SCIENTIFIC DISCUSSION

1. Introduction

Soft tissue sarcoma (STS) constitutes a rare and heterogeneous group of tumours generally classified according to the normal tissue they mimic. Despite control of the primary site, about 50% of the patients ultimately succumb to metastases or local recurrence. In adults, there are only few active chemotherapeutic options available and the expected median survival after diagnosis of metastatic disease is about 1 year. Established first-line treatment options include doxorubicin and ifosfamide in mono-therapy or in combination regimens. DTIC is also regarded as an active drug. Despite numerous drugs being tested for phase II activity, there has been little progress with respect to new active compounds since the introduction of ifosfamide in the late eighties, the exception being imatinib for the treatment of gastrointestinal stromal tumours. From a regulatory perspective, doxorubicin, ifosfamide and DTIC are licensed in at least some EU countries for the treatment of STS.

Yondelis, formerly known as ET-743 PharmaMar, (ecteinascidin, trabectedin [INN]) is an anti-cancer medicinal product with claimed new mechanisms of action. It is a tetrahydro-isoquinoline and was originally extracted from the marine tunicate *Ecteinascidia turbinata* a colony forming tunicate that grows in the coastal platform of several temperate seas. Today a synthetic manufacturing process has been developed. Trabectedin is proposed to block the transcriptional activation of a subset of inducible genes without affecting their constitutive expression. Yondelis drug product is presented as a lyophilized powder for concentrate for solution for infusion, in vials of 0.25 mg and 1 mg trabectedin.

An application for a Marketing Authorisation was submitted through the Centralised Procedure in November 2001 for Yondelis in the treatment of patients with advanced STS, who had failed anthracyclines and ifosfamide, or had failed ifosfamide and were unsuitable to receive anthracyclines/ifosfamide. The demonstration of efficacy was based on three single-arm studies. Following the scientific assessment procedure the CHMP concluded that the benefit/risk profile of was not favourable. The negative opinion was mainly based on the fact that clinical efficacy had not been adequately demonstrated.

The current application includes data from a randomised phase II study in patients with liposarcoma or leiomyosarcoma. CHMP scientific advice has not been sought. At the time of submission of the marketing authorisation application, Yondelis had not been registered in any country. The claimed indications for trabectedin is as follows: Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. The proposed posology can be summarised as follows: The recommended 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. Administration through a central venous line is strongly recommended (se SPC, section 4.2).

2. Part II:Chemical, pharmaceutical and biological aspects

Introduction

Yondelis is a powder for concentrate for solution for infusion containing 0.25 mg and 1 mg of trabectedin per vial. Each vial is reconstituted with 5 ml and 20 ml of sterile water for injections, respectively. The reconstituted solution is a clear, colourless or slightly yellowish solution, essentially free of visible particles. The solution obtained has a concentration of 0.05 mg/ml and is for single-use only. Yondelis is supplied in either 10 ml or 25 ml Type I colourless glass vial with a grey bromobutyl rubber stopper with fluoropolymer coating. The stopper is sealed to the vial with an aluminium flip-off seal.

The excipients used in the preparation of Yondelis are sucrose, potassium dihydrogen phosphate, phosphoric acid and potassium hydroxide (for pH-adjustment), and water for injections.

Active Substance

The active substance trabectedin is a new chemical entity initially obtained by isolation from the marine tunicate *Ecteinascidia turbinata* by extraction and purification. A synthetic process was subsequently developed and the active substance is since then produced synthetically. The synthetic route starts from the secondary metabolite safracin-B, isolated from fermentation media of *Pseudomonas fluorescens*. The Active Substance Master File (ASMF) procedure was followed for the active substance.

Trabectedin is a white to off-white powder, soluble in polar organic solvents. Trabectedin is insoluble in hydrocarbons. In aqueous media, trabectedin is practically insoluble in water but solubility increases at acidic pH.

Trabectedin is a single enantiomer with a total of seven stereogenic centres. Most of these centres are linked together through a short bridge, which means that the stereochemistry of these centres is interrelated. No change has been observed in the crystalline form of trabectedin during storage, therefore, no evidence has been found of polymorphism.

- Manufacture

Trabectedin is manufactured utilising a three or five steps synthetic process., it was demonstrated that the trabectedin produced from the manufacturers is equivalent.

Confirmation of the chemical structure of the starting materials was provided by spectroscopic techniques and the impurity profile was characterised. The starting materials specification includes test for appearance, assay, identification, water content, impurities, heavy metals, and solvents.

A comparison between the synthetic and natural trabectedin has been performed by HPLC and TLC, IR and proton NMR, optical rotation and X-ray diffractometry. It was concluded that the active substance obtained by both processes is equivalent.

The structure of trabectedin was confirmed by elemental analysis, IR spectroscopy, high field NMR, UV spectroscopy, MS, X-ray crystallography and optical rotation.

- Specification

The active substance specification set by the manufacturers of the active substance are identical and the same as that of the Applicant. The analytical methods used for the release of the active substance are also equivalent in all sites.

The active substance specifications include tests for description, identification (IR, HPLC and optical rotation), assay (HPLC), water content (coulometric determination), impurities (HPLC), residual solvents (GC), heavy metals, inorganic impurities and bacterial endotoxins.

The method for assay and related substances by HPLC were validated for specificity, linearity and range, limit of quantitation, precision, accuracy, stability of solutions and robustness. The GC method for residual solvents was validated for specificity, linearity and range, limit of quantitation, precision, accuracy and stability of solutions. The coulometric determination of water was validated for specificity, linearity, precision and accuracy.

Batch analysis data was performed on a total of 25 batches of trabectedin. All batches complied with the proposed set of specifications.

- Stability

Three commercial scale batches were stored at -20^{o}C ± 5^{o}C for 24 months (2 batches) and for 18 months (1 batch) in the proposed primary packaging. In addition, the effect of short term excursions outside the storage conditions was evaluated on one batch at 25^{o}C/60% RH for 30 days and 5^{o}C for 6 months. All the batches placed on stability studies complied with the requirements in the active substance specifications. The results from the short excursions study showed no significant changes at the end of the study periods for any parameter although there was a trend towards increased water content at higher temperature. Phostostability and stress testing using thermal, oxidative, acidic and alkaline conditions was also carried out. Stress conditions showed a slight increase in the impurities content and the photostability studies showed that the active substance is not affected by exposure to light.

The data provided is sufficient to confirm the proposed re-test period.

Drug Product

• Pharmaceutical Development

The aim of the pharmaceutical development was to obtain a formulation of trabectedin, which could be administered by intravenous infusion after appropriate dilution. The intended route of administration precluded the use of several excipients, such as stabilizers and non-aqueous solvents. Therefore, a simple aqueous solution was considered the most appropriate dosage form. Initially a formulation based in mannitol and phosphate buffer solution was designed. Further pharmaceutical development led to an improved sucrose-based formulation using synthetic trabectedin in phosphate buffer that was selected for scale up and commercialisation, that allows the storage of the product at 2-8ºC.

- Adventitious Agents

Starting materials and excipients used for the manufacture of trabectedin powder for concentrate for solution for infusion do not contain materials that are of animal or human origin and are not in contact with materials of animal or human origin, during their manufacture.

- Manufacture of the Product

The manufacturing process for trabectedin powder for concentrate for solution for infusion is carried out under aseptic conditions in restricted areas and comprises: (1) sterilization and depyrogenation of primary packaging materials and equipment that comes into contact with the product (2) preparation of the bulk solution (3) sterilising filtrations (4) filling (5) lyophilization and stoppering (6) final packaging.

