.1-5.4 months) in the q3wk 24-h group (log-rank p=0.0302), which represents an increment of 61% in median TTP with the q3wk 24-h regimen. Based on the Statistical Analysis Plan, the required level of significance for 206 events in this final TTP analysis was 0.0340 to qualify for statistical significance.[24] Therefore, the difference in TTP between both

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[23] M Van Glabbeke, J Verweij, I,Judson, OS Nielson, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002; 38: 543-549.

[24] The overall 5% significance level was spread over 2 TTP analyses, one when 147 events were seen, and one when approximately 217 events were seen. The exact significance level of 0.034 was calculated from the exact number of events known at the interim analysis.

study arms was statistically significant in this analysis. Kaplan-Meier plots based on independent review for all randomized patients are shown in Figure 7.

Investigator's assessment (supportive only): In this assessment, the HR showed a 33.2% reduction in the relative risk of progression for patients treated in the q3wk 24-h group (HR=0.668; p=0.0046). The median TTP was 2.5 months (95% CI, 2.1-3.5 months) in the qwk 3-h group and 4.2 months (95% CI, 2.6-6.5 months) in the q3wk 24-h group (log rank p=0.0042), supporting the results of the primary analysis.

Figure 7: Kaplan-Meier plot of TTP
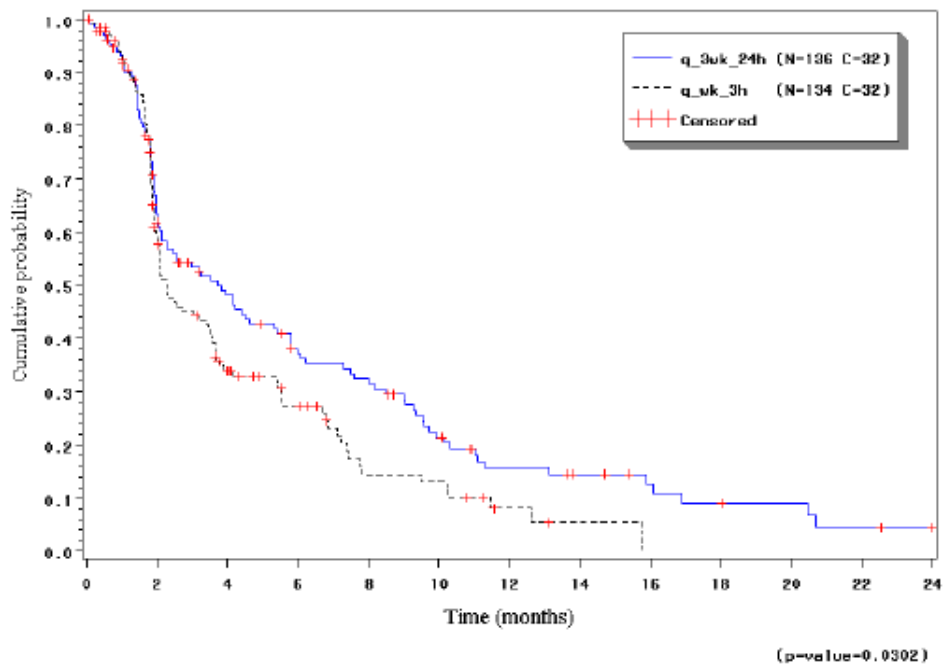
N, number of patients; C, number of censored patients. SAP Source: FEFF01a.

Evaluator's comment: The difference between the TTP of each treatment may be due to chance in only 32 cases in 1000 (p= 0.032), and so is likely to represent a true difference. It is uncertain, however, what the true difference is. This is informed by the 95% confidence intervals given. For the qwk 3-h group, the 95% CI was 2.0 to 3.5 months for TTP, giving a point estimate of 2.8 months (the median value was 2.3 months). For the q3wk 24-h group, the CI was 2.1 to 5.4 months, with a point estimate of 3.8 months (the median value was 4.2 months). For the qwk 3-h group, the true value of the TTP could be any value between 2.1 and 3.5 months (with a probability >0.025% [half of 0.05%]). This could be 3.5 months. For the q3wk 24-h group, there is the same probability (>0.025%) that the true value of TTP is the lower value of the CI interval, namely 2.1 months. Because of the first statistic, this is unlikely, as a true difference favouring q3wk 24-h is likely. However the value of true difference between the two groups remains uncertain.

Sensitivity analyses of the Primary Endpoint: In response to a request from the Committee for Medicinal Products for Human Use (CHMP) of the EU, sensitivity analyses were done. Another request was from the FDA. Overall the analyses supported the results from the independent assessments of the primary endpoint above, as shown in Table 6. In the table, the p-value for the HR for the primary analysis was 0.0302, where a value of 0.0340 was required for significance.

Table 6: Time to progression – summary of primary and sensitivity analyses

Time to progression	Number of events	HR (95% CI)*	LR p-value
Primary analysis			
All randomized	206	0.734 (0.554 - 0.974)	0.0302**
Sensitivity analyses			
All treated	201	0.717 (0.538 - 0.954)	0.0208
Confirmed L-sarcoma	160	0.647 (0.468 - 0.895)	0.0076
Conservative analysis	231	0.736 (0.561 - 0.964)	0.0242
First imputation (midpoint)	225	0.716 (0.549 - 0.934)	0.0129
Second imputation (scheduled times)	225	0.784 (0.601 -1.021)	0.0210
Independent review-modified charter	194	0.768 (0.576 - 1.024)	0.0697

All analyses according to the independent review.
*HR: q3wk 24-h compared to qwk 3-h group. HR and p-value as determined by Cox regression.
**Difference in TTP between both study arms statistically significant in this primary analysis (p-value lower than the required level of significance for 206 events = 0.0340 after alpha spending adjustment).
HR, hazard ratio; LR, unstratified log-rank.

<u>Secondary Efficacy Endpoints – Overall Response Rate (ORR), Duration of Response, Progression Free Survival (PFS), and Overall Survival (OS)</u>

For these secondary endpoints, the "All randomized" set was used for the primary analysis. The results of the analyses by investigator's assessments were included as supportive. Sensitivity analyses were also done based on the "All treated" set or on the "confirmed L-sarcoma" set for ORR, PFS and OS. In the following, only the results of the independent review are presented for the main analysis, not for the sensitivity analyses.

Overall Response Rate (ORR): Twenty two out of the 270 randomized patients were not evaluable for response according to the independent review. Nine patients achieved a PR: two patients in the qwk 3-h group and seven patients in the q3wk 24-h group. Therefore, the ORR per independent review was 1.5% (95% CI, 0.2%-5.3%) in the qwk 3-h group and 5.1% (95% CI, 2.1%-10.3%) in the q3wk 24-h group, respectively (Fisher's p-value=0.1724). Additionally, 118 patients had SD as overall best response: 52 patients (38.8%) in the qwk 3-h group and 66 patients (48.5%) in the q3wk 24-h group.

Duration of Response: Only two patients were responders in the qwk 3-h group and 7 in the q3wk 24-h. The durations of response of the former were 7.8 and 3.4 months. For the q3wk 24-h group, the durations of response were 7.8, 5.3, 6.1, 3.7+, 7.6, 7.5, and 11.3+ months, with a median of 7.5 months.

Progression Free Survival (PFS): A total of 218 events were independently confirmed and formed the basis of this analysis. The number of events in the TTP group was 206. According to the independent review, the HR showed a 24.5% risk reduction in PFS for patients treated in the qQ3wk 24-h group (HR=0.755; p=0.0438), compared to 26.6% in the TTP analysis. The median PFS was 2.3 months (95% CI, 2.0-3.4 months) in the Qwk 3-h group and 3.3 months (95% CI, 2.1-4.6 months) in the q3wk 24-h (log-rank p=0.0418), compared to 2.3 and 3.7 months respectively in the TTP analysis (log-rank p=0.0302).

Evaluator's comment: The study report states: "Based on the Statistical Analysis Plan, the required level of significance for 206 events in this final TTP analysis was 0.0340 to qualify for statistical significance after alpha spending adjustment." If the more usual PFS had been used as the primary end-point instead of TTP, the p value of 0.0418 for the difference between the arms, would not meet the required value for statistical significance.

Overall Survival: At the cut-off date (31 May 2006), 64.8% of all patients had died and the remaining 35.2% (n=95) were censored in the OS analysis. The median follow-up was similar in both groups - 18.7 months (95% CI, 14.9-25.8) in the qwk 3-h arm and 19.3 months (95% CI, 17.0-26.9) in the q3wk 24-h arm. The HR showed a non-significant 17.7% reduction in the relative risk of death for patients treated in the Q3wk 24-h group (HR=0.823; p=0.1985). The difference in the median OS (Figure 8) was also not significant - 11.8 months (95% CI, 9.9-13.9) in the qwk 3-h group and 13.8 months (95% CI, 12.5-17.9) in the q3wk 24-h group (log-rank p=0.1984).

Figure 8: Kaplan-Meier plot of OS
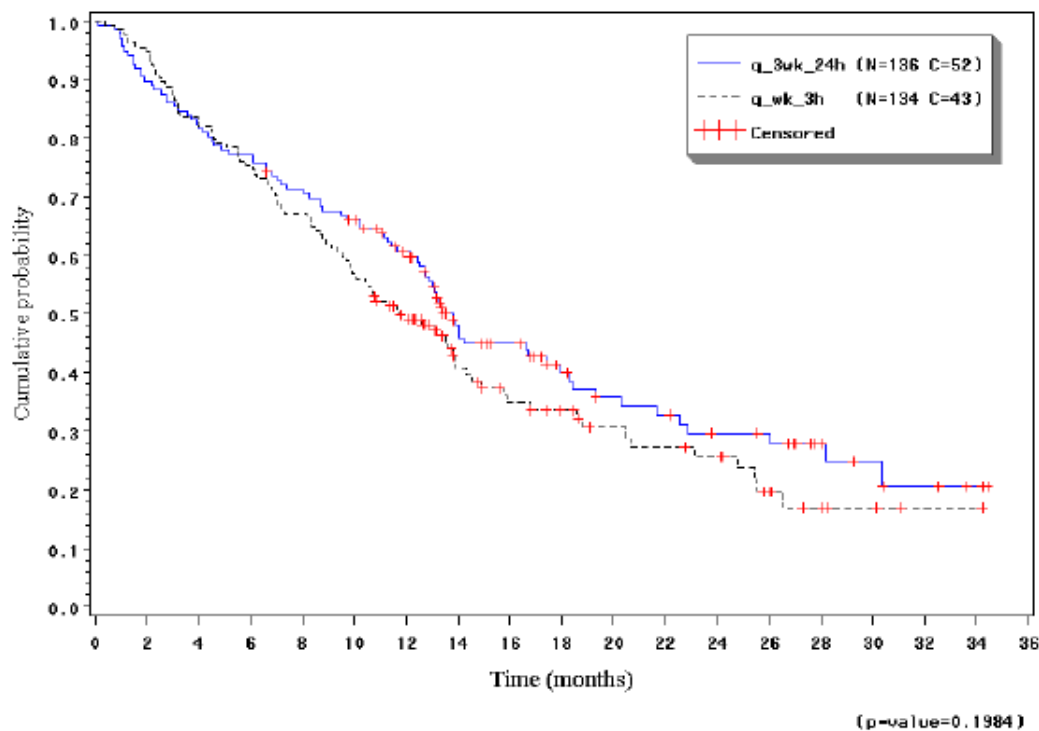
N, number of patients; C, number of censored patients.

Next-Line Therapies: As discussed previously, cross-over treatment and next-line therapies may have an effect on the survival outcome.

An analysis of anti-tumour therapies administered after the end of trabectedin treatment in the ET743-STS-201 study was therefore performed as requested by the CHMP. The Case Report Form in the ET743-STS-201 included the item "further anti-cancer therapy" with a response "yes" or "no", so no other details on the next-line therapies were collected, although the number of patients crossing over to the other treatment arm of the trial was known. The two treatment arms were well-balanced since about half of patients received next-line anticancer therapies other than trabectedin in each group. No differences were found in the time at which these next-line therapies were administered after progression on trabectedin. Based on these results, next-line therapies was not a confounding factor in the analysis of survival in comparing the two arms, but as follows, cross-over therapy was.

Of patients in the qwk 3-h arm, 32.1% of patients of those initially treated with this schedule received next-line trabectedin q3wk 24-h (14.9% of patients prior to other next-line therapies and 17.2% with no further next-line therapies). In the q3wk 24-h arm, only 4.4% of patients received the

alternate trabectedin regimen. This would be a confounding factor in the analysis of differences in survival between the qwk 3-h and q3wk 24-h treatment arms.

Consistency in Analyses of Time-to-Event Endpoints (Primary and Secondary): The study report compared the various analyses in Figure 9.

Figure 9: Time-to-event Hazard Ratios (HR)

Time-to-event hazard ratios (HR) with trabectedin q3wk 24-h *vs.* qwk 3-h in the different analysis subsets (ET743-STS-201 study).
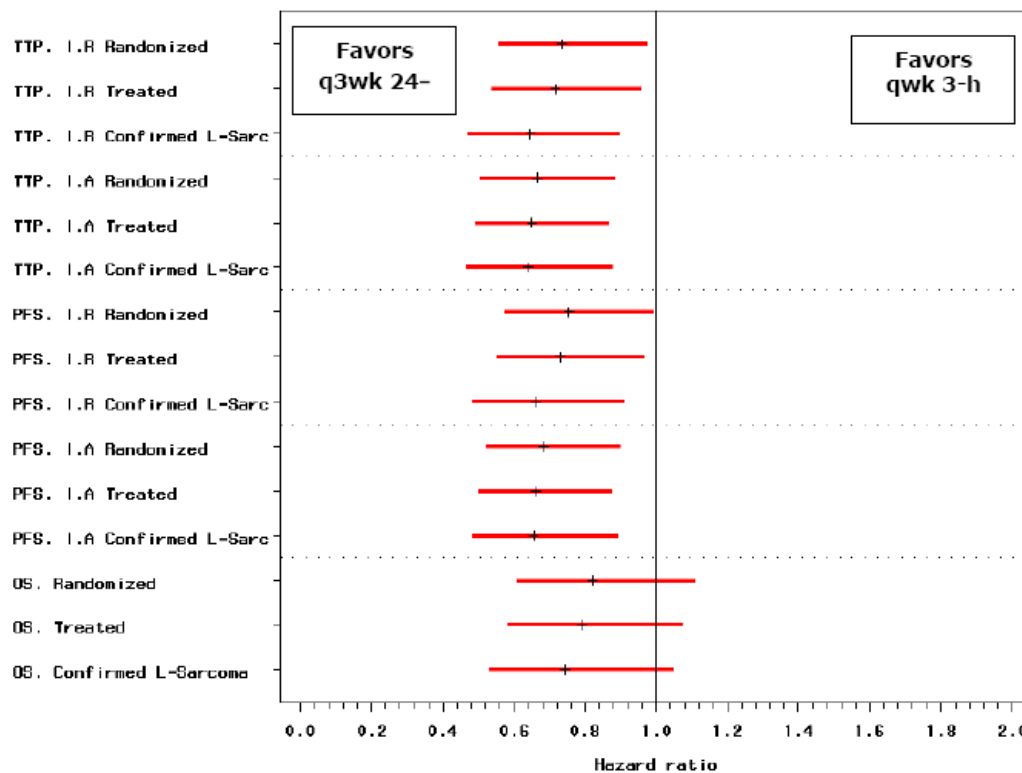
The central vertical line denotes a HR of 1. Each black mark denotes an individual HR and the horizontal red lines their 95% CI. HR <1 indicates lower risk of the event in the q3wk 24-h trabectedin arm relative to the qwk 3-h arm. Results reach statistical significance (at a 5% significance level) if the red line does not cross the vertical line.
I.A., investigator's assessment; I.R, independent review; L-sarc, L-sarcoma; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Evaluator's comment: The figure shows the results were consistent in the numerous patient populations. The smallest benefits were seen in the ITT population (all-randomized), the population relevant to the primary analysis. As discussed above, the true difference in the TTP between the two arms is uncertain, and when PFS was used the statistical significance as defined in the protocol was not reached for the ITT population. As well, no difference was shown for OS in any population.

Results in Patient Subgroups: Univariate and multivariate analyses were done to assess variables as prognostic factors for several endpoints. The conclusion was that the multivariate analysis which included all covariates was more accurate and comprehensive, and indicated that treatment arm and histology were prognostic variables for TTP.

Impact of the Protocol Amendment INT-3 on Efficacy Outcomes and Study Interpretability:

1. Overview - Because about half the patients in the study had been randomized before this amendment was made, analyses were done on the patient populations before and after the amendment was introduced. These showed that patient and disease characteristics, treatment parameters, and treatment outcomes were not significantly different for the two periods.