The validation of the manufacturing process was carried out at the proposed manufacturing sites The size of the validation batches corresponded to the proposed commercial manufacturing batch size. All the controls performed along the process validation complied with the pre-set acceptance criteria

- Product Specification

The specifications for both strengths of trabectedin powder for concentrate for solution for infusion at release and shelf-life are identical, exception being the related substances test, assay and the uniformity of content, which is only carried out at release. The specifications include tests for appearance before and after reconstitution (visual inspection), reconstitution time, pH, particulate matter, identification of trabectedin (UV and HPLC), assay (HPLC), related substances (HPLC), water content, uniformity of content (mass variation), bacterial endotoxins and sterility.

All analytical procedures used for testing the finished product were adequately described and validated. The majority of the methods were pharmacopoeial methods and therefore validation was deemed unnecessary. The endotoxin determination and sterility test were validated at both manufacturing sites. The HPLC method for the determination of assay and degradation products in the finished product was satisfactory validated for specificity, linearity, range, limits of quantitation and detection, precision (equipment and method repeatability) and accuracy. The intermediate precision, the stability of solutions and the robustness of the method were also evaluated.

- Stability of the Product

Stability data was provided on batches manufactured at both sites and stored at 5ºC ± 3ºC (long term conditions) for either 18 or 24 months, and under accelerated conditions (25ºC ± 2ºC / 60% RH ± 5% RH) for 6 months.

Stability studies included tests for appearance before and after reconstitution, reconstitution time, pH of reconstituted solution, particulate matter, identification, water content, assay, degradation products, sterility and bacterial endotoxins. The particulate matter sterility and endotoxins were tested at different checkpoints depending on the manufacturer and stability protocol.

Stability studies on the reconstituted and diluted solutions have also been performed for 30 hours at room temperature/ambient light and refrigerated conditions (5ºC ± 3ºC) in order to simulate the conditions typically encountered in a clinical setting. It was demonstrated that the drug product

reconstituted concentrated solutions are physically and chemically stable for 30 hours both at room temperature/ambient light and under refrigerated (5ºC ± 3ºC) conditions.

In addition, photostability studies were also performed to identify possible sensitivity to light of the drug product both in the solid state and after reconstitution with water. The results showed that trabectedin powder for concentrate for solution for infusion is not sensitive to light.

In conclusion, the real time stability data provided support the shelf life and storage conditions as stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Trabectedin was initially obtained by isolation from *Ecteinascidia turbinata* but was subsequently produced synthetically, which resulted in a decrease in the level of impurities. The excipients used in the preparation of the product were chosen based on the physico-chemical properties of the active substance and the intended route of administration (intravenous), which precluded the use of several excipients. The results showed that both the active substance and the finished product can be manufactured reproducibly. This indicates that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product to be addressed as follow-up measure. The Applicant gave a Letter of Undertaking and committed to resolve the Follow Up Measures after the opinion, within an agreed timeframe.

3. Part III: Toxico-pharmacological aspects

Introduction

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 sarcoma, breast, non-small cell lung, ovarian and melanoma.

Pharmacology

- Primary pharmacodynamics

The antitumour effect of trabectedin has been investigated in a panel of human tumour cell lines of mesenchymal origin or directly established from tissue specimens obtained from untreated sarcoma patients. In 23/29 human tumour cell lines of mesenchymal origin exposed to trabectedin in vitro for 72-96 hours, the IC_{50} value was below the expected C_{max} in patients (13 nM). Those with higher IC_{50} values included 2/4 chondrosarcomas, 1/2 fibrosarcomas, 1/4 osteosarcomas, 1/1 malignant peripheral nerve sheath tumour and 1/1 nephroblastoma. In the most sensitive cell lines (HT-1080, M8805, HS-90, M9110, HS-16, HS-18, HS-30, HS-42), trabectedin was more potent (IC_{50} = 0.0002-0.3 nM) than methotrexate (IC_{50} = 15-230 nM), doxorubicin (IC_{50} = 10-160 nM), etoposide (IC_{50} = 16-90 nM) and paclitaxel (IC_{50} = 0.2-1.2). There was no obvious correlation between the sensitivity seen for trabectedin and the comparators. Furthermore, trabectedin was highly effective in cisplatin-resistant sublines of osteosarcoma U-2OS and Ewing's sarcoma Saos-2 cells and in methotrexate-resistant osteosarcoma cells. When tested in SK-LMS-1 leiomyosarcoma, OSA-FH osteosarcoma or CHSA chondrosarcoma cells, there was no difference between the antiproliferative effects of natural and synthetic trabectedin.
Trabectedin was tested for antitumour activity in a number of sarcoma xenografts of murine and human origin (Table 1).

Table 1. Antitumour effect in sarcoma xenografts of murine and human origin

Tumour origin	Cell line	Route and schedule	Dose (mg/m^2/day)	Tumour growth inhibition (%)	Reference
Mouse fibrosarcoma	UV2237	IV qdx1	0.6	63	Meco et al. (2003)
Mouse ovarian reticulosarcoma	M5076	IV q7dx2	0.45	64	Donald et al. (2003)
Human chondrosarcoma	CHSA	IV qdx2	0.3	76	Morioka et al. (2003)
Human osteosarcoma	OSA-FH	IV qdx5	0.12	67	Faircloth et al. (2001)
Human rhabdomyosarcoma	TE-671	IV qdx1	0.6	33	Donald et al. (2003)

In vivo, trabectedin had significant antitumour effects in five sarcoma xenograft models of murine or human origin, causing 33-76% tumour growth inhibition at dose levels between 0.12-0.6 mg/m^2/treatment.
There is a substantial body of published data addressing the mode of action of trabectedin. In summary, these findings suggest that trabectedin binds to DNA by alkylating guanine at the exocyclic N2 position in the minor groove and bends the DNA towards the major groove, triggering a cascade of events affecting several transcription factors and DNA repair pathways. These events result in delayed entry into the S phase and arrest in the G2/M interphase, leading to apoptosis through a p53-independent mechanism. Other mechanistic investigations have shown that trabectedin may induce topoisomerase I cleavage complexes and cause disorganisation in the microtubule network around the nuclear membrane. These effects, however, were only observed in cells exposed to trabectedin concentrations that were higher than those required to induce cytotoxicity and above the therapeutically active levels in cancer patients. They are therefore unlikely to be clinically relevant.

- Secondary pharmacodynamics

Secondary pharmacodynamics comprised studies of the myelotoxic effects of trabectedin in normal haematopoietic cells in vitro. Dog CFU-GM progenitors were markedly more sensitive to the myelotoxic effects of trabectedin than those of murine or human origin. In human and murine cells, the IC_{50} values were within or not much above expected plasma levels in patients (13 nM); CFU-Meg progenitors were slightly more sensitive than CFU-GM progenitors.

- Safety pharmacology programme

Safety pharmacology studies comprised a modified Irwin's test in rats, a HERG assay and a test for cardio-respiratory effects in anaesthetised Cynomolgus monkeys. In the modified Irwin's test, groups of 5 male rats were injected IV with a single dose of 0, 12.5, 25 or 50 µg/kg of trabectedin (about 0, 75, 150 and 300 $\mu g/m^2$). There were no signs of adverse behavioral effects, neurological impairment or adverse autonomic responses at any dose level. In the HERG assay, trabectedin had no effect over a concentration range of 10-1000 nM. At 10,000 nM (7600 ng/mL), a 10% reduction relative to solvent was observed. In groups of 4 male Cynomolgus monkeys anaesthetised with pentobarbitone and infused with 0 or 90 µg/kg (1 mg/m^2) of trabectedin IV over 60 minutes, there was a transient fall of about 20 mm Hg in diastolic arterial blood pressure after 180 minutes, but no effect on PR, QT, QTcF, QTcV intervals and QRS duration), ECG waveform and rhythm, left ventricular variables, cardiac output, stroke volume, arterial blood variables or respiratory variables. The C_{max} level attained in this study was 10-11 ng/mL, which is similar to that observed in patients.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interactions studies have focused on potential synergism associated with concomitant or sequential use of trabectedin and other antineoplastic agents such as doxorubicin and cisplatin, which was investigated in vivo using xenografts of different origin.

Pharmacokinetics

PK studies were primarily conducted in the rat and the Cynomolgus monkey using a validated LC-MS/MS method with a limit of detection of 0.05 ng/mL for rat plasma and 0.02 ng/mL for monkey plasma. Distribution and metabolism studies used trabectedin labeled with ^{14}C in a metabolically stable position.

In both species, trabectedin plasma levels dropped rapidly at the end of the infusion, followed by a much more gradual decrease, suggesting multi-compartmental kinetics. Although the number of animals investigated was limited (1-2 per dose level), there were no obvious differences in exposure

between sexes or between the first and the last treatment cycle and exposures increased fairly proportionally with dose. In the monkey, estimates of terminal half-lives ranged from 2 to 6 days. The apparent volume of distribution (94.4-287 L/kg) was larger than total body water indicating extensive distribution in the tissues, and systemic clearance was moderate to high (1.43-3.68 L/h.kg). Similar findings were obtained in a population analysis in patients treated with trabectedin 1500 μg/m^2 every 3 weeks, indicating that trabectedin plasma kinetics is similar in humans and the Cynomolgus monkey.

Tissue distribution studies were conducted in non-pregnant animals. Studies in the rat using ^{14}C-labelled drug substance showed trabectedin to be rapidly and extensively distributed to peripheral tissues including bone marrow, lymphoid organs, gastro-intestinal tissue, liver, kidney and muscle. After peak time, total radioactivity levels declined very slowly and appreciable amounts remained in the carcass at 1 week post-dose, indicating significant retention of trabectedin and/or its metabolites, particularly in females. In the monkey, trabectedin levels were determined in target organs of toxicity. The derived tissue to plasma concentration ratios were estimated at 7.85-73.4 in liver, 11.5-27.1 in kidney and 5.11-68.6 in bone marrow, indicating that tissue concentrations were greater than corresponding plasma concentration by a 5 to 70-fold factor.

Trabectedin was a substrate for P-glycoprotein (P-gp) in vitro and experiments with P-gp knock-out mice showed elevated levels of total radioactivity in the brain (13-fold increase) and testis (2-fold increase) relative to the wild-type controls. Less pronounced increases were observed in other P-gp expressing organs such as the small intestine and heart whereas parent drug levels were similar in the plasma and liver of both strains.

Plasma protein binding of trabectedin was studied in vitro in plasma from mice, rats, rabbits, dogs, Cynomolgus monkeys and humans, and blood distribution was examined in the same species except the monkey. Plasma protein binding was high (90-99%) in all species studied, including man, and the blood to plasma ratio ranged from 0.69 to 1.51 across species, reflecting the observed differences in the free fraction.

Metabolism studies carried out in vitro showed that the hepatic metabolism of trabectedin is fast and extensive. The hepatic metabolism of trabectedin displayed substantial species differences; however, human and monkey liver fractions had similar metabolic profiles and all metabolites produced by human material were also detected in Cynomolgus monkey fractions. The major in vitro metabolic routes identified in man and monkey include *N*-demethylation (ET-729 formation), *O*-demethylation, carboxylic acid formation with and without additional oxidation, mono-oxidation and di-oxidation, aliphatic ring opening and demethylation in combination with mono-oxidation or with di-oxidation. Whereas ET-729 was detected after incubation with hepatic subcellular fractions of all species in vitro, only trace amounts were found in monkeys in vivo and it was not detected in plasma, urine or bile of trabectedin-treated patients. Several major CYP isoforms including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2D6, 2E1, 3A4 and 3A4 were able to metabolise trabectedin in vitro, however, CYP3A4 was shown to be the main isoform at low, therapeutically achievable concentrations.

In rats, mice and humans, the excretion of trabectedin-related radioactivity was slow and occurred principally via the faeces (90-97% of the recovered radioactivity). Biliary excretion of trabectedin and its metabolites was confirmed in bile duct cannulated rats, but did not appear to involve P-gp transport as the excretion pattern was similar between wild-type and P-gp knock-out mice. In the rat, male animals exhibited greater faecal excretion and less body retention of trabectedin-related material than females, but no such sex-differences have been found in humans. There were no excretion studies in the Cynomolgus monkey and no studies of the excretion of trabectedin in milk in any species.

PK interactions caused by plasma protein binding were not investigated as therapeutic plasma levels are too low (typically less than 10 nM) to cause concern. Although trabectedin is metabolised in the liver by CYP3A4, there was no clear evidence of cytochrome P450 inhibition or induction in in-vitro studies using human liver microsomes, human hepatocytes or ex-vitro liver microsomes from rats and Cynomolgus monkeys treated with 3-weekly infusions of up to 300 and 1200 μg/m^2 of trabectedin for 3-4 cycles.

Toxicology

- Single dose toxicity

Single-dose toxicity studies were carried out in mice, rats, dogs and Cynomolgus monkeys administered trabectedin by IV bolus injection or short-term infusion. The maximum non-lethal dose was 450 μg/m^2 in mice, 300 μg/m^2 in female and 450 μg/m^2 in male rats, 700 μg/m^2 in dogs and 1050 μg/m^2 in the Cynomolgus monkey. Common clinical signs included diarrhoea, emesis, inappetence, lethargy, and loss of body weight. Predominant toxicities included myelosuppression characterised by neutropoenia, thrombocytopoenia, leukopoenia associated to hypocellularity in the bone marrow, and atrophy of the lymphoid tissues, and hepatotoxicity, characterised by increased serum transaminases, and focal hepatocyte necrosis in all species. In rodents and dogs, acute cholangitis, hepatobiliary fibrosis and proliferation were observed as well. This toxicity was irreversible in rats, and more pronounced in female animals. In rodents, microscopic evaluation further revealed epithelial necrosis and ulceration in the gastro-intestinal tract and pancreatic acinar single cell necrosis and inflammation at the injection site.

- Repeated dose toxicity

Repeat-dose toxicity studies were conducted in mice, rats, dogs and Cynomolgus monkeys and are summarised in Table 2. In all studies, trabectedin was administered IV either as a bolus injection or a 3- or 24-hour infusion.