2. Overall Survival – The amendment allowed cross-over of patients with PD to the other arm after half the patients had been enrolled. As noted above, more patients crossed-over to the 3 weekly treatment which was possibly more effective for survival than the once a week treatment. The study report attempted to show no bias was introduced in this way.

Evaluator's comment: The analyses showed that when the OS of the patients who crossed-over was compared for the pre-amendment and post-amendment periods, the HR values were 0.791 and 0.866 respectively.[25] When the patients who crossed over were excluded, the HR values for the remaining patients were 0.784 and 0.738. In neither case did the p value indicate a statistically significant difference, although a trend was present in the first case, in which the HR was not reduced as much as when the effect of the cross-over q3wk 24-h treatment was included. The report claims that "The significantly better clinical benefit of trabectedin given as a [q3wk 24-h] regimen appears robust despite the plausible bias introduced with the implementation of the ET743-STS-201 INT-3 amendment."

Evaluator's Conclusions on Efficacy

The study report has five pages arguing for the greater efficacy of trabectedin given 3-weekly compared to weekly in advanced STS. The conclusions can be stated more simply – the 3-weekly treatment resulted in a statistically significant extension of the TTP compared to weekly treatment. There were no demonstrated differences in the other endpoints, including OS. The response rates were very low (1.5% and 5.1%, respectively). The report argued that response rates were largely irrelevant in this disease. If the usual PFS had been an endpoint, the difference in the treatments would not have been statistically significant.

It is important to remember that the comparison is of two treatment regimes with no untreated control. If the weekly treatment had no significant activity in this patient population, then the 3 weekly treatment could be said to be only marginally better. The response rates suggest this, and the TTP found with the weekly treatment may be the natural course of the disease, that was slightly increased by the 3-weekly treatment. There is therefore a need to examine the evidence that weekly trabectedin is effective as shown by the three Phase 2 studies submitted.

Assuming this is found to be so, the next question is whether there is any clinical benefit to the patient in such a short duration without progressive disease, and with such a low response rate. This will require a risk-benefit decision that also considers the safety of the two regimes, as well as the possibility of errors from the design of the study (see later discussion).

Phase 2 Supporting Studies – Does trabectedin have activity against STS?

The pivotal study ETA743-STS-201 was designed assuming that trabectedin was effective in treating recurrent STS after prior treatment with an anthracyline and ifosfamide. The three Phase 2 trials, ET-B-005-98, ET-008-98, and ET-B-017-99 in this application provided the evidence for this assumption, and were summarized in the sponsor's *Clinical Summary*. The studies included a variety of tumour types, including gastrointestinal stromal cell-tumours (GIST), but only data from patients with STS excluding GIST were included in the integrated analyses in the summary. The following is largely based on the *Clinical Summary* with reference to the study reports.

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[25] these patients were those enrolled and treated before the amendment, not crossed-over before the amendment.

With regard to trial design, the evaluator noted that in Study ETA743-005-98, after the first 47 patients were registered and clinical activity of the study drug was detected, the EORTC investigators suggested that an additional cohort of patients be recruited in which the response rate would be evaluated with the WHO criteria (as in the first cohort), and also with the RECIST criteria.[26] These two cohorts of patients are referred in this report as "Group A" and "Group C", respectively. Only the WHO criteria were used for the final conclusions.

In study ET-B-008-98, patients were divided into two groups, Group 1, moderately pre-treated STS patients (≤2 single agents or one combination regimen), and Group 2, extensively pre-treated STS patients (≥3 different single agents or > 1 combination regimen, or one combination and one or more single agents).

Patients whose disease had relapsed or became refractory following treatment with an anthracycline and ifosfamide, administered in combination or in sequence, were further described as either resistant or not resistant (responsive or not responsive) to previous chemotherapy based upon evaluations by an independent group of oncologists.

Evaluator's comment: As stated, GIST was excluded from study ET-B-005-98, as well as malignant mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma and embryonal rhabdomyosarcoma, and from study ET-B-017-99. Study EY-B-008-98 included all STSs.

Evaluations and Endpoints

The evaluator noted that as these studies were not randomised, the TTP and PFS were measured from the beginning of treatment with trabectedin. Also, response was assessed in a patient population that had received a minimum of two cycles of treatment ("evaluable patients"), rather than the total (ITT) population as in the pivotal trial.

Results

Types of sarcomas: Most patients in Study ET-B-005-98 in Group A had leiomyosarcoma (23/44, 52.3%), while leiomyosarcoma (17/55, 30.9%) and synovial sarcoma (12/55, 21.8%) were the most reported STS forms in Group C. A similar number of patients had unclassified sarcomas in Groups A and C (11.4% and 14.5%, respectively).

In Study ET-B-008-98, leiomyosarcoma was the most common STS form in Group 1 (9/26 patients, 34.6%). Liposarcoma was also relatively common (5/26 patients, 19.2%), followed by GIST (3/26 patients, 11.5%) and malignant fibrous histiocytoma (2/26 patients, 7.7%). In Group 2, leiomyosarcoma was also the most prevalent STS type in this group of extensively pre-treated patients (13/28 patients, 46.4%). Fibrosarcoma was the second STS type most common (3/28 patients, 10.7%) followed by synovial sarcoma, and endometrial stromal sarcoma (each one found in 2/28 patients, 7.1%).

In Study ET-B-017-99, the most frequent histologies included leiomyosarcoma (13/36, 36.1%), liposarcoma (10/36, 27.8%) and synovial sarcoma (6/36, 16.7%).

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[26] An alternative to the ECPG PS is the WHO performance scale: The World Health Organisation (WHO) designed the scale which has categories from 0 to 4 as follows:
0 : fully active and more or less as you were before your illness
1 - cannot carry out heavy physical work, but can do anything else
2 - up and about more than half the day; you can look after yourself, but are not well enough to work
3 - in bed or sitting in a chair for more than half the day; you need some help in looking after yourself
4 - in bed or a chair all the time and need a lot of looking after

Efficacy

Response rates: For the studies in their above order, the partial response (PR) rates were 9.1% (Group A) and 10.1% (Group C); 0 (Group 1) and 7.1%; and 8.3%. No CRs were seen.

Progression Free Survival: In the same order as above, the median PFS in the three studies were 2.6 (Group A) and 2.9 (Group B) months; 1.8 (Group 1) and 1.9 (Group 2) months; and 1.6 months.

Overall Survival: In the same order as above, the median overall survival in the three studies were 8.7 (Group A) and 13.9 (Group B) months; 13.8 (Group 1) and 10.7 (Group 2) months; and 12.6 months.

Evaluator's comment: As shown, all response rates were 10% or less. Subsequently the EORTC's sarcoma group decided that response rates were not a good measure of response in this disease, and much space was devoted in this application to arguing this case. For these 3 studies however, the prospective endpoint was response rate, unqualified, and this was low. In the application, the case was put (many times) that these patients had been previously treated and that subsequent treatment produced low response rates, most being less than the rates seen in these studies. The problems of such historical comparisons are well known. However it can be concluded that trabectedin as second line therapy has some activity against STSs, although how active is uncertain.

For PFS and OS, since the trials were single armed, no comparative control exists. Instead the times were compared to historical controls, and to the EORTC sarcoma group's conclusion that any OS of 12 months or more is significant in this setting.

Taking the above into account, the evaluator accepted that trabectedin is active against STSs in this setting.

Safety

Advanced Ovarian Cancer

Phase 3 Study ET743-OVA-301

This section presented treatment-emergent adverse events (TEAEs) as MedDRA System Organ Class (SOC) and Preferred Terms (PTs), with an assessment of their relationship to the study drug and toxicity grade. The safety results included a discussion of reported deaths, treatment-emergent serious adverse events, and treatment-emergent adverse events that led to the permanent discontinuation of study treatment, dose reductions, or cycle delays.

Adverse events considered to be particularly pertinent were discussed separately, by specific groupings of MedDRA SOC terms or syndrome. These adverse events included hepatic toxicity, neutropenia, thrombocytopenia and bleeding events, cardiac toxicity, abdominal pain, CPK elevation/rhabdomyolysis, alopecia, extravasation, respiratory disorders, myelodysplasia and acute myeloid leukemia, neurotoxicity, ototoxicity, and renal toxicity.

Treatment-emergent adverse events were those events that occurred on or after the administration of the first dose of study drug and up to 30 days after the last dose. Laboratory abnormalities were included in the summaries of clinical laboratory data.

Data Sets Analysed

Safety data were presented for the 333 subjects in the trabectedin + Caelyx/Doxil arm and 330 subjects in Caelyx/Doxil monotherapy arm, who received at least 1 dose of study drug (Caelyx/Doxil and/or trabectedin). These 663 subjects comprised the all treated subjects analysis set.

Adverse Events

An overview of TEAEs, defined as those that occurred on or after the administration of the first dose of study drug and up to 30 days after the last dose, are shown in Table 7.

Table 7: Safety profile – Study ET743-OVA-301

	DOXIL (N=330) n (%)	Trabectedin/DOXIL (N=333) n (%)
Treatment-Emergent Adverse Events (TEAEs)	326 (99)	333 (100)
Drug-related	312 (95)	332 (>99)
Grade 3-4 TEAEs	237 (72)	304 (91)
Drug-related	193 (58)	295 (89)
Serious TEAEs	101 (31)	130 (39)
Drug-related	44 (13)	90 (27)
Grade 3-4	77 (23)	112 (34)
TEAE Leading to Treatment Termination	50 (15)	78 (23)
Drug-related	31 (9)	57 (17)
All deaths within 30 days of last dose	8 (2)	11 (3)
Deaths due to TEAE	1 (<1)	5 (2)
Progressive disease	6 (2)	6 (2)
Other	1 (<1)	0

Evaluator's comment: Although all patients in both treatment arms had some TEAEs, the frequency in all categories was significantly higher in the combination arm, which had 70% more drug-related Grade 3-4 events, 48% more serious TEAEs, and 89% more TEAEs leading to treatment discontinuation than the monotherapy arm. As well, one of 330 patients died of a TEAE in the monotherapy arm compared to 5 of 333 in the combination arm.

Adverse events and age

Evaluator's comment: The data show the same higher incidence of toxicity as above for the combination therapy arm compared to the monotherapy arm. An effect of age was seen in the higher frequency of TEAES in the older age group (>65) for Grade 3-4 events in the Caelyx/Doxil arm compared to the frequency in the younger age group (69% compared with 78%). This difference was not apparent in the trabectedin + Caelyx/Doxil arm because the incidences in both age groups were over 90% (91% and 92%). The other age-related change was in the percentage of deaths due to TEAEs. Compared to a rate of 1% of patients over 65 who died in the monotherapy arm, the rate in the combination therapy arm was 4%.

Adverse events and race

Most subjects in both treatment arms were white - 77% of the 330 subjects in the monotherapy arm and 79% of the 333 subjects in the combination therapy arm.

In the monotherapy arm, nonwhite subjects had a higher incidence (16%) of Grade 3-4 adverse events than white subjects (80% compared with 69%, respectively) and a higher incidence (40%) of serious adverse events (39% compared with 28%).

In the trabectedin + Caelyx/Doxil arm, nonwhite subjects had a higher incidence (10%) of drug-related Grade 3-4 adverse events (96% compared with 87%, respectively), serious adverse events (51% compared with 36%, respectively[42%]), drug-related serious adverse events (44% compared

with 23%, respectively[91%]), and Grade 3-4 serious adverse events (46% compared with 30%, respectively[53%]).

Evaluator's comment: The data show that in each of the treatment arms, severe and serious adverse events were increased from between 10% and 90% in nonwhite subjects compared to white subjects. Moreover the frequency of adverse events was higher for all categories in the combination arm compared to the monotherapy arm.

Baseline ECOG Performance Status Score

At baseline, 143 (43%) of the 330 subjects in the Caelyx/Doxil monotherapy arm and 104 (31%) of the 333 subjects in the trabectedin + Caelyx/Doxil arm had ECOG performance status scores greater than 0. A comparison of the incidence of TEAEs in these groups and those with a baseline ECOG PS of 0 showed no significant differences. The incidence of TEAEs however in the combination therapy arm was as above greater than that in the monotherapy arm.

Nature and Grades of Adverse Events

Table 8 shows the nature and grades of the TEAEs occurring in 5% or more subjects in the All-Treatment population.

Table 8: Nature and grades of adverse events

MedDRA SOC Term	DOXIL (N=330)						Trabectedin/DOXIL (N=333)					
MedDRA Preferred Term	Total n (%)	Ns	1	2	3	4	Total n (%)	Ns	1	2	3	4
Gastrointestinal disorders	273 (83)	0	70	128	67	8	297 (89)	0	76	142	73	6
Nausea	140 (42)	0	76	52	12	0	246 (74)	0	110	103	33	0
Vomiting	98 (30)	0	37	47	14	0	185 (56)	0	56	89	39	1
Constipation	92 (28)	0	53	33	6	0	107 (32)	0	71	31	5	0
Diarrhoea	63 (19)	0	40	16	7	0	86 (26)	0	53	25	8	0
Abdominal pain	79 (24)	0	30	31	17	1	70 (21)	0	42	24	4	0
Stomatitis	108 (33)	0	43	48	16	1	68 (20)	0	40	25	3	0
Dyspepsia	35 (11)	0	24	9	2	0	43 (13)	0	31	11	1	0
Abdominal distension	24 (7)	0	10	9	5	0	19 (6)	0	12	5	2	0
Abdominal pain upper	23 (7)	0	15	8	0	0	19 (6)	0	11	8	0	0
Ascites	20 (6)	0	2	4	14	0	17 (5)	0	0	9	8	0
Mouth ulceration	23 (7)	0	10	9	4	0	11 (3)	0	6	4	1	0
Blood and lymphatic system disorders	180 (55)	0	26	58	60	36	293 (88)	0	10	51	106	126
Neutropenia	126 (38)	0	13	39	46	28	258 (77)	0	7	41	97	113
Leukopenia	87 (26)	0	16	39	23	9	161 (48)	0	15	35	83	28
Anaemia	84 (25)	0	22	42	18	2	160 (48)	0	32	83	34	11
Thrombocytopenia	27 (8)	0	16	3	6	2	121 (36)	0	33	27	33	28
Febrile neutropenia	7 (2)	0	0	0	6	1	27 (8)	0	0	0	19	8
General disorders and administration site conditions	203 (62)	0	81	77	42	3	238 (71)	0	87	99	49	3
Fatigue	120 (36)	0	55	47	17	1	154 (46)	0	61	65	27	1
Pyrexia	44 (13)	0	32	10	2	0	65 (20)	0	48	13	4	0
Asthenia	39 (12)	0	21	13	5	0	55 (17)	0	28	22	5	0
Mucosal inflammation	64 (19)	0	23	22	19	0	41 (12)	0	19	15	7	0
Oedema peripheral	27 (8)	1	21	4	0	1	30 (9)	0	19	9	2	0
Pain	13 (4)	0	10	2	1	0	18 (5)	0	11	6	1	0
Non-cardiac chest pain	11 (3)	0	10	0	1	0	16 (5)	0	8	6	2	0

(continued)

MedDRA SOC Term / MedDRA Preferred Term	DOXIL (N=330)						Trabectedin/DOXIL (N=333)					
	Total n (%)	Ns	1	2	3	4	Total n (%)	Ns	1	2	3	4
Investigations	92 (28)	0	47	34	10	1	223 (67)	0	38	61	111	13
Alanine aminotransferase increased	31 (9)	0	18	10	3	0	182 (55)	0	27	52	95	8
Aspartate aminotransferase increased	34 (10)	0	21	10	2	1	134 (40)	0	50	60	21	3
Blood alkaline phosphatase increased	28 (8)	0	19	7	2	0	76 (23)	0	66	7	3	0
Blood creatine phosphokinase increased	10 (3)	0	10	0	0	0	24 (7)	0	9	9	3	3
Blood creatinine increased	19 (6)	0	11	7	1	0	21 (6)	0	14	5	1	1
Weight decreased	15 (5)	0	8	6	1	0	15 (5)	0	9	5	1	0
Skin and subcutaneous tissue disorders	223 (68)	0	62	90	67	4	171 (51)	0	103	53	15	0
Palmar-plantar erythrodysaesthesia syndrome	177 (54)	0	44	68	61	4	81 (24)	0	41	27	13	0
Alopecia	45 (14)	0	33	11	1	0	40 (12)	0	34	6	0	0
Rash	57 (17)	0	32	21	4	0	36 (11)	0	26	10	0	0
Skin hyperpigmentation	23 (7)	0	15	8	0	0	21 (6)	0	19	2	0	0
Dry skin	10 (3)	0	8	2	0	0	18 (5)	0	16	2	0	0
Erythema	19 (6)	0	13	5	1	0	18 (5)	0	15	2	1	0
Pruritus	19 (6)	0	16	3	0	0	12 (4)	0	10	2	0	0
Metabolism and nutrition disorders	135 (41)	0	63	45	25	2	160 (48)	0	82	49	24	5
Anorexia	86 (26)	0	43	33	9	1	105 (32)	0	58	40	7	0
Hypokalaemia	25 (8)	0	23	0	2	0	37 (11)	0	22	2	12	1
Hypoalbuminaemia	20 (6)	0	11	7	2	0	21 (6)	0	10	10	1	0
Hyponatraemia	11 (3)	0	8	0	3	0	19 (6)	0	9	1	8	1
Dehydration	18 (5)	0	3	7	8	0	17 (5)	0	4	4	7	2
Infections and infestations	103 (31)	1	47	39	15	1	136 (41)	0	36	64	32	4
Urinary tract infection	19 (6)	0	4	14	1	0	17 (5)	0	2	12	2	1
Catheter site infection	5 (2)	0	4	0	1	0	15 (5)	0	1	9	5	0
Nasopharyngitis	16 (5)	0	11	5	0	0	15 (5)	0	10	5	0	0