Table 2. Summary of repeat-dose toxicity studies

Study ID	GLP	Species/sex/number per group	Duration and dose (μg/m^2)	Type of IV administration	NTEL (μg/m^2)	Principal findings
4311-M001-94	Yes	Mouse/M+F/10	5 days 120, 180, 240	Bolus injection	< 120	Mortality, bone marrow depletion
1589/2	Yes	Mouse/M/20	5 days 60, 120	Bolus injection	< 60	Mortality, reduced body weight, increased liver weight and enzymes, bone marrow and spleen depletion and reversible blood cell reductions
1589/5	Yes	Mouse/M/10-15	q 3 w x 1-3 60, 300	Bolus injection	< 60	Mortality, reduced body weight, injection site lesions, gall bladder oedema and reversible blood cell reductions
1589/3	Yes	Rat/M/10	5 days 12, 105	Bolus injection	< 12	Reduced body weight and WBC, increased liver enzymes and atrophy or necrosis in liver, bile ducts, thymus, spleen and GI tract
M049-95	Yes	Rat/F/15	5 days 30, 60, 90	Bolus injection	< 30	Mortality, reduced body weight, RBC parameters and WBC, increased liver enzymes, injection site lesions and atrophy or necrosis in liver, bile ducts, thymus, spleen and GI tract
M050-95	No	Rat/F/5	1-3 5-day treatments each followed by a 30-day break 15, 30, 60	Bolus injection	< 15	As above
5536	Yes	Rat/M+F/10	q 3 w x 3 15, 60, 150, 300, 450	3-hour infusion	< 15	As above, but lesions more severe in females than males
M008-95	Yes	Dog/M+F/1	5 days 140, 280	Bolus injection	< 140	Diarrhoea, prostration, reduced body weight, blood cell reduction, increased liver enzymes, microscopic lesions (atrophy, necrosis or inflammation) in multiple organs
196	Yes	Dog/M+F/2	5 days 100, 160, 220	Bolus injection	< 100	As above in HD and MD animals, but limited to reversible liver and bone marrow pathology in LD dogs

Study ID	GLP	Species/sex/number per group	Duration and dose (μg/m²)	Type of IV administration	NTEL (μg/m²)	Principal findings
5537	Yes	Cynomolgus monkey/M+F/2	q 3 w x 3-4 300-1440 (range-finding)	3- or 24-hour infusion	< 300	Mortality, reduced body weight, RBC parameters and WBC, increased liver weight and enzymes, increased kidney weight, injection site lesions and hypoplasia of bone marrow, spleen and thymus
TOX5702	Yes	Cynomolgus monkey/M+F/2	q 1-3 w x 3-4 120-840 (range-finding)	3-hour infusion	< 120	Mortality, reduced RBC parameters and WBC, increased liver enzymes, intestinal lesions, injection site lesions and hypoplasia of bone marrow, spleen and thymus
TOX6809	Yes	Cynomolgus monkey/M+F/2	q 3 w x 4 300, 600, 840	24-hour infusion	< 300	Study terminated prematurely because of severe injection site lesions
TOX7106	Yes	Cynomolgus monkey/M+F/2	q 3 w x 4-8 300, 600, 780	3-hour infusion through central v. cava catheter	< 300	Mortality due to neutropoenia and intestinal infections, dropsy, reduced RBC parameters and WBC, increased liver enzymes, severe injection site lesions

In mice, the target organs of toxicity comprised the bone marrow, liver and injection site.

In rats, trabectedin induced dose-dependent hepatotoxicity characterised by increased transaminases, ALP and bilirubin, focal hepatocyte necrosis, cholangitis, bile duct inflammation, proliferation, and fibrosis. Most of these changes failed to recover three weeks after the last injection and were far more pronounced in females. Myelosuppression was characterized by reduced bone marrow cellularity and diffuse atrophy of the lymphoid tissues. These changes recovered partially or completely after each treatment cycle. In addition, inflammation and necrosis at the injection site and single cell necrosis, ulceration and epithelial atrophy in the gastro-intestinal tract were common.

In dogs, the target organs of toxicity comprised the bone marrow, liver and gut.

In monkeys, repeated i.v. dosing every three weeks resulted in mortality at doses of 420 μg/m² and above. Myelosuppression was characterized by anaemia, neutropoenia, thrombocytopoenia, leucopoenia associated with depletion in the lymphoid organs and hypocellularity in the bone marrow. Most of these changes recovered at least partially between treatment cycles, with exception of anaemia, which was slightly cumulative. Dose-dependent local intolerance at the injection site resulted in severe thrombophlebitis extending to adjacent tissues. Hepatotoxicity in monkeys was less pronounced than in rats, not systematically observed and was found to be reversible, non-cumulative in nature and characterised by transient increase in transaminase levels, rare increase in ALP, hepatocellular hypertrophy, focal hepatocyte degeneration and necrosis, and mixed inflammatory cells in the sinusoids and portal tracts, without biliary damage. Kidney tubular dilatation, with flattened epithelium and slight epithelial degeneration/necrosis were seen in some animals at high doses. Finally, focal necrotic ulcerations of the colon/rectum were reported, sometimes with bacteria-mediated intestinal inflammatory, hemorrhagic and necrotic lesions, in the animals sacrificed or found dead after the first cycles of treatment. A NTEL was not established in any species.

- Genotoxicity

Trabectedin was evaluated for its potential to induce mutations in bacteria, chromosome aberrations in mammalian cells in vitro and micronucleated polychromatic erythrocytes in mice in vivo. Trabectedin proved genotoxic in all three tests (data not shown).

- Carcinogenicity

No carcinogenicity studies have been conducted.

- Reproduction Toxicity

Trabectedin was tested in conventional developmental toxicity studies in the rat and rabbit (data not shown).

- Toxicokinetic data

Toxicokinetic evaluations were conducted in rats and monkeys. Based on AUC levels, animal to human exposure ratios did not exceed 0.3 in any study. Since a NTEL could not be established, animal to human safety ratios cannot be calculated. It is nevertheless obvious that trabectedin, like other cytotoxic agents, is a highly toxic drug requiring careful monitoring of the target organs of toxicity such as the liver, blood forming organs and gastro-intestinal tract.

- Local tolerance

Local tolerance was examined in male rabbits after single and repeated IV and perivenous dose administration. Single intravenous injection induced a dose-related subacute inflammation, oedema with focal fibrinoid necrosis and endothelial necrosis. Repeated IV administrations (4 times) increased the local irritation. After single perivenous doses of 12 and 120 $\mu g/m^2$ at concentrations of 2.5 and 25 μg/mL in a total volume of 0.3 mL, marked irritation (swelling of the injection site, mild to severe erythema, haematoma and vessel dilation) was seen. These changes corresponded histologically to ulceration, focal fibrinoid necrosis, cutaneous epithelial necrosis, subacute inflammation, and oedema. Similar injection site lesions were a consistent finding in all toxicity studies in which trabectedin was administered by IV injection or infusion, irrespective of species.

Ecotoxicity/environmental risk assessment

No environmental risk assessment has been submitted.

Discussion on the non-clinical aspects

Pharmacodynamics

Trabectedin binds to the minor groove of the 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.

Preclinical data indicate that trabectedin has limited effect on the cardiovascular, respiratory and central nervous system at exposures below the therapeutic clinical range, in terms of AUC.

The effects of trabectedin on cardiovascular and respiratory function have been investigated *in vivo* (anesthetized Cynomolgus monkeys). A 1-hr infusion schedule was selected to attain maximum plasma levels (C_{max} values) in the range of those observed in the clinic. The plasma trabectedin levels attained were 10.6 ± 5.4 (C_{max}), higher than those reached in patients after infusion of 1500 $\mu g/m^2$ for 24 (C_{max} of 1.8 ± 1.1 ng/ml) and similar to those reached after administration of the same dose by 3-hr infusion (C_{max} of 10.8 ± 3.7 ng/ml).

Pharmacokinetics

No studies have been submitted on the potential impact of other CYP substrates on the metabolism of trabectedin. However, Brandon et al. (2005) reported that the cytotoxic activity of trabectedin could be increased in combination with the CYP inhibitors metyrapone (3A4), phenanthrene (substrate for 2E1, 3A4), piperonyl butoxide (3A), proadifen (2C9, 2E1, 3A4), ritonavir (3A4), and warfarin (2C9, 2C19) in the Hep G2 cell line in vitro, suggesting that combination therapy of trabectedin with CYP inhibitors, e.g. other anticancer drugs, could lead to changes in hepatotoxicity and therefore might be of clinical importance. The same applies to co-administration of trabectedin and other Pg-p substrates.