(continued)

MedDRA SOC Term / MedDRA Preferred Term	DOXIL (N=330)						Trabectedin/DOXIL (N=333)					
	Total n (%)	Ns	1	2	3	4	Total n (%)	Ns	1	2	3	4
Respiratory, thoracic and mediastinal disorders	99 (30)	0	53	33	10	3	115 (35)	0	63	28	14	10
Dyspnoea	32 (10)	0	12	14	5	1	51 (15)	0	30	10	10	1
Cough	38 (12)	0	29	9	0	0	39 (12)	0	29	10	0	0
Pulmonary embolism	8 (2)	0	0	3	3	2	17 (5)	0	2	4	3	8
Pharyngolaryngeal pain	24 (7)	0	16	8	0	0	16 (5)	0	15	1	0	0
Nervous system disorders	76 (23)	0	60	13	3	0	109 (33)	0	74	22	13	0
Headache	25 (8)	0	21	3	1	0	53 (16)	0	36	15	2	0
Dizziness	22 (7)	0	20	1	1	0	31 (9)	0	25	5	1	0
Dysgeusia	10 (3)	0	8	2	0	0	18 (5)	0	15	2	1	0
Peripheral sensory neuropathy	9 (3)	0	7	2	0	0	16 (5)	0	15	1	0	0
Musculoskeletal and connective tissue disorders	72 (22)	0	47	18	6	1	91 (27)	0	57	26	7	1
Back pain	31 (9)	0	17	9	4	1	29 (9)	0	18	8	3	0
Arthralgia	15 (5)	0	7	7	0	1	21 (6)	0	16	5	0	0
Pain in extremity	17 (5)	0	13	3	1	0	20 (6)	0	14	5	1	0
Myalgia	11 (3)	0	9	2	0	0	18 (5)	0	11	6	1	0
Psychiatric disorders	43 (13)	0	28	13	2	0	63 (19)	0	38	20	5	0
Insomnia	15 (5)	0	13	2	0	0	32 (10)	0	22	10	0	0
Anxiety	11 (3)	0	5	6	0	0	23 (7)	0	12	9	2	0
Hepatobiliary disorders	28 (8)	0	18	6	4	0	62 (19)	0	34	20	7	1
Hyperbilirubinaemia	24 (7)	0	16	6	2	0	52 (16)	0	35	13	4	0

Note: Adverse events reported any time from the first treatment dose to within 30 days of last treatment dose are included.
Note: Incidence is based on the number of subjects, not the number of events.
Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Toxicity Grade: NCI common toxicity criteria, version 3.0 (CTC, v3.0).
NS=not specified

Evaluator's comments: The commonest events were gastrointestinal, of which nausea, vomiting, constipation and diarrhoea were more common (all grades) in the combination arm than in the monotherapy arm. Grade 2 and 3 nausea and vomiting were about twice as frequent.

For TEAEs of the hematopoietic system, a higher incidence was seen for all grades in the combination arm. Grade 4 events were strikingly increased in this arm with an incidence of 44%

compared to 22% in the monotherapy arm. Of special note was the incidence of febrile neutropenia. Grades 3 and 4 neutropenia were reported in 6 and 1 of 330 patients respectively in the monotherapy arm and in 19 and 8 of 333 patients in the combination therapy arm.

Events from the *General Disorders and Administration Site Conditions* SOC were of approximately the same incidence in each arm.

Abnormal LFTs found on laboratory investigations showed a high frequency of all grades in the combination therapy group compared to those in the monotherapy group, especially those of Grade 3 severity. For example, for Grade 3 increased alanine aminotransferase, the frequency was 52% in the combination therapy arm compared to 10% in the monotherapy arm.

Skin and Subcutaneous Tissue Disorders were the only TEAEs showing a higher frequency in the Caelyx/Doxil alone arm, including four Grade 4 cases of palmar-plantar erythrodysaesthesia syndrome compared to none in the combination arm.

Metabolism and Nutrition Disorders of Grade 1 severity were more frequent in the combination arm due to a higher numbers of cases of anorexia. Other TEAEs in this group were of similar frequency.

Of *Infections and Infestations*, the incidence of Grade 3 events was 15% in the monotherapy arm and 24% in the combination arm.

For *Respiratory, Thoracic and Mediastinal Disorders*, Grade 4 events were more frequent in the combination arm (9%) compared to the monotherapy arm (3%).

For *Nervous System Disorders*, Grades 1, 2, and 3 events were more frequent in the combination arm, while musculoskeletal and connective tissue disorders were of about the same frequency, as were psychiatric disorders.

Grades 1,2, and 3 of hyperbilirubinaemia were more frequent in the combination therapy group also.

The results for drug-related adverse events were similar.

Special Groupings of TEAEs

Special groupings of body systems, selected from prior experience - hepatobiliary disorders (Table 9), abdominal pain, renal and urinary disorders, cardiac disorders, bleeding, rhabdomyolysis and CPK increase, and extravasation were discussed separately in the report.

Table 9: TEAEs – special groupings – *Hepatobiliary/Infections and Infestations*

AE Special Group MedDRA Preferred Term	DOXIL (N=330) n (%)	Trabectedin/DOXIL (N=333) n (%)
Hepatobiliary disorders	66 (20)	217 (65)
Alanine aminotransferase increased	31 (9)	182 (55)
Aspartate aminotransferase increased	34 (10)	134 (40)
Blood alkaline phosphatase increased	28 (8)	76 (23)
Hyperbilirubinaemia	24 (7)	52 (16)
Gamma-glutamyltransferase increased	6 (2)	13 (4)
Gamma-glutamyltransferase	3 (1)	8 (2)
Hepatotoxicity	1 (<1)	6 (2)
Transaminases increased	1 (<1)	5 (2)
Liver function test abnormal	1 (<1)	4 (1)
Bilirubin conjugated increased	0	3 (1)
Hepatic enzyme abnormal	1 (<1)	3 (1)
Hepatic enzyme increased	0	3 (1)
Alanine aminotransferase abnormal	0	2 (1)
5'nucleotidase increased	0	1 (<1)
Aspartate aminotransferase abnormal	0	1 (<1)
Hepatic pain	1 (<1)	1 (<1)
Hepatitis	0	1 (<1)
Hepatitis toxic	0	1 (<1)
Blood bilirubin abnormal	1 (<1)	0
Hepatitis cholestatic	1 (<1)	0
Jaundice	1 (<1)	0
Infection and infestation	106 (32)	149 (45)
Febrile neutropenia	7 (2)	27 (8)
Urinary tract infection	19 (6)	17 (5)
Catheter site infection	5 (2)	15 (5)
Nasopharyngitis	16 (5)	15 (5)
Upper respiratory tract infection	5 (2)	14 (4)
Pneumonia	5 (2)	10 (3)
Pharyngitis	5 (2)	9 (3)
Catheter related infection	1 (<1)	8 (2)
Cystitis	6 (2)	8 (2)
Sinusitis	2 (1)	8 (2)
Bronchitis	4 (1)	7 (2)
Cellulitis	3 (1)	6 (2)
Oral herpes	4 (1)	6 (2)
Localised infection	0	5 (2)
Oral candidiasis	9 (3)	5 (2)
Rhinitis	3 (1)	5 (2)
Viral infection	1 (<1)	5 (2)
Herpes virus infection	1 (<1)	4 (1)
Influenza	4 (1)	4 (1)
Lower respiratory tract infection	0	4 (1)
Bacteraemia	0	3 (1)
Candidiasis	2 (1)	3 (1)
Catheter site cellulitis	1 (<1)	3 (1)
Conjunctivitis	1 (<1)	3 (1)
Gastrointestinal infection	0	3 (1)
Herpes zoster	1 (<1)	3 (1)
Neutropenic infection	0	3 (1)
Respiratory tract infection	0	3 (1)
Folliculitis	0	2 (1)
Fungal infection	7 (2)	2 (1)
Infection	7 (2)	2 (1)

(continued)

1. Hepatotoxicity: Five times as many patients in the combination therapy arm showed an abnormally high alanine transaminase as patients in the monotherapy arm, while the increase was 4-fold for aspartate transaminase and 3-fold for SAP and 2-fold for hyperbirubinaemia. To address the increase, the sponsor applied "Hy's law".[27] Although 247 (73%) of subjects in the trabectedin + Caelyx/Doxil arm had an elevated ALT or AST level that was ≥3 times ULN and had an ALP value ≤2 times ULN, only 3 of these subjects had an increased bilirubin that was ≥2 times ULN. These 3 subjects met the criteria for Hy's law, as being at risk of hepatotoxicity from long term treatment with the drug combination. However, none of the three developed serious hepatotoxicity on follow-up. Two had subsequent therapy and died from disease progression, and one subject is still in the follow-up phase of the study.

Evaluator's Comment: According to Temple, Hy's law is an attempt to distinguish changes such as increases in transaminase levels that are not followed by hepatotoxicity, as with drugs such as tacrine and aspirin, from the increases that are.[27] Temple also cites examples where hepatotoxicity has occurred without prior significant increases in transaminases. The evaluator expressed reservations about accepting Hy's law as used in the present trial mainly because the specificity and sensitivity of the test have not been determined. Also, Temple does not say how long patients need to be treated or followed after they meet the criteria of Hy's law before hepatotoxicity is observed.

In summary, the evaluator regarded the combination of trabectedin + Caelyx/Doxil as causing a marked increase in liver enzymes and a lesser increase in bilirubin, and considered this to be a warning sign of possible late hepatotoxicity that requires continuing postmarketing assessment.

2. Cardiac Events: Possible cardiotoxic effects of doxorubicin (Caelyx/Doxil), especially at high cumulative dose, are routinely monitored by measuring the left ventricular ejection fraction (LVEF), as it was in this trial. Although the proportion of subjects who had a protocol-defined LVEF decrease from baseline was similar for the Caelyx/Doxil monotherapy (15 subjects, 9%) and trabectedin + Caelyx/Doxil (13 subjects, 7%) treatment arms, all other cardiac events were more frequent in the trabectedin + Caelyx/Doxil arm, including clinically significant adverse events and abnormal ECG changes.

3. Renal and Urinary Disorders: These disorders were of equal frequency in each arm and were not especially frequent or severe.

4. Extravasation-Related Adverse Events: The rate was low (1%) and equal in both treatment arms.

5. Respiratory Disorders: Although the number of serious events, mainly pulmonary embolism, was small, they were consistently higher in the combination arm including one death from pulmonary embolism, although classed as non-drug related.

6. Creatine Phosphokinase / Rhabdomyolysis: The only case of rhabdomyolysis occurred in the trabectedin + Caelyx/Doxil arm, while an additional 24 patients had abnormally elevated CPK compared to 11 in the Caelyx/Doxil only arm.

Myelodysplasia and acute myeloid leukaemia, abdominal pain, alopecia, neurotoxicity, ototoxicity and hypersensitivity were similar in both arms (except the latter due to the greater use of dexamethasone in the combination arm) and require no special comment.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths: One patient in the Caelyx/Doxil monotherapy arm died of drug-related sepsis, and five (2%) in the trabectedin + Caelyx/Doxil arm, three of which were drug-related. The causes were acute renal failure and neutropenic sepsis; pancytopenia and sepsis; and thrombocytopenia and febrile neutropenia.

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[27] Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidem Drug Safety 2006; 15: 241–243.

Other Serious Adverse Events: The study report states, "The percentage of subjects experiencing at least 1 serious adverse event from the time of the first dose of study medication through 30 days after the last dose of study drug was similar for the Caelyx/Doxil monotherapy arm (31%) and the trabectedin + Caelyx/Doxil arm (39%)."

Evaluator's comment: This statement requires careful attention. The figures quoted refer to the percentage of patients with at least one serious adverse event, and correctly show these percentages to be similar in each treatment arm. An inspection of percentages from the relevant Table (not reproduced because of its length), however, (see below), shows that in the combination arm each patient suffered many more individual serious adverse events than patients in the monotherapy arm - that is, such patients often suffered multiple events in contrast to single events in the monotherapy arm. This is consistent with the high toxicity of the combination therapy arm, as noted in the above section on the frequency of TEAEs in each treatment arm.

The following figures for the major groupings of serious adverse events taken from the Table referred to above illustrate this point. The first number in the comparison below is the number of affected patients and their percentage of the 330 patients in the monotherapy arm, and of the 333 patients in the combination therapy arm. The percentages are the percent of patients with a serious adverse event named within the groupings shown. The same patient may therefore be included more than once, if he/she had different events, so that percentage totals in the Table did not equal 100%.

Blood and Lymphatic System Disorders: 18 (5%) vs 59 (18%)
Gastrointestinal Disorders: 54 (16%) vs 45 (14%)
General Disorders and Administration Site Conditions: 15 (5%) vs 31 (9%)
Infections and Infestations: 16 (5%) vs 30 (9%)
Respiratory, Thoracic and Mediastinal Disorders: 11 (3%) vs 18 (5%)
Metabolism and Nutrition Disorders: 12 (4%) vs 13 (4%)
Vascular Disorders: 3 (1%) vs 12 (4%)
Investigations: 0 vs 10 (3%)
Hepatobiliary Disorders: 2 (1%) vs 5 (2%)
Nervous System Disorders: 4 (1%) vs 5 (2%)
Renal and Urinary Disorders: 5 (2%) vs 5 (2%)
Cardiac Disorders: 1 (<1%) vs 4 (1%)
Injury, Poisoning and Procedural Complications: 4 (1%) vs 4 (1%)
Neoplasms Benign, Malignant, Unspec(incl cysts,polyps): 1 (<1%) vs 3 (1%)
Immune System Disorders: 6 (2%) vs 2 (1%)
Musculoskeletal and Connective Tissue Disorders 1: (<1%) vs 2 (1%)
Skin and Subcutaneous Tissue Disorders: 5 (2%) vs 2 (1%)
Congenital, Familial and Genetic Disorders: 0 vs 1 (<1%)
Reproductive System and Breast Disorders: 3 (1%) vs 1 (<1%)
Psychiatric Disorders: 1 (<1%) vs 0.

It is important to note that these are serious adverse events, and were increased in the combination therapy arm by from 80% to 400% in at least 9 groupings, while only three increases (gastrointestinal system, immune system and psychiatric disorders) were seen in the monotherapy arm.

Effects of Serious Adverse Events – a Comparison of the Treatment Arms:

1. Hospitalisation: Fewer subjects treated with Caelyx/Doxil monotherapy (123 [37%] of 335 subjects) were hospitalized for any reason compared with subjects treated with trabectedin + Caelyx/Doxil (163 [48%] of 337 subjects)

2. Drug-Related Adverse Events Leading to Treatment Termination: Drug-related adverse events that led to treatment termination occurred in 9% of subjects in the Caelyx/Doxil

monotherapy arm and 17% in the trabectedin + Caelyx/Doxil arm. The most frequent were drug-related *Blood and Lymphatic Disorders*, reported for 2% of subjects in the Caelyx/Doxil monotherapy arm compared with 7% in the trabectedin + Caelyx/Doxil arm. In this grouping, neutropenia was the most frequently reported adverse event leading to treatment termination (2% of subjects in the Caelyx/Doxil monotherapy arm and 4% in the trabectedin + Caelyx/Doxil arm).

3. Drug-Related Adverse Events Leading to Dose Adjustment: Cycle delays were more common than dose adjustments for drug-related adverse events in both treatment arms.

Dose Adjustment: Fewer subjects in the Caelyx/Doxil monotherapy arm had at least 1 drug-related adverse event that resulted in a dose adjustment than in the trabectedin + Caelyx/Doxil arm (35% and 43%, respectively). Hand-foot syndrome was the most common drug-related adverse event leading to a dose adjustment, occurring in 19% of subjects in the Caelyx/Doxil monotherapy arm and 4% in the trabectedin + Caelyx/Doxil arm. Neutropenia was the second most common adverse event leading to a dose adjustment in the trabectedin + Caelyx/Doxil arm, occurring in 15% of subjects, compared to 3% in the Caelyx/Doxil alone arm.

Cycle Delays: Cycle delays were less frequent in the Caelyx/Doxil monotherapy arm (37%) than in the trabectedin + Caelyx/Doxil arm (65%). Neutropenia was the primary reason for a cycle delay in both treatment arms (18% in the Caelyx/Doxil monotherapy arm and 53% in the trabectedin + Caelyx/Doxil arm). For 53% of the subjects in the trabectedin + Caelyx/Doxil arm, neutropenia was managed by cycle delays; or by a dose reduction (15% subjects). Hand-foot syndrome resulted in a cycle delay in 12% of subjects in the Caelyx/Doxil monotherapy arm and 4% in the trabectedin + Caelyx/Doxil arm.

Evaluation of Results of Clinical Laboratory Tests

A comparison of baseline tests showed that the results were similar in the two treatment arms, including haematological abnormalities.

During the study, most subjects had or developed hematologic abnormalities. In the Caelyx/Doxil monotherapy arm, 193 (59%) subjects had Grade 1 or 2 abnormalities, 77 (24%) had Grade 3, and 44 (14%) had Grade 4. In the trabectedin + Caelyx/Doxil arm, the corresponding values were 80 (24%), 103 (31%), and 150 (45%), respectively. The incidence of Grade 3-4 hematologic abnormalities during treatment was higher in the trabectedin + Caelyx/Doxil arm (76%) than in the Caelyx/Doxil monotherapy arm (37%).

The most frequently reported Grade 3-4 abnormalities in both treatment arms were low neutrophil counts (30% of subjects in the Caelyx/Doxil monotherapy arm and 72% of subjects in the trabectedin + Caelyx/Doxil arm) and white blood cell (WBC) count (20% and 62% of subjects, respectively).

Almost all subjects in the trabectedin + Caelyx/Doxil arm had an elevation (Grade 1 to 4) in ALT (96%) or AST (89%) at some point during the study; 5% and 2% of subjects receiving trabectedin + Caelyx/Doxil had a Grade 4 ALT or AST elevation, respectively.

Elevations in ALT and AST were seen in 36% and 43% of subjects in the Caelyx/Doxil monotherapy arm. In all but 1 subject the elevation was Grade 3 or less. No subject had a Grade 4 elevation in ALP or bilirubin. Grade 3 elevations in these laboratory parameters occurred in a low percentage of subjects in the 2 treatment arms (1% to 2% for ALP, respectively, and <1% for bilirubin in each arm).

Evaluator's comment: The frequency of Grade 3-4 hematological events in the trabectedin + Caelyx/Doxil arm was about twice that in the Caelyx/Doxil alone arm, as was Grade 3-4 neutropenia. Grade 3-4 WBC events were 3 times more frequent.

Significance of abnormal laboratory tests

Evaluator's comments: The section of the report, headed "Clinically Significant Laboratory Abnormalities During Treatment", did not in fact deal with the question of clinical significance, but presented times and duration for the abnormalities of patients with Grade 3-4 neutropenia, for the neutrophil nadir, for the median values of ALT (Grade 3-4), and for the ALT peaks (Grade 3-4) during the treatment cycles.

The data indicated recovery to normal or lower toxicity grades with time. However the clinical significance has already been shown above, as serious adverse events (see above), which would affect the patients' well being and continuing treatment.

In the last paragraph of the same section, the study report described the management of these abnormalities as follows – "In the trabectedin + Caelyx/Doxil arm, neutrophil abnormalities and transaminase elevations were managed by cycle delay (53% for neutropenia, 4% for ALT, and 1% for AST) and dose reduction (15% for neutropenia, 5% for ALT, and 3% for AST) . In the event of neutropenia, colony-stimulating growth factors were used in 42% of the subjects."

Thrombocytopenia and bleeding events: On-treatment Grade 3 or 4 abnormalities in platelet counts were observed 5-times more frequently with combination therapy (23%) as with monotherapy (4%), although bleeding-related adverse events were reported in a similar percent of subjects in the Caelyx/Doxil (8%) and trabectedin + Caelyx/Doxil (9%) arms of the study. Among subjects receiving the trabectedin + Caelyx/Doxil combination, cycle delays due to thrombocytopenia reported as an adverse event were more common (13%) than treatment withdrawals (3%) or dose reductions (5%).

Grade 3-4 haemoglobin abnormalities were present in 27 (8%) of patients in the monotherapy arm and in 62 (19%) in the combination therapy arm. Five (1.5%) and 9 (2.7%) in the monotherapy and combination arms respectively were given transfusion of blood products, while 1 and 23 respectively received erythropoietin preparations.

Evaluator's Safety Summary

As shown in each of the Sections above, the combination of trabectedin + Caelyx/Doxil was with very few exceptions more toxic than treatment with Caelyx/Doxil alone in the frequency of drug-related adverse events, of severe (Grade 3-4) drug-related adverse events, of serious drug-related adverse events, of treatment modification because of drug toxicity, of drug-related deaths and of clinical laboratory tests.[28] Their impact on treatment and patient well-being was shown by the greater number of delays in treatment and dose reduction, and the greater number of serious drug-related events during treatment with the combination of trabectedin and Caelyx/Doxil compared to Caelyx/Doxil alone. Serious AEs, by definition, have a negative effect on patient well-being that is clinically significant.

Phase 2 studies of trabectedin as a single agent in the treatment of relapsed ovarian cancer

Integrated Phase 2 ovarian safety analysis set (N=295)

Reasons for terminating treatment

Disease progression was the primary reason for the permanent discontinuation of study treatment across all treatment arms resulting in the termination of 173 (59%) of the 295 subjects (48% to 67% across 3 trabectedin treatment arms). Adverse events resulted in the discontinuation of study treatment for 42 (14%) of the 295 subjects.

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[28] the one significantly greater toxicity seen with Doxil alone was palmar-plantar erthryodysaesthenia syndrome with a frequency of 54% in the monotherapy arm versus 24% in the combination therapy arm.

Dose delays and reductions

One hundred fifty-seven subjects (53%) had a delay in at least 1 cycle of trabectedin therapy. Seventy-three percent (73%) of these subjects had cycle delays due to adverse events (115 of 157), with hematological toxicity being the most prevalent reason (78 of 115 subjects).

Overall, dose reductions occurred in 47% of subjects receiving trabectedin as a single agent in the integrated Phase 2 ovarian safety analysis set, and most subjects had dose reductions due to non-hematological toxicity (104 of 138 subjects). In the q3wk 3-h trabectedin arm, 64% of subjects did not require any dose reduction, 30% had 2 reductions and 6% had 3 or more reductions.

Evaluator's comment: For the combined therapy used in the pivotal trial, more cycle delays occurred (83%) and dose reductions (43 %) were of similar frequency. In both cases, drug-related adverse events were the cause.

Use of medications to treat adverse events

The use of filgrastim and blood and related products was low (filgrastim [5%], and of blood and related products [human red blood cells, 2%; blood, whole, <1%; red blood cells, 5%; red blood cells, concentrated, 1%; blood cells, packed human, 1%]). In the pivotal trial, the use of colony stimulating factors was 17% in the Doxil arm and 42% in the Doxil+trabectedin arm, and of blood and blood products, 7% and 17% respectively.

Evaluator's comment: As above, in the safety section of the pivotal trial, the combination of Doxil and trabectedin was more toxic than Doxil alone. The Phase 2 studies here show the combination was also more toxic than trabectedin alone.

Adverse events

As shown in Table 10, Grade 3 or 4 adverse events were reported for 46% of subjects in the q3wk 3-h treatment arm compared with 62% in the qwk 3-h arm and 72% for the q3wk 24-h arm. A higher proportion of subjects in the q3wk 24-h arm compared with the other 2 treatment arms also had drug-related Grade 3 or 4 adverse events and adverse events leading to treatment discontinuation. The incidence of serious adverse events, regardless of grade and relatedness, was similar across the treatment groups. For 2% of subjects, death was due to an adverse event; death due to a drug-related adverse event occurred in 2 of the 295 subjects (1%).

Evaluator's comment: Comparable figures for Grade 3 or 4 adverse events in the Doxil and Doxil+trabectedin arms of the pivotal trial were 72% and 91% respectively, for serious drug-related adverse events 13% and 27%, and for drug-related deaths <1% and 2%.

Table 10: Safety profile – integrated Phase 2 ovarian studies

	q 3 wk; 24-h (1.5 mg/m^2) (N=54) n (%)	q wk; 3-h (0.58 mg/m^2) (N=147) n (%)	q 3 wk; 3-h (1.3 mg/m^2) (N=94) n (%)	Total (N=295) n (%)
Treatment-emergent adverse events (TEAEs)	52 (96)	146 (99)	92 (98)	290 (98)
Drug-related	50 (93)	141 (96)	87 (93)	278 (94)
Grade 3-4 TEAEs	39 (72)	91 (62)	43 (46)	173 (59)
Drug-related	38 (70)	58 (39)	32 (34)	128 (43)
Serious TEAEs	13 (24)	48 (33)	24 (26)	85 (29)
Drug-related	8 (15)	22 (15)	14 (15)	44 (15)
Grade 3-4	13 (24)	40 (27)	21 (22)	74 (25)
Drug-related Grade 3-4	8 (15)	14 (10)	14 (15)	36 (12)
TEAE leading to discontinuation	13 (24)	18 (12)	11 (12)	42 (14)
Death due to TEAE	0	3 (2)	3 (3)	6 (2)
Within 30 days of last dose	0	3 (2)	1 (1)	4 (1)
Within 60 days of first dose	0	2 (1)	3 (3)	5 (2)
Drug-related TEAE leading to death	0	1 (1)	1 (1)	2 (1)

qwk = once weekly; q3wk = once every 3 weeks; TEAE = treatment-emergent adverse event
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
Note: All adverse events with toxicity Grade 1-5 and unknown toxicity grades are included in the analysis.

Nature and frequency of treatment emergent adverse events

Adverse events reported by at least one-third of subjects receiving trabectedin as a single agent included nausea (76%), constipation (56%), vomiting (56%), and fatigue (60%) (Table 11). These four adverse events, along with asthenia, were also the adverse events reported by at least one-third of subjects receiving the q3wk 3-h regimen. In patients receiving the 3 weekly treatment by 3 hour infusion, haematological toxicity occurred in 21%, and neutropenia in 17%.

Evaluator's comment: A number of TEAEs seen in both arms of the pivotal trial related to those seen with Doxil, such as stomatitis and hand-foot syndrome, and were not seen in the Phase 2 trials. Those TEAES common to both Doxil and trabectedin, such as haematological toxicity, were more frequent and more severe in the combination arm than in the Doxil arm, and more so than those in the Phase 2 studies. For example haematological toxicity was reported in 55% of patients in the Doxil arm and in 88% in the combination arm; neutropenia 38% and 77%; and thrombocytopenia 8% and 36%, much lower than with trabectedin as a single agent.

Drug-related TEAEs: Drug-related adverse events in the phase 2 studies showed a similar difference to those above, when compared with those in the pivotal trial. Drug-related adverse events reported by at least 10% of all subjects receiving trabectedin in the Phase 2 studies were nausea (69%), fatigue (52%), vomiting (48%), constipation (31%), neutropenia (27%), ALT increased (20%), blood alkaline phosphatase increased (20%), asthenia (18%), anorexia (18%), diarrhea (16%), AST increased (11%), and anaemia (11%). Nausea (71%), vomiting (47%), fatigue (36%), constipation (31%), and asthenia (30%) were the drug-related adverse events reported in at least 20% of the 94 subjects in the q3wk 3-h trabectedin arm.

Table 11: TEAEs by SOC and PT in integrated Phase 2 ovarian studies

MedDRA SOC Term MedDRA Preferred Term	q 3 wk; 24-h (1.5 mg/m^2) (N=54) n (%)	q wk; 3-h (0.58 mg/m^2) (N=147) n (%)	q 3 wk; 3-h (1.3 mg/m^2) (N=94) n (%)	Total (N=295) n (%)
Total no. subjects with TEAEs	52 (96)	146 (99)	92 (98)	290 (98)
Gastrointestinal disorders	43 (80)	141 (96)	83 (88)	267 (91)
Nausea	37 (69)	115 (78)	71 (76)	223 (76)
Constipation	22 (41)	94 (64)	50 (53)	166 (56)
Vomiting	31 (57)	83 (56)	51 (54)	165 (56)
Diarrhoea	7 (13)	61 (41)	21 (22)	89 (30)
Abdominal pain	9 (17)	52 (35)	19 (20)	80 (27)
Dyspepsia	1 (2)	29 (20)	15 (16)	45 (15)
Abdominal pain upper	4 (7)	23 (16)	11 (12)	38 (13)
Abdominal distension	2 (4)	29 (20)	1 (1)	32 (11)
Stomatitis	6 (11)	11 (7)	8 (9)	25 (8)
Ascites	2 (4)	14 (10)	4 (4)	20 (7)
Gastrooesophageal reflux disease	0	14 (10)	1 (1)	15 (5)
Mouth ulceration	0	14 (10)	0	14 (5)
General disorders and administration site conditions	38 (70)	131 (89)	72 (77)	241 (82)
Fatigue	34 (63)	103 (70)	39 (41)	176 (60)
Asthenia	4 (7)	29 (20)	31 (33)	64 (22)
Pyrexia	8 (15)	32 (22)	12 (13)	52 (18)
Oedema peripheral	4 (7)	27 (18)	6 (6)	37 (13)
Pain	2 (4)	24 (16)	2 (2)	28 (9)
Chest pain	3 (6)	19 (13)	2 (2)	24 (8)
Chills	0	14 (10)	1 (1)	15 (5)
Injection site reaction	7 (13)	0	5 (5)	12 (4)
Investigations	29 (54)	85 (58)	39 (41)	153 (52)
Alanine aminotransferase increased	11 (20)	41 (28)	10 (11)	62 (21)
Blood alkaline phosphatase increased	18 (33)	29 (20)	12 (13)	59 (20)
Aspartate aminotransferase increased	5 (9)	21 (14)	7 (7)	33 (11)
Nervous system disorders	16 (30)	98 (67)	28 (30)	142 (48)
Headache	4 (7)	53 (36)	7 (7)	64 (22)
Dizziness	1 (2)	28 (19)	5 (5)	34 (12)
Paraesthesia	6 (11)	19 (13)	8 (9)	33 (11)
Dysgeusia	4 (7)	17 (12)	5 (5)	26 (9)
Lethargy	0	22 (15)	0	22 (7)

(continued)

MedDRA SOC Term MedDRA Preferred Term	q 3 wk; 24-h (1.5 mg/m^2) (N=54) n (%)	q wk; 3-h (0.58 mg/m^2) (N=147) n (%)	q 3 wk; 3-h (1.3 mg/m^2) (N=94) n (%)	Total (N=295) n (%)
Blood and lymphatic system disorders	32 (59)	61 (41)	20 (21)	113 (38)
Neutropenia	29 (54)	37 (25)	16 (17)	82 (28)
Anaemia	2 (4)	32 (22)	4 (4)	38 (13)
Respiratory, thoracic and mediastinal disorders	10 (19)	80 (54)	23 (24)	113 (38)
Dyspnoea	6 (11)	46 (31)	18 (19)	70 (24)
Cough	7 (13)	27 (18)	7 (7)	41 (14)
Musculoskeletal and connective tissue disorders	8 (15)	79 (54)	24 (26)	111 (38)
Back pain	2 (4)	31 (21)	5 (5)	38 (13)
Myalgia	3 (6)	18 (12)	8 (9)	29 (10)
Arthralgia	2 (4)	18 (12)	5 (5)	25 (8)
Pain in extremity	0	18 (12)	5 (5)	23 (8)
Metabolism and nutrition disorders	11 (20)	78 (53)	21 (22)	110 (37)
Anorexia	11 (20)	41 (28)	19 (20)	71 (24)
Decreased appetite	0	19 (13)	0	19 (6)
Psychiatric disorders	6 (11)	62 (42)	10 (11)	78 (26)
Insomnia	2 (4)	33 (22)	4 (4)	39 (13)
Anxiety	1 (2)	20 (14)	6 (6)	27 (9)
Depression	3 (6)	19 (13)	1 (1)	23 (8)
Vascular disorders	11 (20)	41 (28)	19 (20)	71 (24)
Hot flush	1 (2)	19 (13)	1 (1)	21 (7)
Phlebitis	5 (9)	1 (1)	11 (12)	17 (6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (17)	2 (1)	12 (13)	23 (8)
Cancer pain	9 (17)	0	12 (13)	21 (7)

incl. = including; MedDRA = Medical Dictionary for Regulatory Activities; no. = number; qwk = once weekly; q3wk = once every 3 weeks; SOC = system organ class; TEAE = treatment-emergent adverse events

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.

Note: Sorted by descending frequency in Total dose group.

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: Only preferred terms reported by designated incidence cutoff value in any dose group were included in the table.