Toxicology

Myelosupression and hepatoxicity were identified as the primary toxicity for trabectedin. Findings observed included hematopoietic toxicity (severe leucopenia, anemia, and lymphoid and bone marrow depletion) as well as increases in liver function tests, hepatocellular degeneration, intestinal epithelial necrosis, and severe local reactions at the injection site. Renal toxicological findings, mainly histopathological changes, were detected in multi-cycle toxicity studies conducted in monkeys. Since the interpretation of these toxicological results might have been hampered due to the occurrence of

secondary histological kidney lesions, uncertainly attributable to the severe local reactions at the injection site, caution must be guaranteed in the interpretation of these renal findings, and treatment-related renal toxicity cannot be excluded.

Trabectedin is genotoxic both *in vitro* and *in vivo*. Long-term carcinogenicity studies have not been performed.

Fertility studies with trabectedin were not performed but limited histopathological changes were observed in the gonads in the repeat dose toxicity studies. Considering the nature of the compound (cytotoxic and mutagenic), it is likely to affect the reproductive capacity.

Trabectedin, like other cytotoxic agents, is a highly toxic drug requiring careful monitoring of the target organs of toxicity such as the liver, blood forming organs and gastro-intestinal tract.

Trabectedin was a strong irritant causing severe injection site inflammation, necrosis and fibrosis in all IV toxicity studies, irrespective of species, as well as in a conventional rabbit test for local tolerance using single and repeated IV and perivenous dose administration. It is therefore appropriate that the SPC recommends administration by slow intravenous infusion through a central venous line.

The proposed impurity specifications comprise six substances at levels above the qualification threshold. These have been qualified in single- and repeat-dose toxicity studies and/or clinical studies using batches of drug substance or drug product containing impurity levels in excess of the proposed specifications. None of the impurities has been tested for genotoxicity, but since trabectedin is itself a genotoxic substance intended for the treatment of cancer patients with a poor prognosis, this is not a cause for concern.

No environmental risk assessment has been submitted. The small number of patients suffering from the proposed indication would preclude any substantial environmental exposure to the drug.

4. Part IV: Clinical aspects

Introduction

The clinical development program supporting the efficacy of trabectedin in the treatment of STS includes one ongoing pivotal, randomised, unblinded, dose-finding, Phase-II study (ET743-STS-201) and 3 completed Phase II, non-controlled studies, ET-B-005-98, ET-B-008-98, and ET-B-017-99. The original Phase II studies included a variety of different histological types of STS, whereas the randomised, pivotal Phase II study was restricted to patients with L-sarcoma (liposarcoma and leiomyosarcoma).

Yondelis must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxic agents. The recommended dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24-hr with a three-week interval between cycles. Administration through a central venous line is strongly recommended (see SPC section 6.6).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Absorption

Trabectedin is administered as a constant rate, intravenous infusion. Therefore, the clinical pharmacology program did not include conventional studies that assess bioavailability, bioequivalence, food, and effect.

- Distribution

Trabectedin is extensively bound to plasma proteins. The mean free (unbound) fraction, evaluated by equilibrium dialysis, was 2.23% and 2.72% at 10 ng/mL and 100 ng/mL, respectively. Trabectedin was more extensively bound to alpha-1 acid glycoprotein (free fraction, 9.95% at 0.05 g/dL of protein and 3.34% at 0.1 g/dL of protein) as compared to albumin (free fraction, 13.98% at 4.3 g/dL of protein) in purified solutions of each protein at physiological concentrations. Binding to plasma proteins was also assessed by ultracentrifugation. The free fraction was 5.8% at a total trabectedin concentration of approximately 3 ng/ml.

The ratio of trabectedin concentration in blood versus plasma averaged 0.89 during *in vitro* studies. Thus, trabectedin distributes to the cellular components of whole blood to some degree.

The population estimate of distribution volume in the central compartment is 16.1 L and 13.9 L in male and female patients, respectively. The distribution volume at steady state is 6070 L and 5240 L, respectively.

- Elimination

Trabectedin is metabolized by various routes that produce a wide range of metabolites upon incubation with human hepatic subcellular fractions and hepatocytes. Those identified include *N*-demethylation (formation of N-desmethyl trabectedin or ET-729), *O*-demethylation, carboxylic acid formation with and without additional oxidation, mono-oxidation and di-oxidation, aliphatic ring opening, and demethylation in combination with mono-oxidation or with di-oxidation. No appreciable glucuronidation of trabectedin was demonstrated. In addition, no metabolites were formed after incubation with trabectedin with human whole blood. Although most major CYP enzymes metabolize trabectedin *in vitro*, CYP3A4 is considered to be the main CYP enzyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations.

Experiments were conducted using membrane preparations of *E. coli* expressing individual human CYPs together with human reductase. Disappearance of trabectedin (5 μM or 3.81 μg/mL) and concomitant formation of radiolabelled metabolites after incubation with CYP1A2, 2A6, 2C8, 2C9, 2C18, 2D6, 2E1, and 3A4 was observed. Virtually no metabolite formation was seen with CYP1B1, 2C19, and 4A11. *In vitro* experiments with cDNA expressed human enzymes indicated CYP2C9, 2D6, 2E1, and 3A4 metabolize trabectedin (50 μM or 38.1 μg/mL), whereas no notable metabolism by CYP1A1, 1A2, 2A6, 2B6, 2C8, and 2C19 was observed.

As supra-therapeutic concentrations were used, another set of experiments was conducted aimed at identifying the major CYP enzymes involved at clinically relevant concentrations of trabectedin (7.62 nM or 10 ng/mL). Trabectedin was incubated together with pooled human liver microsomes (male and female donors) and the disappearance of unchanged drug from the incubation mixture was quantified. Selective chemical inhibitors and inhibitory antibodies directed against specific CYPs were used as diagnostic tools.

Trabectedin metabolism was markedly diminished by chemical inhibitors of CYP3A4 (ketoconazole and troleandomycin) and selective inhibitory antibodies directed towards this enzyme. Chemical inhibitors and/or antibodies of other CYP enzymes had no effect. The latter experiments strongly suggest CYP3A4 is the predominant CYP enzyme responsible for the hepatic metabolism of trabectedin.

Study ET-A-013-01 was mass balance study of ET-743 administered as a 3- or 24-hour intravenous infusion to patients with advanced cancer conducted in order to characterize the metabolic profile and routes of excretion of trabectedin in patients with solid tumors (mass balance and metabolism study). The study included 8 patients and was an open-label, non-randomized study including full PK sampling during Cycle 1. Urine and fecal samples were collected for metabolite profiling and identification. A majority of the radio labelled material excreted was recovered in the faeces (57.6% of the dose) and smaller amounts recovered in the urine (5.8% of the dose) over a collection interval of up to 24 days and 10 days, respectively (ET-A-013-01). Negligible quantities of unchanged drug were recovered in urine (<1% of the dose) and faeces, confirming the extensive metabolism of trabectedin *in vivo*. The insignificant urinary excretion of unchanged trabectedin was confirmed during 3 other Phase I studies.

The active metabolite ET-729, which was extracted from faecal samples only under acidic conditions, accounted for a minor fraction of the total radioactivity recovered in faeces and has not been recovered in urine.

The population pharmacokinetics model used a single clearance parameter to describe elimination of trabectedin by all routes (Population Pharmacokinetic Analysis of Trabectedin (ET-743) in Patients With Cancer). The typical value of trabectedin plasma clearance and the corresponding intersubject variability were 31.5 L/h and 51%, respectively.

Most trabectedin-derived metabolites have not been identified due to, in part, the low concentrations of metabolites, low faecal extraction recoveries, and complex metabolite profile of trabectedin. N-desmethyl-trabectedin (ET-729) is a pharmacologically active metabolite of trabectedin. Its concentrations in plasma were below the limit of quantification of 0.1 ng/mL in samples collected from 14 patients administered trabectedin as a 3-hour or 24-hour infusion during 6 Phase I and II studies. The glucuronide conjugates of trabectedin could not be measured in plasma samples of trabectedin-treated patients. The metabolism of trabectedin was investigated using urine and faeces collected from patients with cancer administered a single-dose of 14C-labelled trabectedin as a 3- or a 24-h intravenous infusion (ET-A-013-01). Radio-chromatograms of faeces showed that trabectedin was extensively metabolized to several radio labelled metabolites including ET-745 (carbonyl metabolite), ET-731, and ETM-217. Metabolites ET-729, ET-759A, and ETM-259 were recovered in faeces only under acidic conditions. Metabolites recovered in urine included ET-745, ET-759A, ETM-259, and ETM-204. There was no evidence that unchanged trabectedin undergoes direct glucuronidation. However, at least one oxidative metabolite appears to be glucuronidated prior to urinary excretion.

These results are supported data indicating that urine and bile samples of trabectedin-treated patients did not contain measurable concentrations of ET-729 or glucuronide conjugates of trabectedin.

Both ET-745 and ET-759A are known degradants of trabectedin. In addition, the “ETM compounds” may have been produced via fragmentation of trabectedin and/or its metabolites in the mass spectrometer during sample analysis. Therefore, it is not clear if these compounds are genuine metabolites or artefacts.

- Dose proportionality and time dependencies

Dose-proportional pharmacokinetics were demonstrated for the 3-hour intravenous infusion as well as for the 24 hour infusion.

- Special populations

A formal clinical study to evaluate the impact of renal impairment on the pharmacokinetics of trabectedin has not not performed since only a minor fraction of the total dose is excreted in the urine as unchanged drug or derived metabolites.

A population analysis showed no relationship between the concentration of liver enzymes in serum (ranges: AST, 0.15 to 3.49 x ULN; ALT, 0.03 to 4.76 x ULN; alkaline phosphatase, 0.17 to 6.82 x ULN; LDH, 0.25 to 20.38 x ULN; total bilirubin, 0.08 to 4.00) and the plasma clearance of trabectedin.

Clinically significant association between gender and plasma clearance was not observed during the population pharmacokinetic analysis.

A study to evaluate the impact of race/ethnicity on the clinical pharmacokinetics of trabectedin has not been performed.

In light of the available information on the distribution and elimination of trabectedin, clinically significant effects of race/ethnicity on the pharmacokinetics of trabectedin are not expected and dose adjustments are not recommended.

The population pharmacokinetic analysis indicated that the plasma clearance and distribution volume of trabectedin is not influenced by patient age (range, 19 to 83 years).

Study ET-A-008-00 was a phase 1 open-label, non-randomised, dose-escalating multicenter study enrolling 12 patients with pediatric refractory solid tumours (data not shown). Definitive conclusions cannot be drawn given the relatively small sample size of paediatric patients in each dose group.

- Pharmacokinetic interaction studies

CYP3A4 is the main CYP enzyme responsible for the hepatic metabolism of trabectedin at clinically relevant concentrations. Therefore, co-administration with potent inducers or inhibitors of CYP3A4 is expected to reduce or increase, respectively, the plasma concentrations of trabectedin. Trabectedin metabolism was markedly diminished by chemical inhibitors of CYP3A4 (ketoconazole and troleandomycin) and selective inhibitory antibodies directed towards this enzyme in vitro.

Weekly administration of 0.3 to 0.65 mg/m2 of trabectedin as a 3-hour infusion (with dexamethasone prophylaxis) to patients with cancer had minimal impact on the *in vivo* activity of the CYP3A4 enzyme.

A pharmacokinetic study of liposomal doxorubicin and trabectedin has been conducted (data not shown).

Pharmacodynamics

- Mechanism of action

No clinical studies on the mechanism of action of trabectedin have been submitted.

- Primary and Secondary pharmacology

No clinical studies on the primary and secondary pharmacolgy of trabectedin have been submitted.

Discussion on Clinical Pharmacology

Systemic exposure after administration as a 24 hour constant rate intravenous infusion is dose proportional at doses up to and including 1.8 mg/m^2. Trabectedin pharmacokinetic profile is consistent with a multiple-compartment disposition model.

Following intravenous administration, trabectedin demonstrates a high apparent volume of distribution, consistent with extensive tissue and plasma protein binding (94 to 98% of trabectedin in plasma is protein bound). The distribution volume at steady state of trabectedin in human subjects exceeds 5000 l.

Clinically significant effects of race/ethnicity on the pharmacokinetics of trabectedin are not expected and, therefore, dose adjustments are not recommended at the moment. Nevertheless, the applicant commited to analyse the influence of race on pharmacokinetics when the data of the ongoing Phase 3 study ET743-OVA-301 in ovarian cancer be available.

Pharmacokinetics in children have not been established.

Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. Other P450 enzymes may contribute to metabolism. Trabectedin does not induce or inhibit major cytochrome P450 enzymes. Trabectedin metabolism was markedly diminished by chemical inhibitors of CYP3A4 (ketoconazole and troleandomycin) and selective inhibitory antibodies directed towards this enzyme. Chemical inhibitors and/or antibodies of other CYP enzymes had no effect.

Trabectedin was administered as a 1-, 3-, 24-, or 72-hour constant rate, intravenous infusion. Maximum concentrations of trabectedin in plasma were typically observed either during or immediately prior to the end of the infusion. The drug concentrations then declined in a multiexponential manner upon cessation of the intravenous infusion. Initially, a marked and rapid decline in plasma concentrations was observed which was followed by more prolonged distribution and terminal phases.

The pharmacokinetics of trabectedin, with respect to plasma Cmax and AUC, are dose-proportional when administered as a 24-hour or 3-hour intravenous infusion within the clinically relevant dose range.. Furthermore, it is agreed that assessments of dose-proportional pharmacokinetics for other time points are deemed to be inconclusive. It is considered likely that only little or no accumulation of

trabectedin in plasma will occur upon repeat administration of 1-hour or 3-hour infusions at 3-week intervals.

Little or no accumulation was apparent in the plasma concentrations of trabectedin when 1.5 mg/m2 was given as a 24-hour infusion every 3 weeks. In agreement with this, simulated plasma concentration-time profiles also predicted minimal accumulation of trabectedin following this dosing regimen

The clearance of trabectedin in whole blood is approximately 35 L/h. Thus, trabectedin may be classified as drug with a moderate extraction ratio. Variability in the pharmacokinetics of trabectedin was moderate to large. This can not be ascribed to one factor including gender, age body weight, body surface area, plasma clearance, or measures of hepatic function. The difference demonstrated in central volume in distribution associated to gender should be considered without clinical relevance

The distribution volume at steady state of trabectedin in human patients exceeds 5000. These results suggest trabectedin distributes extensively into peripheral tissues (outside the central compartment).