Deaths

Of the 91 subjects in the integrated Phase 2 ovarian safety analysis set who died at any time during the study or follow-up, most (n=82) occurred more than 30 days after the last dose of trabectedin, mainly as a result of disease progression.

• Four of the 9 deaths that occurred within 30 days of the last dose of trabectedin were associated with adverse events, 1 of which occurred in the q3wk 3-h treatment arm.

• Two of the adverse events resulting in death were assessed as drug-related by the investigator. One died from cardio-pulmonary effects, and the other from multiple organ failure following neutropenic sepsis.

Serious Adverse Events

The percentage of subjects with serious adverse events was 26% for the q3wk 3-h arm. Vomiting and nausea were the only serious adverse events reported for 5% or more of all subjects in this safety analysis set.

Adverse events leading to discontinuation of treatment

Of patients in the q3wk-3hr treatment arm, 13% discontinued treatment due to a drug-related adverse event. Neutropenia, ALT increased, dyspnoea, and fatigue were the adverse events leading to discontinuation of more than 1% of subjects (2% for each event).

Evaluator's comment: In the pivotal trial, the figures were similar to the above, with 9% and 17% of patients stopping treatment because of drug-related adverse events in the Doxil and Doxil+trabectedin arms respectively.

Adverse events of interest

Elevation of liver enzymes: Effects on liver enzymes were similar to those in the pivotal trial with 96% and 83% of patients in the q3wk-3hr group having elevations of ALT and AST respectively, of which 32% and 16% were Grade 3 or 4. These reduced in a short time during the treatment cycle and were rarely (about 1% of cases) accompanied by increases in serum alkaline phosphatase or bilirubin. The increases reduced with continuing treatment. Two subjects (0.7%) in the integrated Phase 2 ovarian safety analysis set satisfied the criteria for Hy's law. Neither of these subjects had another reason for hepatocellular injury. Serious hepatotoxicity did not develop in either subject.

Hepatic toxicity: The frequency of hepatobiliary-related adverse events was 3% (n=10) for the total integrated Phase 2 ovarian safety analysis set (n=2, 2% for q3wk 3-h arm). These adverse events were considered drug related for all but 1 of the 10 total subjects. The most common of hepatobiliary related adverse events was hepatotoxicity (n=6, 2%; all drug related). For 5 subjects (2%), the hepatobiliary-related adverse event that was assessed as Grade 3 or 4, and for 1 subject, the adverse event was serious (hepatotoxicity). This latter serious adverse event was considered very likely related to study treatment and had an outcome of 'Death'. For three subjects (1%), the hepatobiliary-related adverse event resulted in treatment discontinuation (all for hepatotoxicity and all in q3wk 24-h arm).

In one Phase 1 study (ET743-USA-11), post-treatment liver biopsies were performed in 8 subjects who received Doxil and increasing doses of trabectedin. Four subjects receiving ongoing treatment underwent a single random liver biopsy after Cycles 14, 19, 21, and 30. An additional 4 subjects agreed to pre-and post-treatment biopsies. None of the 8 subjects who had biopsies in this fashion during treatment had significantly abnormal liver tests at the time of biopsy, however, all did have Grade 2 or higher acute liver transaminase levels prior to the liver biopsies. Expert independent review of the post-treatment biopsy slides demonstrated that nonalcoholic steatohepatitis (NASH) was present in 7 of the 8 biopsies, ranging in severity from minimal steatosis to moderate steatosis with fibrosis. Of the 4 subjects with biopsies pre-and post-treatment, 3 subjects showed no change in the severity of NASH pre- and post treatment. In the remaining subject, the pre-treatment liver biopsy was normal and the post-treatment biopsy showed minimal steatosis. One patient without a pre-treatment biopsy for review and who had moderate NASH on a post-treatment biopsy after Cycle 21 was morbidly obese. Thus review of the liver biopsies of these 8 patients did not demonstrate any evidence of serious liver abnormalities attributable to study treatment.

Haematological toxicity: Neutrophil count - While on treatment, 39% of subjects in the q3wk 3-h trabectedin arm had Grade 3 or 4 neutrophil counts (26% Grade 4). Across all trabectedin arms for this analysis set, 27% had Grade 3 or 4 neutrophil counts (15% Grade 4). Across the 78 subjects who developed a Grade 3 or 4 neutrophil value, the median time to first occurrence of this abnormality was about 5 weeks (range: 13, 382) and the median duration of this abnormality was approximately 2 weeks (range: 1, 260).

Median neutrophil counts for subjects receiving trabectedin in any of the 3 treatment arms did not show a cumulative pattern, even among subjects who received prolonged treatment (6 cycles or more). Of the 25 subjects with a Grade 3 or 4 neutrophil count in Cycle 1, 28% (n=7) were treated with a colony-stimulating growth factor.

Evaluator's comment: These results compared to 30% and 72% in the Doxil and Doxil+trabectedin arms respectively of the pivotal trial, indicating that the 72% resulted from the addition of the neutrophil toxicities of Doxil (30%) and trabectedin (39% in the Phase 2 trials, above). This explains the severe neutropenic toxicity seen with the drug combination.

Infection-related adverse events: Infection-related adverse events occurred in 34% of All-Treated Subjects in the integrated Phase 2 ovarian safety analysis set (23% in the q3wk 3-h arm). Drug-related, Grade 3 or 4 infection-related adverse events were reported for 2% of subjects (2% in q3wk 3-h arm). For 6% of subjects (6% in the q3wk 3-h arm), infection-related adverse events were serious (most common, catheter-related infection [2%]), and for 2% of subjects (4% in the q3wk 3-h arm), trabectedin treatment was discontinued for such an event (most common, catheter-related infection). Six subjects (2%) had febrile neutropenia reported as an adverse event (n=5 [5%] in the q3wk 3-h arm), and for each of these subjects, the event was Grade 3 or 4 in severity, and serious. Two of the 6 subjects in this treatment arm with febrile neutropenia had trabectedin therapy withdrawn because of the event.

Evaluator's comment: The sponsor's *Summary of Clinical Safety* is contradictory on this point. After quoting the above figures, it states: "There were no reports of neutropenic sepsis in the integrated Phase 2 ovarian safety analysis set. Four subjects (1%) had sepsis, all in the qwk 3-h arm".

In Study 99, the MedDRA term "Neutropenia aggravated" was conventionally used for coding all infections with Grade 3-4 neutropenia, and were reported as AEs. The difference between neutropenia and infection, and neutropenic sepsis may be that the latter refers to the clinical syndrome of septic shock and neutropenia, although the difference was not defined in the study reports. The sponsor could be asked to clarify this point.

To compare results, the above figure of 23% for the same dose regimen of trabectedin as in the pivotal trial compares with 45% in the combination arm of the pivotal trial; the 2% incidence of Grade 3 or 4 infection-related events with 11% in the pivotal trial; febrile neutropenia of 2% compared to 8% in the pivotal trial; and for "neutropenic infection" or "neutropenic sepsis", none compared to two subjects (0.6%) in the pivotal trial.

CPK Elevations/Rhabdomyolysis: The percentage of subjects in the integrated Phase 2 ovarian safety analysis set with Grade 3 or 4 abnormalities in CPK levels was 3% (1% Grade 4) for all subjects and for subjects in the q3wk 3-h arm. Rhabdomyolysis/elevated CPK-related (select terms) adverse events were reported for 4% of the subjects in the integrated Phase 2 ovarian safety analysis set, and all but 1 of these events consisted of the PT "blood CPK increased". For 3% of subjects in the integrated Phase 2 ovarian safety analysis set, the adverse event of blood CPK increased resulted in a cycle delay; no subject had a reduction in the dose of trabectedin as a result of this event. The adverse event, "rhabdomyolysis", was reported for a single subject in the q3wk 3-h arm. This subject experienced Grade 2 rhabdomyolysis (serious) on Day 85 (Cycle 4). The subject also had febrile neutropenia, thrombocytopenia, and pneumonia at this time. Trabectedin was

discontinued due to the rhabdomyolysis, febrile neutropenia, and pneumonia. The rhabdomyolysis was assessed by the investigator as not study drug related and resolved after approximately 2 weeks.

Evaluator's comment: In the Doxil arm of the pivotal trial, increased blood CPK concentrations were reported in 14% of patients, and in 22% in the Doxil+trabectedin arm, and "rhabdomyolysis/CPK elevated adverse events" in 3% and 8% respectively. Of these all but one had elevated blood CPK concentrations only, and only one patient had "rhabdomyolysis" as an adverse event.

However, increased blood concentrations of CPK have been found on repeated dose testing of trabectedin in monkeys, and the report states: "rhabdomyolysis and/or elevations in CPK in the early Phase 2 studies was associated with death in 3 subjects (Studies ET-B-008-98 and ET-B-005-98, 269 subjects treated, 1%), commonly as a component of a syndrome that included neutropenia, sepsis, renal failure and elevated liver enzymes".

The evaluator therefore recommended that an increase in the blood concentration of CPK be considered a warning sign of rhabdomyolysis due to trabectedin, enhanced by concomitant use of Doxil, until further data show otherwise.

Summary

A comparison with the combination of Doxil+trabectedin in the pivotal trial showed that toxicity of trabectedin alone was significantly increased by all parameters when combined with Doxil. The greatest increases in severity and seriousness were in those toxicities that were additive with each treatment, such as haematological and gastrointestinal toxicity, and raised blood levels of CPK and the rare occurrence of rhabdomyolysis. Other adverse events seen with the combination were due to more specific toxicities of each of the components - for example, hand-foot syndrome associated with Doxil and hepatic transaminasaemia with trabectedin. A comparison of the safety data from the Phase 2 trials and the Phase 3 trial showed that no new or unexpected adverse events occurred in the Phase 2 trials.

Advanced Soft Tissue Sarcoma (STS)

Phase 2 Study ET743-STS-201

Analysis of Safety

This section contained descriptive statistics and tabulations of data for the safety evaluation, including AEs, deaths, SAEs, clinical laboratory data, and physical examination results. The "All treated" analysis data set (n=260) was used for the safety analyses and included all patients in the two schedules who received at least one dose of trabectedin - 130 patients in each treatment arm. Safety data were included in the Updated Clinical Study Report from the time of first study related procedure to cut-off date for final TTP analysis (31 May 2006).

Extent of exposure

Cycles administered and dose intensity: Of note is that 83% more treatment cycles were administered to the q3wk 24-h group compared to the Qwk 3-h group, whereas the expected increase, based on the 21/28 treatment days per cycle, was 33%.

The median treatment duration was 13.1(range, 2.0-140.9) weeks: 11.5 (range, 2.0-89.4) weeks in the qwk 3-h group and 15.4 (range, 3.0-140.9) weeks in the q3wk 24-h group. The maximum duration of treatment was 89.4 weeks (20.6 months) with the qwk 3-h schedule and 140.9 weeks (32.4 months) with the q3wk 24-h schedule. The median dose intensity was 0.4 mg/m^2/week in both study groups. This resulted in a median relative dose intensity of 85.9% (range, 30.5-133.3%) in the qwk 3-h group and 81.4% (range, 49.1-120.0%) in the q3wk 24-h group.

Evaluator's comment: The greater increase in the number of treatment cycles in the q3wk 24-h group may be due to the high usage of the 3-weekly treatment after crossover, as discussed above. The median duration of treatment of 15.4wks in the q3wk 24-h group will be important is assessing risk-benefit. Over 80% of the planned dose was delivered in both groups, indicating that any drug toxicity was reasonably managed.

Cycle delays: A total of 162 patients (62.3%) experienced cycle delays at some time during the study period evaluated in this final TTP analysis: 66 patients (50.8%) in the qwk 3-h group and 96 patients (73.8%) in the q3wk 24-h group. In both groups, most of these patients had only one cycle delayed: 33 patients in the qwk 3-h group and 38 patients in the q3wk 24-h group. Delay was more frequently due to hematological toxicity in the q3wk 24-h arm (43%) than in the Qwk 3-h arm (27.3%).

Dose modifications: Dose modification was infrequent, and mainly due to transient AST, ALT or AP increases.

Adverse events

A summary of the number of patients with adverse events is given in Table 12.

Table 12: Number of patients reporting AEs

	qwk 3-h (n=130)	q3wk 24-h (n=130)	Total (n=260)
Any AE	129 (99.2%)	129 (99.2%)	258 (99.2%)
Any drug-related AE	104 (80.0%)	113 (86.9%)	217 (83.5%)
Any grade 3/4 AE	55 (42.3%)	76 (58.5%)	131 (50.4%)
Any grade 3/4 drug-related AE	21 (16.2%)	42 (32.3%)	63 (24.2%)
Hospitalizations associated with AEs	31 (23.8%)	39 (30.0%)	70 (26.9%)
Hospitalizations associated with drug-related AEs	6 (4.6%)	7 (5.4%)	13 (5.0%)
Discontinuations associated with AEs	10 (7.7%)	11 (8.5%)	21 (8.1%)
Discontinuations associated with drug-related AEs	4 (3.1%)	8 (6.2%)	12 (4.6%)
Deaths associated with AEs	6 (4.6%)	6 (4.6%)	12 (4.6%)
Deaths associated with drug-related AEs	3 (2.3%)	2 (1.5%)	5 (1.9%)
Deaths associated with drug-related SAEs	3 (2.3%)	4 (3.1%)*	7 (2.7%)

Data shown are n (%). Drug-related AEs=possibly, probably or very likely related to the study drug.

Evaluator's comment: The table shows that almost all patients suffered at least one AE, with about 50% being of Grade 3 or 4 severity. Drug-related Grade 3 or 4 AEs were twice as frequent in the q3wk 24-h group (32.3%) as in the qwk 3-h group (16.2%). The most common Grade 3/4 AEs related to the study medication were fatigue, nausea and vomiting.

Nature and Grades of Adverse Events

Tables 13 and 14 show the type of AE and its grade for all causes and those classed as drug-related.

Evaluator's comment: No haematological AEs were included, as these were presented separately in the results of clinical laboratory assessments.

Table 13: AEs regardless of relationship, worst grade per patient, occurring in at least 5% of patients in either treatment group.

Adverse Event. Preferred term	qwk 3h (n=130) 1 n	%	2 n	%	3 n	%	4 n	%	q3wk 24-h (n=130) 1 n	%	2 n	%	3 n	%	4 n	%
GASTROINTESTINAL DISORDERS	58	45	33	25	13	10	.	.	41	32	50	38	17	13	4	3
Abdominal pain	14	11	13	10	6	5	.	.	12	9	9	7	5	4	1	<1
Constipation	31	24	11	8	2	2	.	.	25	19	20	15	.	.	.	.
Diarrhea	25	19	3	2	.	.	.	.	25	19	5	4	1	<1	.	.
Nausea	52	40	12	9	3	2	.	.	53	41	37	28	7	5	.	.
Vomiting	19	15	11	8	2	2	.	.	25	19	25	19	7	5	.	.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	48	37	41	32	13	10	2	2	53	41	44	34	14	11	3	2
Fatigue	42	32	38	29	9	7	.	.	49	38	38	29	9	7	1	<1
Pyrexia	13	10	7	5	1	<1	.	.	29	22	3	2	.	.	1	<1
INFECTIONS AND INFESTATIONS	15	12	15	12	7	5	1	<1	18	14	20	15	15	12	2	2
INVESTIGATIONS	13	10	3	2	3	2	.	.	10	8	5	4	9	7	.	.
METABOLISM AND NUTRITION DISORDERS	29	22	7	5	4	3	.	.	31	24	16	12	3	2	1	<1
Anorexia	15	12	6	5	.	.	.	.	19	15	9	7	1	<1	.	.
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	38	29	22	17	10	8	.	.	33	25	13	10	12	9	.	.
Back Pain	14	11	7	5	4	3	.	.	13	10	2	2	4	3	.	.
NERVOUS SYSTEM DISORDERS	38	29	15	12	4	3	4	3	47	36	12	9	5	4	1	<1
Dizziness	8	6	5	4	.	.	.	.	16	12	1	<1	1	<1	.	.
Dysgeusia	8	6	.	.	.	.	.	.	13	10	.	.	.	.	.	.
Headache	26	20	7	5	1	<1	.	.	28	22	8	6	1	<1	.	.
PSYCHIATRIC DISORDERS	21	16	9	7	.	.	.	.	29	22	7	5	2	2	1	<1
Insomnia	13	10	3	2	.	.	.	.	17	13	3	2	.	.	.	.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	30	23	15	12	9	7	3	2	27	21	13	10	8	6	3	2
Cough	18	14	3	2	1	<1	.	.	19	15	4	3	.	.	.	.
Dyspnea	15	12	13	10	8	6	.	.	11	8	6	5	4	3	1	<1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	22	17	7	5	.	.	.	.	25	19	8	6	1	<1	1	<1
VASCULAR DISORDERS	8	6	4	3	3	2	.	.	16	12	7	5	10	8	3	2

Table 14: Drug-related AEs, worst grade per patient, occurring in at least 5% of patients in either treatment group.