Trabectedin is extensively metabolized. Renal elimination of unchanged trabectedin in humans is low (less than 1%). The terminal half-life is long (population value of the terminal elimination phase: 180-hr). After a dose of radiolabelled trabectedin administered to cancer patients, faecal mean (SD) recovery of total radioactivity is 58% (17%), and urinary mean (SD) recovery is 5.8% (1.73%). Based on the population estimate for plasma clearance of trabectedin (31.5 l/h) and blood/plasma ratio (0.89), the clearance of trabectedin in whole blood is approximately 35 l/h. This value is approximately one-half the rate of human hepatic blood flow. Thus the trabectedin extraction ratio can be considered moderate. The inter-patient variability of the population estimate for plasma clearance of trabectedin was 51% and intra-patient variability was 28%.

A population pharmacokinetic analysis indicated that the plasma clearance of trabectedin is not influenced by age (range 19-83 years), or gender. The effects of race and ethnicity on trabectedin pharmacokinetics have not been studied.

There is no relevant influence of renal function measured by creatinine clearance on trabectedin pharmacokinetics within the range of values (≥ 34.4 ml/min) present in the patients included in the clinical studies. No data are available in patients with a creatinine clearance of less than 34.4 ml/min. The low recovery (< 9% in all studied patients) of total radioactivity in the urine after a single dose of ^{14}C-labelled trabectedin indicates that renal impairment has little influence on the elimination of trabectedin or its metabolites.

Although the population analysis showed no relationship between the serum liver enzymes concentrations and the plasma clearance of trabectedin, systemic exposure to trabectedin may be increased in patients with hepatic impairment; therefore close monitoring of toxicity is warranted.

Clinical efficacy

- Dose response study(ies)

In the first application, four phase I studies in patients with solid tumours were provided (ET-A.001, PMA-002-95, ET-A-003-95 and ET-A-004-97). These studies evaluated different schedules (1, 3, 24 and 72 hour infusions weekly, every 21 days and 1 hour infusion for 5 days in a 21 day cycle). Doses evaluated ranged from 50 to 1800 μg/m^2 every three weeks. DLT were thrombocytopenia, pancytopenia, fatigue, lethargy, emesis, rhabdomyolysis and hepatotoxicity. MTD for both 3h and 24 hour infusions were 1.8 mg. The 1h and 72h infusional regimes were considered less appropriate for further phase II studies. In this application, an additional study (ET-A-005-99) was provided. This study tested 3 hour infusions weekly for three weeks in four week cycles at doses ranging from 300 to 650 μg/m^2 weekly, in 31 patients. DLT were neutropenia, hepatotoxicity and rhabdomyolysis and the MTD was 650 μg/m^2. Antitumour activity was only evaluated in study ET-A-004-97 (72 h infusion) and ET-A-005-99.

- Main study(ies)

A randomized, multicenter, open-label study of Yondelis (ET-743 Ecteinascidin) administered by 2 different schedules (weekly for 3 of 4 weeks vs. q3 weeks) in subjects with locally advanced or

metastatic liposarcoma or leiomyosarcoma following treatment with an anthracycline and ifosfamide (ET743-STS-201).

METHODS

Study Participants

Treatments

Objectives

The study was originally designed to select the most appropriate schedule for further testing. Following protocol amendment, the objective was to compare the 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.

Outcomes/endpoints

The initial primary efficacy endpoint was the point estimate (95% CI) for clinical benefit, a composite rate of confirmed CR or PR or SD lasting for at least 24 weeks. If the true clinical benefit rate was less than 20% (14 or fewer patients achieving clinical benefit), this would lead to not recommending further evaluation of the dose regimen. Alternatively, further development would have been recommended if 15 or more patients achieved clinical benefit.

Promising preliminary descriptive data were publicly disclosed during an oral presentation at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO). These early descriptive data in 80 evaluable patients suggested that the q3wk 24-h regimen might be more efficacious than the qwk 3-h schedule. Moreover, these early data also suggested that the qwk 3-h schedule was active in this clinical setting. This led to extension of the study expanding the sample size in order to allow a formal comparison between the two trabectedin schedules, changing the endpoint to time to progression (TTP). Crossover from one treatment schedule to the alternate was allowed in patients after progressive disease to the treatment assigned by randomization.

Secondary endpoints included to estimate the rate and duration of best overall objective response, to compare progression-free survival (PFS) and overall survival (OS), to characterize the safety profile, and to estimate the pharmacokinetics of trabectedin.

TTP was calculated as time between date of randomization (in ET743-STS-201 randomized study) or first dose (in the single-arm studies) and date of disease progression. Patients who were progression-free at the time of data cut-off or died without disease progression in each study were censored at the date of the last tumor assessment. TTP was assessed by independent review.

PFS was calculated as time between date of randomization (in ET743-STS-201 randomized study) or first dose (in non-randomized initial studies) and date of disease progression or death. Patients who were progression-free at the time of data cut-off in each study were censored at the date of the last tumor assessment. PFS was assessed by independent review. OS was calculated between date of randomization (in ET743-STS-201 randomized study) or first dose (in the initial studies) and date of death. All patients who died, regardless of the cause of death, were considered to have had an event.

Objective response was graded according to RECIST.

Sample size

The initial sample size of the original study was 45 patients in each study arm. The sample size was recalculated with the protocol amendment. With 260 evaluable patients and the observation of 217 TTP events (final analysis), the study would have greater than 90% power to detect a minimum of 60% improvement in median TTP at a 2-sided 5% significance level.

Randomisation

Subjects were centrally assigned to either arm in a 1:1 ratio by permuted-block randomisation and were stratified according to ECOG status (0-1).

Blinding (masking)

It was an open-label study, although a blinded independent radiological review panel of tumour assessments and an IDMC were instituted.