Adverse Event. Preferred term	qwk 3h (n=130) 1 n	%	2 n	%	3 n	%	4 n	%	q3wk 24-h (n=130) 1 n	%	2 n	%	3 n	%	4 n	%
GASTROINTESTINAL DISORDERS	58	45	20	15	5	4	.	.	43	33	46	35	9	7	.	.
Constipation	22	17	1	<1	.	.	.	.	16	12	8	6	.	.	.	.
Diarrhea	15	12	3	2	.	.	.	.	15	12	4	3	.	.	.	.
Nausea	49	38	11	8	3	2	.	.	53	41	35	27	5	4	.	.
Vomiting	16	12	10	8	2	2	.	.	24	18	24	18	3	2	.	.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	35	27	27	21	6	5	1	<1	43	33	39	30	7	5	2	2
Fatigue	31	24	26	20	6	5	.	.	41	32	36	28	7	5	1	<1
METABOLISM AND NUTRITION DISORDERS	15	12	5	4	1	<1	.	.	25	19	13	10	2	2	.	.
Anorexia	12	9	4	3	.	.	.	.	18	14	6	5	1	<1	.	.
Decreased appetite	2	2	.	.	.	.	.	.	7	5	1	<1	.	.	.	.
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	16	12	5	4	1	<1	.	.	20	15	3	2	4	3	.	.
Myalgia	6	5	2	2	1	<1	.	.	10	8	1	<1	2	2	.	.
NERVOUS SYSTEM DISORDERS	16	12	7	5	1	<1	.	.	24	18	6	5	3	2	.	.
Dysgeusia	5	4	.	.	.	.	.	.	11	8	.	.	.	.	.	.
Headache	8	6	3	2	1	<1	.	.	15	12	4	3	1	<1	.	.
PSYCHIATRIC DISORDERS	3	2	1	<1	.	.	.	.	7	5	3	2	.	.	.	.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9	7	5	4	2	2	.	.	7	5	4	3	2	2	1	<1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	10	8	2	2	.	.	.	.	10	8	2	2	.	.	1	<1
VASCULAR DISORDERS	4	3	.	.	1	<1	.	.	7	5	5	4	2	2	1	<1

Analysis of adverse events

An analysis of drug-related AEs was presented with a special emphasis on drug-related AEs achieving Grade 3 or Grade 4 and affecting at least 1% of patients. Drug-related AEs were usually reported in less than 5% of patients or cycles.

Evaluator's comment: Adverse events of the musculoskeletal system (defined as arthralgia, back pain, chest wall pain, muscular weakness, myalgia, and weakness in an extremity) occurred in 2%, <1%, 0, 2%, 4%, and 2% respectively in the q3wk-3hr arm, and 4%, 2%, 2%, <1%, 8%, and <1% respectively in the q3wk-24hr arm. As these were <5% frequency they did not appear in Tables 12 and 13, but are important because of the conclusion from the safety data of the Phase 2 studies in ovarian cancer that raised blood levels of CPK and a case of rhabdomyolysis have been reported with single agent trabectedin.

Deaths and Other Serious Adverse Events (SAEs)

Deaths

A total of 167 patients (64.2% of all treated patients) had died at cut-off date: 88 patients (67.7%) in the qwk 3-h group and 79 patients (60.8%) in the q3wk 24-h group. The most common cause of death was disease progression in both studies.

Evaluator's comment: The number of deaths was similar in each treatment group. Of note is the one death due to recall of radiation pneumonitis, that was "very likely/certain" due to trabectedin.

Other SAEs

In the qwk 3-h group, 12 (9.2%) of the 130 patients treated experienced 23 drug-related SAEs, and in the q3wk 24-h group, 18 (13.8%) of the 130 patients treated experienced 31 drug-related SAEs. In the former group, six drug-related SAEs resulted in fatal outcome in three patients, and in the latter six drug-related SAEs resulted in fatal outcome in four patients.

Evaluator's comments: The two groups showed similar results. The frequency of serious infection, often fatal and drug-related was noted.

Clinical Laboratory Results

Haematology

The frequency of Grade 3 (26.2%) neutropenia and Grades 3 (9.2%) and 4 (2.3%) thrombocytopenia in the Q3wk 24-h treatment group was roughly twice those in the Qwk 3-h treatment group (11.7%; 4.7% and 0.8%) respectively. However the frequency of Grade 4 neutropenia was much higher in the 3-weekly treatment group (20.8% vs 1.6%). In spite of this high frequency (n=27; 20.8%), only two patients (0.8% of all treated) suffered from Grade 3/4 febrile neutropenia related to the study treatment. Severe neutropenia did not follow a cumulative trend with subsequent cycles of treatment showing that the dose-adjustment guidelines were appropriate. G-CSFs support was more utilized in the q3wk 24-h group: 28.5% of patients (25.6% of cycles) versus 12.3% of patients (14.5% of cycles) in the qwk 3-h group.

No major bleeding events were associated with thrombocytopenia. Platelet transfusions were more utilized in the q3wk 24-h group: 6.2% of patients (0.8% of cycles) versus 1.5% of patients (0.4% of cycles) in the qwk 3-h group.

Regardless of severity, anaemia was overall the most common of the hematological abnormalities. About half of patients entered the study with pre-existing anaemia, as expected. However Grade 3/4 anaemia was the least frequent (8.5% of patients and 1.7% of cycles) of the severe hematological toxicities. Severe anaemia did not worsen with subsequent cycles of treatment or sometimes showed a trend to recovery. A similar percentage of patients received red blood cell (RBC) transfusions in both schedules: 14.6% (3.6% of cycles) in the qwk 3-h group and 16.9% (3.0% of

cycles) in the q3wk 24-h group. Erythropoietin support was more utilized in the qwk 3-h group: 33.9% of patients (23.5% of cycles) versus 27.7% of patients (17.8% of cycles) in the q3wk 24-h group.

Biochemistry

The most common Grade 3/4 biochemical toxicities were increases in the serum levels of transaminases (AST/ALT). Higher incidences were reported in the q3wk 24-h group (31.5% of patients and 6.0% of cycles for AST; 47.7% of patients and 13.2% of cycles for ALT) compared with the qwk 3-h group (3.1% of patients and 0.8% of cycles for AST; 9.4% of patients and 2.9% of cycles for ALT). Grade 4 was experienced only for ALT in three patients (2.3%; all from the q3wk 24-h group and in one cycle each).

In the q3wk 24-h group, AST Grade 3/4 increases showed a rapid onset after infusion (Day 5), had a short median duration (3.5 days), and recovered to Grade ≤2 by Day 8. In the qwk 3-h group, AST Grade 3/4 increases showed an onset after infusion on Day 25, had a median duration of 8.5 days, and recovered to Grade ≤2 on day 33.5. ALT Grade 3/4 increases showed a similar pattern. Although the incidence of Grade 3/4 transaminase increases was higher with the q3wk 24-h schedule, its duration and the time to recovery was substantially shorter than for the qwk 3-h regimen. This was observed despite an overall longer duration of treatment with the q3wk 24-h schedule. Increases in AST or ALT did not follow a cumulative trend with subsequent cycles of treatment, showing that the dose-adjustment guidelines were appropriate.

Grade 1 and 2 abnormalities of bilirubin concentration were more frequent in the q3wk group (14.6% and 6.2%) than in the qwk group (7.0% and 3.9%), while only one patient (0.8%) in each group had Grade 3 levels, and none had Grade 4.

The potential clinical relevance of transaminase and bilirubin increases was assessed by an additional analysis of the AE group that included events reported under additional MedDRA high-level terms. The results confirmed that the incidence of individual severe hepatobiliary disorders was very low (<1% of patients), indicating that there were no clinical consequences of laboratory abnormalities of liver function in the vast majority of patients.

Evaluator's Conclusions on Safety

Although cycle delays were frequent in the 3 weekly group (43%) compared to the weekly group (27.3%), dose modification was infrequent, and more than 80% of the planned dose was delivered overall, indicating that the toxicity of the treatment was manageable.

Severe AEs (Grade 3/4) of fatigue, nausea and vomiting were twice as frequent (32.3%) with 3-weekly treatment as with weekly treatment (16.2%), and by their nature would interfere with the patients' quality of life. The median period of treatment was 13 weeks, the same duration as the time free of disease progression.

Grade 3 and 4 neutropenia was very frequent in the 3 weekly group (47%) compared to the weekly group (10.8%), and twice as much G-CSF was needed in these patients. However febrile neutropenia was uncommon and was not cumulative, probably because dose reduction helped avoid this toxicity.

A variety of other infections occurred that were drug-related and fatal. Of importance is the one case that showed trabectedin exacerbated prior radiation pneumonitis and led to death.

The most marked difference in the two treatment groups was in the increases of the serum concentrations of transaminases of Grade 3 and 4 severity, which were frequent, especially in the 3 weekly group (31.5% for AST, and 47.7% for ALT) compared with the weekly group (3.1% and 9.4%). However the increases were largely reversible and of short duration, and not associated with significant hepatobiliary disorders.

Conclusions: Three weekly treatment with trabectedin was more toxic than weekly treatment. The adverse effects were severe, often serious, but manageable. The period of treatment during which the adverse events occurred was the same as the period free of disease progression

Phase 2 Supporting Studies – Does trabectedin have activity against STS?

The safety data from the three supporting trials were similar to those reported for the pivotal trial and do not require separate descriptions.

Post-Marketing Data

The first approval of trabectedin was in the European Union, via the centralized procedure, on 17 September 2007. The post-marketing data were presented for trabectedin as monotherapy up until 31 May 2008. No new safety issues were raised by the post-marketing reports.

Clinical Summary and Conclusions

Risk-Benefit Analysis

In the following analysis and assessment, the primary endpoint of the studies are the main deciding factors, with secondary endpoints considered as support, while the assessment of independent reviewers (radiologists, oncologists) takes precedence over other assessments and results from other sources.

Relapsed Ovarian Cancer

The demonstrated benefit of treatment with the combination of trabectedin plus Doxil compared to Doxil alone was to increase the time free from progressive disease by 1.5 months in patients whose life span was a median of 22.4 months from the start of treatment. The 6 weeks free from progressive disease occurred after the start of treatment, which itself lasted a median of 22 weeks. The period free from disease progression was therefore only about one-quarter of the time spent in treatment. No statistically significant improvement in the patients' quality of life was demonstrated after treatment with either therapy, and no better outcome from the combination. Overall survival was not increased by the combination treatment. Exploratory analyses confirmed the results with other drugs in this disease that patients with "platinum-sensitive" recurrent disease do better than those with "platinum-resistant" disease. This result suggested that a definitive prospective study in this group of patients would be important to establish a role for trabectedin in treating this sub-group with ROC, and to resolve the conflict in the present results from patients with a "platinum-free interval" of 6-12 months and of >12 months.

The risks in using the combination therapy in patients with ROC are of two types. The first is methodological, in the design of the trial itself, and the use of the endpoints selected. Although PFS has received regulatory endorsement in this disease in this particular trial, PFS has not been shown to be a surrogate for the definitive endpoint of OS, perhaps because of the cross-over design that confounded the survival data. This risk, however, is not the main concern. More important is the risk associated with the toxicity that trabectedin added to Doxil therapy. These toxicities included the greater frequency of drug-related AEs, of severe AEs, of serious AEs, of drug-related deaths, and of abnormal laboratory deaths, and the association with longer delays in treatment and with dose reduction.

Taking all the above into consideration, the evaluator concluded that the risk associated with treatment using trabectedin plus Doxil outweighs the benefit obtained. The evaluator therefore recommended that the combination not be approved for this indication.

Advanced Soft Tissue Sarcoma (STS)

The question asked in the present application was whether weekly or three-weekly trabectedin therapy is the preferred treatment of advanced STS, and was addressed in the pivotal trial ET743-

STS-201. Three other supporting Phase 2 trials examined the efficacy of trabectedin in STSs that had progressed or relapsed after previous therapy.

The three trials had the following problems: the STSs were of a variety of tumour types and the trials needed adjustments to eliminate those not wanted; the response criteria were changed to included the RECIST criteria; response assessments required patients to have completed two cycles of treatment; the studies were single arm (active treatment only) and comparisons of response and survival were with those from historical controls, and from the recommendations of the EORTC Soft Tissue Sarcoma Group. In spite of these problems, the evaluator accepted that trabectedin has some anticancer activity in the treatment of soft tissue sarcoma, although the quantification of that activity is uncertain.

The pivotal trial also had a number of problems in its design and conduct. They included redesigning the original Phase 2 trial to a randomised Phase 2 trial; change of the primary endpoint from response rate to TTP; use of TTP instead of PFS; a high frequency of violations of eligibility criteria that changed the patient population in the study; an imbalance of sarcoma types in the two treatment arms; and imbalanced cross-over of patients after disease progression, so affecting OS. In spite of these problems, the evaluator accepted that the 3-weekly treatment resulted in a statistically significant extension of the TTP by 1.4 months, compared to weekly treatment, although that there were no demonstrated differences in the other endpoints, including OS. More worrying, however, was that it PFS had been an endpoint, statistical significance would not have been achieved. The median time free from disease progression (TTP) after the 3-weekly treatment was (4.2 months; 17 weeks), and the median duration of treatment 15.4 weeks. The median OS of patients in this group was 13.8 months, so that about 28% of the survival time was taken up with treatment.

The risks of the 3-weekly treatment included approximately a doubling of severe and serious toxicity that were manageable in the specialised centres of the study.

Taking the above into consideration, and the seriousness of the patients' disease, the evaluator recommended that trabectedin be approved for the treatment of recurrent or metastatic soft tissue sarcoma. However given the above concerns, the marginal difference in efficacy between the schedules, and the fact that the 3-weekly schedule doubles the toxicity of treatment, it is difficult to be enthusiastic about the 3-weekly regime compared to the weekly regime. The latter could be an option for patients who are older and sicker patients. The evaluator left this question open and recommended the 3-weekly regime.

Conclusions and Recommendations

Relapsed Ovarian Cancer

For the reasons stated above, the evaluator recommended that the application to use the combination of trabectedin plus Doxil to treat patients with ROC be rejected.

Advanced Soft Tissue Sarcoma

For the reasons stated above, the evaluator recommended approval of the 3-weekly treatment with Yondelis of patients with advanced soft tissue sarcoma after failure of anthracycline and ifosfamide, or of those who are unsuited to receive these agents.

V. *Pharmacovigilance Findings*

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

The sponsor identified the following important identified risks:

- Hepatic reactions

- Neutropenia and infection
- Thrombocytopenia/bleeding
- Anaemia
- Creatine phosphokinase (CPK) elevations/rhabdomyolysis
- Emesis
- Respiratory disorders
- Local infusion reactions

The sponsor identified the following important potential risks:

- Myelodysplasia/AML

There was also consideration of potential risks due to insufficient studies and important missing information in the following populations

- Paediatrics
- Pregnant and lactating females
- Patients with impaired renal function
- Patients with impaired hepatic function

The OMSM reviewer considered that the information provided in the RMP was comprehensive and detailed. However, it was incomplete as information on additional pharmacovigilance (PhV) activities for the trabectedin safety concerns was not provided. Also, there were a number of issues identified in the RMP and PI. Recommendations were made regarding the lack of information on PhV activities and to address the issues identified. Those that deal with the proposed PI are not included in this document.

The recommendations of the OMSM and the sponsor's response to these are detailed below.

1. The clinical practice and safety monitoring implications of the difference in the safety profile between white and non-white patients need to be considered.

The sponsor reiterated the information provided in the RMP. This indicates that the safety profile of the White population was slightly more favourable than the non-White (predominantly Asian) population. There was an increased incidence of Grade 3-4 and serious adverse events (AEs) in the monotherapy arm of Study ET743-OVA-301, a comparison of combination treatment with trabectedin + pegylated liposomal doxorubicin (PLD) D with PLD monotherapy. In the combination therapy arm, there was a higher incidence of Grade 3-4 and serious drug-related AEs in the non-white population.

The sponsor has agreed to consider these but did not provide any information on how this would occur.

2. Information on predicted utilisation in Australia should be provided. This was done.

3. Information on what constituted the most relevant and complete data set and how differences in AEs were measured in the exploratory analyses addressing the safety implications of concomitant use of trabectedin with potentially hepatotoxic products and products with associated risk of rhabdomyolysis and CPK increases should be provided.

4. Information on the types and numbers of potentially hepatotoxic concomitant medications considered and whether other medications as well as statins were considered should be provided.

It was indicated that a sub-group analysis was done on patients receiving potentially hepatotoxic concomitant medication and statins. The concomitant medications were listed. It was understood that this constitutes "the most relevant and complete data set."

Comprehensive data analysis was presented showing that the overall risk of hepatobiliary disorder, rhabdomyolysis and creatine phosphokinase (CPK) is comparable to the Study ET743-OVA-301 population.

Grade 3-4 and serious treatment emergent AEs occurred in 59% and 38% respectively. In the combination therapy arm, most patients (98%) had liver enzyme elevations of any grade. Drug-related hepatobiliary AEs were higher in the combination therapy arm (55% vs 12%). There was a slightly higher incidence of increased CPK in the combination therapy arm (19% vs 16%). Few patients had rhabdomyolysis.

This information was noted.

5. The implications of the lack of definitive results regarding the impact of concomitant PLD and other oncologic agents on trabectedin PK and information on the other oncologic drugs that were investigated should be provided.

The response indicated that information on the potential for trabectedin interaction with other oncological agents is detailed in the submission. There is reference to a study with dexamethasone and it is indicated that two further Phase I studies investigating the effects of a potent enzyme inducer and inhibitor. Information on non clinical studies, potential drug interactions and a study with dexamethasone was provided.

The oncology drugs studied with trabectedin were listed. The statement that there is a lack of definitive results regarding their use with trabectedin was reiterated.

However the implications of this lack of results were not considered. Hence, the sponsor response only partially addressed the recommendation.

6. Information on how the clinical significance of results indicating that the plasma clearance of trabectedin was 19.2% higher in patients who received any concomitant dexamethasone will be evaluated should be provided.

It was indicated that a recent pharmacokinetic analysis shows that median clearance values of trabectedin were comparable for patients receiving / not receiving dexamethasone.

7. The proposed PhV activities for each safety concern and an outline of the study protocols, including time frames for the presentation of interim and final reports on safety data for ongoing clinical trials should be provided.

Information on routine PhV as provided in the RMP was reiterated. It was indicated that the WHO and United States AE databases, and a sponsor AE database called SCEPTRE form the basis of AE analysis. Approaches to AE analysis were presented.

There was no reference to study protocols, including time frames for the presentation of interim and final reports on safety data, for ongoing clinical trials. Hence, the sponsor response only partially addressed the recommendation.

8. Information on why enhanced PhV monitoring for myelodysplasia and AML is occurring and what constitutes enhanced monitoring should be provided.

Cases of myelodysplasia (MDS) and AML that occurred during trabectedin trials were presented. It was indicated that enhanced vigilance comprises a six-monthly case level review of these conditions for the first 2 years after launch or for the duration of the required six-monthly Periodic Safety Update Reports.

The proposed approach was noted. However, given the ongoing concerns about MDS and AML in patients being treated for cancer, it was considered that, if trabectedin is marketed, this should be an ongoing process with a protocol developed to characterise the patient population with these events.

9. Information on activities to measure the effectiveness of, and compliance with, the risk minimisation activities should be provided.

It was indicated that risk minimisation activities will focus on labeling with changes made based on analysis of reported AEs and undertaken in consultation with the regulatory authority.

The question of measure the effectiveness of, and compliance with, the activities was not addressed.

There were remaining concerns subsequent to the sponsor's response. Hence if this drug is to be registered, the OMSM advised that it required an updated and agreed RMP prior to registration of the drug.

The key concerns regarding the sponsor's response are:

- Several of the recommendations were only partially addressed; and
- No information on post marketing study protocols was provided.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The proposed formulation is sucrose-based. Impurities were low. The diluted solutions were compatible with infusion bags and lines.

The application was considered by the Pharmaceutical Subcommittee (PSC) on 29 March 2010. TGA questions to the sponsor were endorsed.

The evaluator supported registration subject to resolution of labelling and product information issues. It is expected the issues would be resolved prior to the ACPM meeting.

Nonclinical

The toxicity studies of trabectedin were limited by excess toxicity and mortality. Doses were lower than the proposed human dose. Trabectedin was toxic to the liver, bone marrow, gastrointestinal tract and infusion site in rats and monkeys. There was dose-dependent inflammation, fibrosis and necrosis at the infusion site. Renal and retinal toxicity were seen in monkeys. The drug was genotoxic.

There were no carcinogenicity or fertility studies. Based on the mechanism of action, trabectedin is likely to be teratogenic. Teratogenicity was not seen in animals (rats and rabbits), but doses were well below the proposed human dose on a mg/m^2 basis.

There were no toxicity studies of trabectedin in combination with doxorubicin.

The evaluator supported registration subject to the clinical data and Risk Management Plan.

Clinical

Pharmacology

A population pharmacokinetic analysis of trabectedin monotherapy included plasma concentration-time data from 14 trials in cancer patients. There were data from 745 subjects. Most (37%) had soft tissue sarcoma. The trabectedin dose was 0.024 to 1.8 mg/m^2 IV every 21 days or days 1, 8 and 15 every 28 days or daily for 5 consecutive days every 21 days.

Mean trabectedin volume of distribution was 5,210 to 6,040 L depending if male or female and if dexamethasone administered or not. This was higher than that from major individual trials (3,718 to 4,981 L); however, within the range of variability. The high volume of distribution implies extensive distribution to tissues. Plasma trabectedin clearance was lower in the population analysis (mean 31.5 L/h) than in the major individual trials (mean 34.8-65.5 L/h), but again within the range

of variability. Mean plasma elimination half-life was 151-181 hours in the population analysis and 96-148 hours in the major individual trials.

The relationship between trabectedin dose and pharmacokinetic parameters was linear over the range of doses studied. However, there was a disproportionate relationship between dose and level of neutropenia, which increased at a greater extent than dose. The frequency of dosing was also important with large, infrequent doses (for example, q3wk) leading to more severe neutropenia than small, frequent doses. Serum bilirubin elevation, but not ALT elevation, was also affected by the frequency of dosing. A subject on the q3wk regimen had a 2.8-fold greater probability of elevated bilirubin ≥ Grade 2 than a subject on the same dose administered weekly for three weeks (q3wk). Dexamethasone was hepato-protective in terms of restricting ALT elevation, justifying its use as a premedication.

A population analysis of trabectedin in combination with liposomal doxorubicin hydrochloride (PLD) contained the trials in the previous analysis plus ET743-OVA301 (n=86 ovarian cancer subjects) and ET743-INT-11 (n=147 ovarian cancer subjects). The plasma clearance of trabectedin was reduced by 31% when co-administered with PLD 30 mg/m^2. The resultant increased exposure to trabectedin may explain the increased toxicity of the combination seen in the pivotal ovarian cancer trial (see below). However, the result was not consistent with that of trial ET743-USA-11 (n=36) which found no interaction. There was considerable variability. The pharmacokinetics of PLD were not affected by trabectedin. The plasma clearance of trabectedin was 19% higher when co-administered with dexamethasone which was consistent with trial ET-B-010-99 (n=28) where it increased by 28% but within the range of variability.

In a mass balance study (ET-A-013-01), trabectedin was extensively metabolised. (*In vitro* studies showed CYP P450 3A4 has a major role). The N-desmethyl metabolite is active. Mean recovery of a radioactive dose administered to 8 cancer patients was 58% in faeces after 24 days and 5.8% in urine after 10 days. Unchanged drug in urine and faeces was negligible (< 1% of the dose). Recovery of only two-thirds of the radioactivity administered may be due to extensive tissue distribution and retention.

The use of trabectedin in patients with hepatic impairment has not been adequately studied. Trial ET-A-006-00 attempted to study it, but was prematurely terminated. Trabectedin clearance is likely to be reduced in patients with hepatic impairment. There was evidence of increased hepatotoxicity when trabectedin was administered to patients with moderate to severe increased plasma alkaline phosphatase concentrations (> 1.5 x ULN).

Trials of various trabectedin IV regimens determined maximum tolerated doses (MTDs). For a 1 hour infusion every 3 weeks, the MTD was 1.1 mg/m^2 and for a 3 hour infusion, 1.8 mg/m^2 (ET-A-001-95). ET743-USA-11 determined the MTD of trabectedin at doses up to 1.3 mg/m^2 when administered in combination with PLD 30 mg/m^2 every 3 weeks. A 3 hour infusion of 1.1 mg/m^2 was chosen as the dose (with PLD) for the pivotal ovarian cancer trial. For a 24 hour infusion every 3 weeks, the MTD was 1.8 mg/m^2 (ET-A-002-95). This regimen with a dose of 1.5 mg/m^2 was used in the pivotal soft tissue sarcoma trial. For a 3 hour infusion weekly for 3 consecutive weeks every 4 weeks, the MTD was 0.65 mg/m^2 (ET-A-005-99). This regimen with a dose of 0.58 mg/m^2 was also used in the pivotal soft tissue sarcoma trial. Dose limiting toxicities included severe neutropenia, severe thrombocytopenia, severe rhabdomyolysis, severe fatigue and Grade 3-4 increases in hepatic enzymes.

Efficacy - Relapsed Ovarian Cancer (with PLD)

In a randomised, open-label, controlled trial (ET743-OVA-301), PLD (Caelyx) 30 mg/m^2 as a 90 minute IV infusion followed by trabectedin 1.1 mg/m^2 as a 3 hour IV infusion every 3 weeks was compared with PLD alone at a higher dose 50 mg/m^2 as a 90 minute IV infusion every 4 weeks, a standard regimen for ROC. Patients had relapsed after standard first-line platinum-based

chemotherapy. Patients were stratified by platinum sensitivity (sensitive, resistant). Patients who relapsed within 6 months of first platinum treatment were not eligible. Those relapsing within 6 months of last platinum treatment were classified as "platinum-resistant" and those relapsing more than 6 months after last platinum treatment were classified as "platinum-sensitive". Treatment continued until disease progression. The median age of subjects was 57 (range 26-87) years. All subjects received prophylactic dexamethasone.

The addition of trabectedin significantly increased progression free survival (PFS) by a median 1.8 months in the intent-to-treat ("independent oncologist") analysis and there was a trend to increased overall survival (OS) (Table 15). An independent radiologist review of subjects with measurable disease obtained similar results (median increase in PFS 1.5 months). This review was presented as the primary analysis. It excluded 9 subjects in the PLD-Trabectedin group and 18 in the PLD group. Improved quality-of-life was not convincingly shown for either treatment.

The increase in PFS with PLD-trabectedin was significant for subjects with a platinum-free interval (PFI) ≥ 6 months ("platinum-sensitive") but not for subjects with PFI < 6 months in the intent-to-treat ("independent oncologist") analysis. Median PFS increased from 3.8 to 8.4 months for PFI 6-12 months and from 9.0 to 11.1 months for PFI > 12 months compared with remaining unchanged at 3.7 months for PFI < 6 months. The results for the independent radiologist analysis were similar except that the result for PFI > 12 months was just outside the 0.05 significance level. In both analyses, it was unusual that the results for PFI 6-12 months were better than those for PFI > 12 months. This contradiction was also evident in the analysis of overall survival.

Table 15: Relapsed Ovarian Cancer Trial ET743-OVA-301 – Results – Intent-to-Treat

	PLD n=335	PLD-Trabectedin n=337	Ratio [95% CI] vs PLD
ORR[1] (Complete + Partial)	19% (1 + 18)	28% (1 + 27)	1.65[2] [1.14, 2.37]
PFS median (months)	5.6	7.4 (n=336)	0.72[3] [0.60, 0.88]
OS[4] median (months)	19.5	22.4	0.85[3] [0.70, 1.03]

[1] Overall Response Rate – RECIST criteria. [2] Odds Ratio (> 1 indicates advantage for PLD-Trabectedin).
[3] Hazard Ratio (< 1 indicates advantage for PLD-Trabectedin). [4] Updated 31 May 2009

Safety - Relapsed Ovarian Cancer (with PLD)

The major safety analysis was from the efficacy trial ET743-OVA-301 of trabectedin in combination with PLD. All subjects receiving study drug were included in the safety analysis: PLD-Trabectedin (n=333) and PLD (n=330). The median (range) of treatment cycles was 6 (1-21) for PLD-Trabectedin (3-week cycles) and 5 (1-22) with PLD (4-week cycles).

Adverse events overall, severe and serious adverse events and adverse events leading to treatment discontinuation were higher with PLD-Trabectedin than PLD. The incidence of severe (Grade 3-4) events was 91% with the combination versus 72% with PLD.

Haematological effects, nausea, vomiting and liver enzyme increases were substantially higher with the combination than PLD. Severe events (combination vs PLD) included neutropenia 63% vs 22%,

leukopenia 33% vs 10%, thrombocytopenia 18% vs 2%, nausea 10% vs 4%, vomiting 12% vs 4%, ALT increase 31% vs 1% and infection 11% vs 5%.

Despite the high incidence of liver enzyme increases and three subjects in the combination arm with potential for serious hepatotoxicity under Hy's Law, there was no clinically severe hepatotoxicity. However, the observation period was short and continuing post-market assessment is required.

The incidence of severe and serious adverse events were increased in non-Whites compared with Whites. Non-Whites comprised 22% of the trial population. Most were Asian (20% of the trial population).

There was a fatal case of rhabdomyolysis as part of a syndrome including neutropenia, sepsis and elevated liver enzymes in a subject receiving the combination treatment. There were 10 deaths (0.4%) associated with elevated CPK and rhabdomyolysis in the integrated safety database of all trials in 2,652 subjects receiving trabectedin (including STS trials). Most deaths occurred in the early trials as part of a syndrome including neutropenia, sepsis and elevated liver enzymes. Subsequently, monitoring of CPK and liver enzymes and dose adjustment guidelines were implemented.

Deaths within 30 days of the last dose occurred in 11 (3.3%) combination subjects and 8 (2.4%) PLD subjects. There were five sepsis-related deaths with the combination versus one with PLD.

Three other trials (ET-B-026-03, ET-B-009-99 and ET743-INT-11) in 289 subjects were of trabectedin monotherapy in ROC (not a proposed use). Two were uncontrolled and one compared two dose regimens. The trabectedin dose was higher than that proposed for combination with PLD (1.3-1.65 mg/m^2 every 3 weeks and 0.58 mg/m^2 weekly for 3 weeks out of 4). The number of subjects was too small to reliably compare the safety of the various dose regimens. Common drug-related Grade 3-4 adverse events for the q3wk 3 hour infusion regimen were neutropenia (13%), vomiting (7%), ALT increase (7%) and fatigue (6%). Grade 3-4 neutropenia and sepsis were lower than with trabectedin-PLD in the pivotal trial. There were no new or unexpected adverse events compared with the pivotal trial.

Efficacy - Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a diverse group of malignancies arising in extra-skeletal connective tissue, for example, muscle, fat, fibrous tissue and blood vessels. Leiomyosarcoma and liposarcoma ("L-sarcomas") represent 40-50% of STSs. Four trials of trabectedin monotherapy in STS after an anthracycline and ifosfamide were submitted (ET743-STS-201, ET-B-005-98, ET-B-008-98 and ET-B-017-99). The combination of an anthracycline and ifosfamide is one of several standard regimens for metastatic STS[29].

In the pivotal trial ET743-STS-201, two trabectedin IV dose regimens were compared in patients with "L-sarcomas" whose disease had relapsed or become refractory after an anthracycline and ifosfamide. Subjects were randomised to either 0.58 mg/m^2 as a 3 hour infusion weekly for 3 out of every 4 weeks (q3wk 3h) or 1.5 mg/m^2 as a 24 hour infusion every 3 weeks (q3wk 24h). The trial was open-label. Trabectedin was continued until disease progression or unacceptable toxicity. The median age of subjects was 53 years (range 20-80), with most being female (63%). All subjects received prophylactic dexamethasone.

Time to progression (TTP), the primary endpoint, was marginally significantly better by a median 1.4 months with the q3wk 24h regimen with trends to better response and survival (Table 16). Bias was possible from misdiagnosis.

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[29] US National Comprehensive Cancer Network (NCCN). *Practice Guidelines in Oncology* v.2.2009.

Table 16: Pivotal Soft Tissue Sarcoma Trial ET743-STS-201 – Intent-to-Treat

Dose	0.58 mg/m^2 q3wk 3h n=134	1.5 mg/m^2 q3wk 24h n=136
TTP[1] median (months) HR [95% CI] vs q3wk 3h Log-Rank	2.3	3.7 0.73 [0.55, 0.97] p=0.030[3]
ORR[1, 2] Fisher's Exact p	1.5%	5.1% 0.17
PFS median (months) HR [95% CI] vs q3wk 3h Log-Rank	2.3	3.3 0.76 [0.57, 0.99] p=0.042[3]
OS median (months) HR [95% CI] vs q3wk 3h Log-Rank	11.8	13.8 0.82 [0.61, 1.11] p=0.2

[1] Independent Assessment. [2] RECIST criteria. [3] Required level for significance p≤0.034.

Three supporting trials ET-B-005-98 (n=99), ET-B-008-98 (n=54) and ET-B-017-99 (n=36) were uncontrolled. Trabectedin 1.5 mg/m^2 q3wk 24h regimen was given to patients with recurrent STS after prior anthracycline and ifosfamide. Leiomyosarcoma (40%) was the most common diagnosis, then liposarcoma 13%, synovial sarcoma 13%. Other diagnoses were malignant fibrous histiocytoma, rhabdomyosarcoma, neurogenic sarcoma, fibrosarcoma, angiosarcoma and unclassified sarcoma. ET-B-008-98 contained four subjects (7%) with gastrointestinal stromal tumours (GIST). GIST was excluded from trials ET-B-005-98 and ET-B-017-99 (imatinib is standard treatment for GIST). Trabectedin was continued until disease progression or unacceptable toxicity. The median age of subjects was 50 years (range 19-81), most being female (56%).

Efficacy was assessed in patients who had received at least 2 cycles of trabectedin ("evaluable population"). ORR and PFS were low and OS about 12 months as in the pivotal trial (Table 17). The *STS* submission excludes 4 subjects from trial ET-B-008-98 and 2 subjects from trial ET-B-017-99. *The sponsor should confirm that the 6 excluded subjects had GIST.*

Table 17: Supporting Soft Tissue Sarcoma Trials – Results – "Evaluable Population" (excluding GIST)

	ET-B-005-98		ET-B-008-98		ET-B-017-99
Group	*A* *n=44*	*C* *n=55*	*1* *n=23*	*2* *n=27*	*Mod Pre-Treated* *n=34*
ORR[1]	9.1%	10.9%	0%	3.7%	8.8%
PFS median (months)	2.6	2.9	1.9	2.2	1.6
OS median (months)	8.7	13.9	12.9	10.7	12.6

[1] WHO criteria. <u>Groups</u>: A – one line of prior single-agent chemotherapy, C – two lines of prior single-agent chemotherapy or a line of combination chemotherapy, 1 – Moderately Pre-Treated (≤ 2 single agents or one combination regimen), 2 – Extensively Pre-Treated.

Tumour responses were seen in leiomyosarcoma, liposarcoma and synovial sarcoma. Patients with L-sarcoma appeared to do better with trabectedin than patients with other sarcomas (Table 18).

Table 18: Supporting Soft Tissue Sarcoma Trials – Pooled Results – "Evaluable Population"

	L-Sarcoma (n=100)	Other Sarcoma (n=83)	All (n=183)
ORR[1]	12.0%	2.4%	7.7%
PFS median (months)	2.7	1.8	2.3
OS median (months)	11.2	8.7	10.3

[1] WHO criteria.

Trabectedin appeared superior to dacarbazine and etoposide but not ifosfamide (overlapping Confidence Intervals) in second-line STS therapy based on a historical comparison with European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group data (Table 19).

Table 19: Comparison of Trabectedin in 2nd-Line Treatment of Soft Tissue Sarcoma with EORTC Historical Data

	Trabectedin (n=453)	Ifosfamide (n=105)	Dacarbazine (n=50)	Etoposide (n=26)
OS median [95% CI] (months)	12.5 [10.8, 13.8]	8.7 [6.9, 11.9]	6.6 [4.3, 8.4]	6.3 [4.4, 8.9]

Safety - Soft Tissue Sarcoma

In the pivotal trial ET743-STS-201, safety was assessed in subjects receiving at least one trabectedin dose: n=130 in each treatment arm. The median (range) of treatment cycles was 5 (1-37) for the 3-week regimen (3-week cycle) and 2 (1-21) for the weekly regimen (4-week cycle). The 3-week regimen was more toxic than the weekly regimen. The incidence of severe adverse events was 58% with the 3-week regimen versus 42% with the weekly regimen. The incidences of severe effects with 3-week versus 1-week trabectedin included neutropenia 47% vs 13%, thrombocytopenia 12% vs 5%, nausea 5% vs 2%, vomiting 5% vs 2%, ALT increase 48% vs 9% and infection 13% vs 6%. There was no clinically severe hepatotoxicity. There were six adverse event-related deaths in each group (5%). Four deaths with the 3-week regimen versus three with the weekly regimen were drug-related.

In the other trials, ET-B-005-98 (n=126), ET-B-008-98 (n=143) and ET-B-017-99 (n=36), the adverse event profile of trabectedin was similar to that in the pivotal trial. The safety population included subjects with GIST and with tumours other than STS.

Risk Management Plan

The Risk Management Plan (RMP) gives a comprehensive picture of the trabectedin safety profile but is deficient in pharmacovigilance and risk minimisation activities. There were a number of recommendations for the RMP.

The sponsor's response and assessment of its adequacy by the OMSM should be considered by the advisory committee if approval of trabectedin is considered.

Risk-Benefit Analysis

Delegate's Consideration

Trabectedin is extensively distributed to tissues and metabolised mainly by cytochrome P450 3A4. There is potential for interactions with inhibitors and inducers of the enzyme. The product information adequately advises of this. Elimination is slow, with mean terminal plasma half life of 180 hours. A population pharmacokinetic analysis showed that co-administration with PLD reduced the clearance of trabectedin which may explain the increased toxicity of trabectedin in the combination in the pivotal ovarian cancer trial.

In ROC, addition of trabectedin to PLD (a standard treatment) significantly increased PFS by a small amount (median 1.8 months in the intent-to-treat analysis and 1.5 months in the per protocol analysis). OS and quality-of-life were not significantly increased. The dose of trabectedin was 1.1 mg/m^2 as a 3 hour IV infusion every 3 weeks and the dose of PLD either 30 mg/m^2 with trabectedin or 50 mg/m^2 without trabectedin as a 90 minute IV infusion.

In subjects who were platinum-resistant (PFI < 6 months), trabectedin did not increase PFS. In

platinum-sensitive subjects, there were contradictions in the results for PFI 6-12 months and PFI > 12 months. For PFI 6-12 months, trabectedin increased PFS by a median 4.6 months in the intent-to-treat analysis; however, for PFI > 12 months, the increase was only 2.1 months. The increase in the PFI 6-12 months group is likely to be clinically significant. The OS data showed similar contradictory results.

In relapsed STS after failure of anthracyclines and ifosfamide, the data were limited. The pivotal trial ET743-STS-201 was not controlled against placebo or best supportive care and was limited to patients with leiomyosarcoma or liposarcoma, two common forms of STS. The supporting trials contained mostly patients with leiomyosarcoma or liposarcoma. The 1.5 mg/m^2 3-week 24 hour infusion trabectedin regimen appeared better than the 0.58 mg/m^2 weekly 3 hour regimen in the pivotal trial. The supporting trials used this regimen. Results across all trials were consistent with low ORR and PFS and overall survival around 12 months. Trabectedin appeared to have greater effect against L-sarcomas than other sarcomas. A historical comparison favoured trabectedin but it had limited validity due to the age of the data, the small number of subjects and lack of information for sarcoma subtypes.

Trabectedin is a very toxic drug. Specific safety issues were severe neutropenia with sepsis-related deaths, severe nausea and vomiting, Grade 3-4 increases in serum transaminases and rhabdomyolysis. Close monitoring of blood count, serum CPK and liver function is required. Risk of severe hepatotoxicity with continuing treatment cannot be excluded in view of the short observation period of the trials. Toxicity was significantly increased when trabectedin was added to PLD in recurrent ovarian cancer. In STS, the toxicity of high-dose 3-week trabectedin was greater than that of lower dose weekly trabectedin. The lower dose regimen may be preferable in view of its greater safety and the doubt over the better efficacy of the 3-weekly regimen.

Non-White subjects (mostly Asian) had a higher incidence of severe and serious adverse events than White subjects in the pivotal ovarian cancer trial. Twenty-two percent of the trial population were non-White (20% Asian and 2% other). The reasons for the higher incidence of severe and serious adverse events were not apparent. Follow-up is recommended within the RMP. A similar effect was not seen in the pivotal STS trial; however, it contained few Asian and other non-White subjects (2% and 7% respectively.

Premedication with corticosteroids (for hepato-protection and anti-emesis) and administration of trabectedin through a central venous line (to reduce severe injection site reactions including necrosis) is recommended.

The evaluator recommended approval for soft tissue sarcoma but not ovarian cancer. In ovarian cancer, the risk outweighed the benefit.

The benefit of trabectedin in ROC appeared to be confined to patients with platinum-sensitive disease. In this group, in spite of the increased toxicity of PLD plus trabectedin, the risk-benefit balance may be favourable. This needs confirmation due to contradictions in the efficacy data outlined above. The increased PFS is possibly clinically significant for PFI 6-12 months but not clinically significant for PFI > 12 months when assessed against the toxicity of the drug. Platinum-sensitive patients have the option of a further course of platinum. This option needs to be compared with PLD-trabectedin in a non-inferiority study. In platinum-resistant patients, the risk-benefit of trabectedin is unfavourable.

In advanced STS, it was not possible to quantify the benefit of trabectedin and determine if the benefit outweighs the significant toxicity. The benefit if any appeared to be confined to patients with L-sarcomas (leiomyosarcoma and liposarcoma). There are difficulties in collecting data on a new drug for STS because of the rarity and diverse nature of the disease. However, in view of the toxic nature of the drug, it is important to show a clinically significant benefit and that the risk-benefit profile is favourable.

The sponsor was invited to submit the following information in their Pre-ACPM Response to clarify the clinical benefit of trabectedin in second-line treatment of soft tissue sarcoma:

- *Detailed information on the EORTC historical data presented in its Clinical Summary, for example, a published paper*
- *Other published data or data from patient registries to confirm the validity of the EORTC data*
- *Breakdown of historical results by sarcoma subtype*
- *Comment on the age of the historical data, the number of patients and why it is representative.*

Depending on additional information, the following indication may be possible:

Yondelis is indicated for the treatment of patients with advanced leiomyosarcoma or liposarcoma who have failed to respond to anthracyclines and ifosfamide or who are unsuited to receive these agents.

The Delegate recommended the application for both indications be rejected on the grounds that efficacy has not been established and risk-benefit is unfavourable.

In ovarian cancer:

- The increase in progression-free survival with trabectedin of 1.5 months (per protocol) was not clinically significant
- There was no significant increase in overall survival or quality of life
- Possible efficacy in platinum-sensitive patients needs confirmation in view of contradictory results for PFI 6-12 months and PFI > 12 months and
- Trabectedin was associated with significant toxicity including toxicity-related deaths.

In soft tissue sarcoma:

- The treatment population likely to benefit was not defined
- The optimal trabectedin dosing regimen was not determined
- The clinical significance of tumour responses and survival with trabectedin was uncertain when compared with the limited historical data provided; a larger historical database including data for sarcoma subtypes is required and
- Trabectedin was associated with significant toxicity including toxicity-related deaths.

Sponsor's Response

The sponsor claimed that currently available data support a favourable benefit-risk balance for patients who receive Yondelis for the treatment of liposarcoma and leiomyosarcoma (L-type) of soft tissue sarcoma (STS) that has progressed after anthracycline and ifosfamide therapy. The sponsor proposed a revised indication to include patients with advanced liposarcoma and leiomyosarcoma. The sponsor disagreed with the current recommendation by TGA for non-approval of the ROC indication in light of updated overall survival (OS) data with an additional year of follow-up. However, the sponsor acknowledged that the benefit of trabectedin in combination with pegylated liposomal doxorubicin hydrochloride (PLD; Doxil, Caelyx) for the treatment of patients with ROC is more evident in the platinum-sensitive group and remains significant even after adjustment of pre-specified covariates.

Consequently, the sponsor proposed a revised indication limited to patients with platinum-sensitive disease. This subgroup, particularly those patients who are not suited to receive retreatment with platinum–based chemotherapy, has the highest unmet medical need among ROC patients.

The sponsor proposed the following modifications to the proposed indications:

Soft-tissue Sarcoma

Yondelis is indicated for the treatment of patients with advanced liposarcoma and leiomyosarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Relapsed Ovarian Cancer

Yondelis in combination with pegylated liposomal doxorubicin hydrochloride is indicated for the treatment of patients with relapsed ovarian cancer, who have platinum-sensitive disease, and who may not be suitable for platinum-based chemotherapy.

In STS, the sponsor noted that Study ET743-STS-201 showed a statistically significant clinical benefit (26.6% reduction in the relative risk of progression, 61% increase in median time to progression [TTP]) for subjects treated with trabectedin once every 3 weeks for 24 hours (q3wk 24-h) when compared with treatment with trabectedin weekly for 3 hours (qwk 3-h). Both trabectedin regimens demonstrated anti-tumour activity. Of note, approximately one third of subjects had received other non-approved agents (including gemcitabine and/or docetaxel) as well as other investigational agents. Intrapatient TTP comparison showed that about one third of subjects in each arm had an increase in TTP >33%, as compared with the immediately prior chemotherapy. Apart from significant TTP differences, the benefits from trabectedin therapy were highlighted by progression-free survival (PFS) rates at 3 months (51.5% in q3wk 24-h; 44.7% in qwk 3-h) and 6 months (35.5% in q3wk 24-h; 27.5% in qwk 3-h). An overview of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) database provided the PFS curves for 2 agents considered active in pre-treated STS patients (ifosfamide and dacarbazine; n=146 patients) and for 9 agents considered inactive (n=234 patients). The 3- and 6-month PFS rates obtained with the qwk 3-h trabectedin schedule (51.5% and 35.5%, respectively) exceeded the 3-month and 6-month rates (39% and 14%, respectively) used by the EORTC STBSG to define a chemotherapy agent as active for pre-treated STS (Van Glabbeke 2002).[20] Several subsequent articles reported activity of the agents according to the 3- and 6-months PFS rate proposed by the EORTC STBSG (Hartmann 2005, Maki 2009, Sleijfer 2009).[30,31,32]

Pooled data from 3 Phase 2 studies using trabectedin and reported in the *Summary of Clinical Efficacy* in the original submission showed median TTP, PFS, and OS values of 3.4, 2.7, and 11.2 months, respectively, for L-sarcoma (n=100); and 1.9, 1.8, and 8.7 months, respectively, for 'Other' sarcomas (n=183).

The cooperative groups' rationale for moving trabectedin forward into earlier stage STS as monotherapy or in combination with standard-of-care chemotherapy is based on their expert opinion that while pivotal Study ET743-STS-201 has sufficiently demonstrated a favourable benefit/risk profile for trabectedin in the relapsed setting, the benefit could be of even greater magnitude for the treatment of newly diagnosed patients.

Though the sponsor agreed with the TGA's recommendation in the clinical evaluation report to approve the STS indication as originally drafted, the sponsor remained open to a revised indication, as recommended in Delegate's overview. Based on the results of Study ET743-STS-201, along with supportive data from previously submitted Phase 2 studies (Studies ET-B-005-98, ET-B-008-98 and ET-B-017-99), the sponsor claimed to have demonstrated extensive experience and favourable

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[30] Hartmann JT, Patel S. Recent developments in salvage chemotherapy for patients with metastatic soft tissue sarcoma. Drugs 2005; 65: 167-178.

[31] Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol 2009; 27 :3133-3140.

[32] Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and teatment of cancer–soft tissue and bone sarcoma group (EORTC Study 62043). J Clin Oncol 2009; 27: 3126-3132.

efficacy outcomes for trabectedin as a treatment for patients with STS in a clinical setting with a high unmet medical need for new therapeutic alternatives.

In relapsed ovarian cancer, the sponsor noted that for the overall study population (platinum-sensitive and platinum-resistant subjects), the updated OS analysis demonstrated a median 2.9-month improvement favouring the trabectedin + PLD combination arm. When these data were adjusted for the significant imbalance in PFI and other covariates, the improvement in median OS was 3.6 months. In subjects with platinum-sensitive disease, the unadjusted analysis of the updated median OS demonstrated an improvement of 2.7 months. When these data were adjusted for the imbalance in PFI and other covariates, the improvement in median OS was 5.1 months, favouring the trabectedin + PLD combination arm. The toxicity profile of trabectedin + PLD combination (neutropenia and increased transaminase) differs from platinum and taxanes (peripheral neuropathy and hypersensitivity). Use of this regimen gives patients who are unsuited for retreatment with platinum access to a new therapy that is more effective than PLD monotherapy.

Updated OS data indicate that trabectedin in combination with PLD offers patients with relapsed ovarian cancer the benefit of increased survival that is more pronounced in patients with platinum-sensitive disease. The sponsor did not agree with the TGA's current recommendation and requested that approval of the newly proposed indication, which limits use to patients with platinum-sensitive disease, is granted based on the overall benefit-risk balance.

Advisory Committee Consideration

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended rejection of the submission to register trabectedin.

In making this recommendation, the ACPM noted the revised indication by the sponsor for ovarian cancer and soft tissue sarcoma proposed for this last resort treatment. However, the ACPM supported the Delegate's assessment that the overall risk benefit profile remains unfavourable, in view of the significant toxicity and toxicity related deaths, combined with the low clinical significance of the level of progression free survival.

Outcome

The sponsor withdrew the application before a decision was made