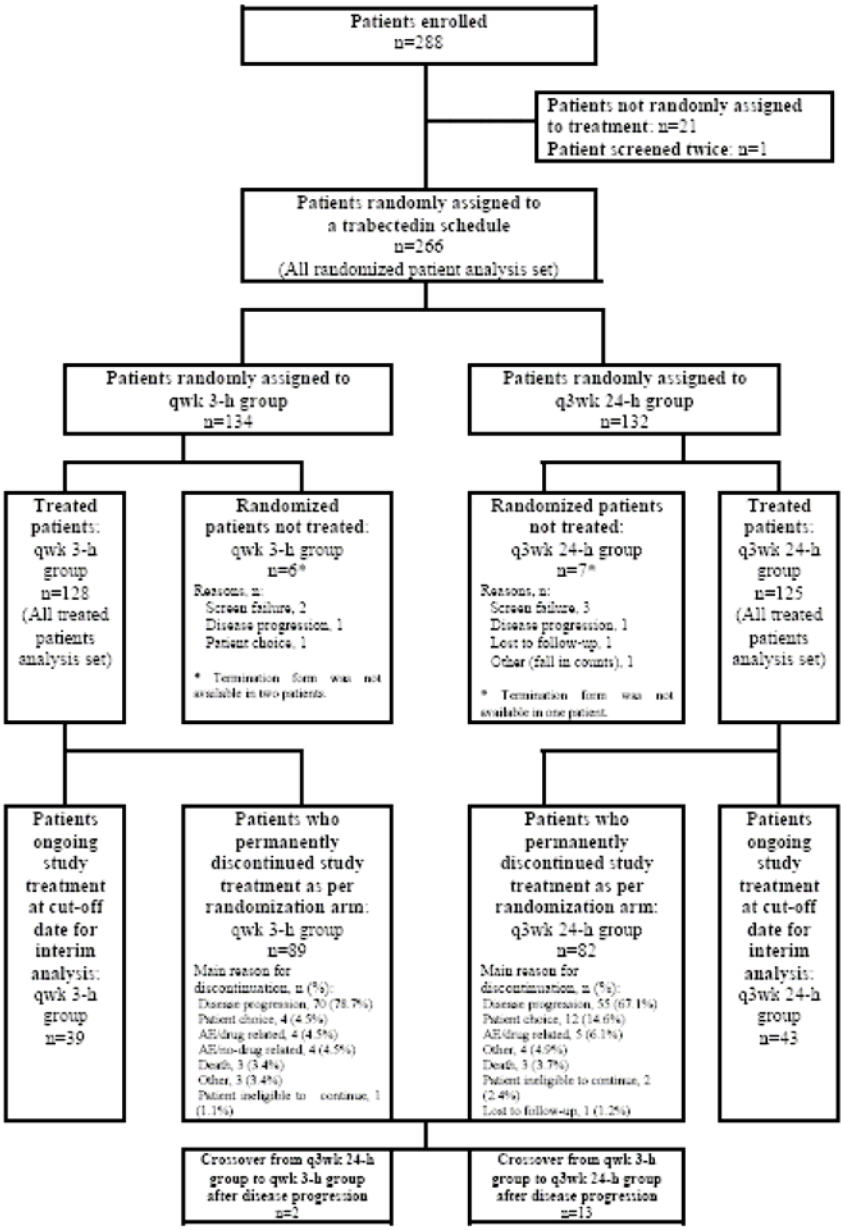
Statistical methods

The final version of the SAP is dated February 3rd, 2006. Apparently, the database for the interim analysis (locked after cut-off date the 31 May 2005) was planned to be made available to the sponsor on 13 February 2006. In August 05, the IDMC conducted an analysis on the interim data and recommended to advise patients still under treatment and progression-free, to cross over from the qwk to the q3wk arm. The efficacy evidence is based on the prospectively planned interim analysis of the amended study, which was to happen when 150 TTP events had taken place. The final analysis is to be performed when 217 events take place, with alpha 0.25 for each analysis. TTP was to be compared using a 2-sided un-stratified log-rank test. The Kaplan-Meier method would be used to estimate the distribution functions for each treatment arm. The effect of baseline prognostic factors on time-to-event endpoints was to be analysed using Cox regression models. The primary analysis was to be based on tumour assessment from the independent radiological review on the "all randomised set".

The date of progression was to be assigned based on the time of the first evidence of progression. Subjects who were lost to follow-up or who were still being treated without documented DP were to be censored at the time of the last tumour assessment. Apparently, no imputation of missing data was performed for the primary analysis. A patient was considered to have a missing tumour assessment if an assessment was not performed within 1.5 weeks of the scheduled assessment. However, the impact of potential missing tumour assessment on the TTP analysis was to be examined by 2 imputation analyses. In the first one, the midpoint of the last 2 assessment dates on or prior to the documented disease progression were to be used to impute the date of DP. In the second one, a predetermined schedule would be used. A TTP analysis based on the imputed data was to be performed. In this analysis, all progression and censoring dates were to be imputed by their corresponding scheduled tumour assessment dates.

RESULTS

Participant flow



Recruitment

Recruitment started on 12 May 2003. By August 2004 (when the major amendment was performed), 146 patients had already been recruited, and by cut-off date (May 2005) 266 patients had been randomized.

Conduct of the study

Eligibility exceptions were noted in 22 patients (16.4%) in qwk 3-h and in 13 (9.8%) in the q3wk 24-h arm. Deviations regarding efficacy assessments were detected in a similar number of patients in each treatment arm (approximately 9%).

Baseline data

Demographic baseline data, including age, seem to be evenly distributed among treatment arms. In general, there were no evident imbalances regarding EOCG status, time from initial diagnosis, histology or histopathological grade, tumour size, liver or lung metastasis, or previous treatments. Virtually all patients had received both anthracyclines and ifosfamide. Information regarding next line therapy has not been provided.

Demographic characteristics

		qwk 3-h (n=134)	q3wk 24-h (n=132)	Total (n=266)	p-value*
Gender	Female	78 (58.2%)	90 (68.2%)	168 (63.2%)	0.0997
	Male	56 (41.8%)	42 (31.8%)	98 (36.8%)	
Race	Asian	3 (2.2%)	3 (2.3%)	6 (2.3%)	0.5145
	Black	4 (3.0%)	9 (6.8%)	13 (4.9%)	
	Other**	2 (1.5%)	3 (2.3%)	5 (1.9%)	
	White	125 (93.3%)	117 (88.6%)	242 (91.0%)	
Age (years)	Median	54	53	53	0.5578
	Range	23-77	20-80	20-80	
	18-65	114 (85.1%)	117 (88.6%)	231 (86.8%)	0.4690
	≥65	20 (14.9%)	15 (11.4%)	35 (13.2%)	
ECOG performance status***	0	65 (48.5%)	67 (50.8%)	132 (49.6%)	0.8063
	1	68 (50.7%)	65 (49.2%)	133 (50.0%)	
	2	1 (0.7%)	.	1 (0.4%)	
Body Mass Index (kg/m^2)	Median	25.8	26.3	26.1	0.6997
	Range	16.7-44.3	15.8-47.8	15.8-47.8	
	<30	100 (74.6%)	91 (68.9%)	191 (71.8%)	0.3410
	≥30	34 (25.4%)	41 (31.1%)	75 (28.2%)	
Height (cm)	Median	168	168	168	0.4892
	Range	151-189	137-193	137-193	
Weight (kg)	Median	73.5	75.8	75	0.8166
	Range	42.3-133.6	41-148.2	41-148.2	
Body surface area (m^2)	Median	1.8	1.8****	1.8	0.7963
	Range	1.3-2.5	1.4-2.7	1.3-2.7	
Age at initial diagnosis (years)	Median	51	49.5	50	0.7323
	Range	20-74	17-76	17-76	0.394
Time from initial diagnosis to randomization (months)	Median	31	30.1	30.5	0.5119
	Range	4.4-171.8	1.6-175.7	1.6-175.7	
	<24	58 (43.3 %)	55 (41.7 %)	113 (42.5%)	0.8052
	≥24	76 (56.7 %)	77 (58.3 %)	153 (57.5%)	
Time from diagnosis to first metastasis (months)	≤12	71 (53.4 %)	68 (51.9 %)	139 (52.7%)	0.9019
	>12	62 (46.6 %)	63 (48.1 %)	125 (47.3%)	
Time from PD in last prior treatment to randomization (months)	Median	1.3	1.3	1.3	0.9975
	Range	0.1-38.8	0.1-42.8	0.1-42.8	0.1846
	<3	98 (73.1 %)	86 (65.2 %)	184 (69.2%)	
	≥3	36 (26.9 %)	46 (34.8 %)	82 (30.8%)	

Data shown are n (%) except for median and range.
* Fisher's exact test (for categorical variables) and Wilcoxon's test (for continuous variables) qwk 3-h *vs.* q3wk 24-h.
**Three Hispanic, one Lebanese, and one from the Maghreb.
***P-value for two categories (0 and 1; one patient with PS=2 was included in PS=1 category).
****Data on 131 patients.

Primary tumour location and histology

		qwk 3-h (n=134)	q3wk 24-h (n=132)	Total (n=266)	p-value*
Diagnosis	Soft Tissue Sarcoma	134 (100.0%)	132 (100.0%)	266 (100.0%)	
Histology	Leiomyosarcoma	85 (63.4%)	90 (68.2%)	175 (65.8%)	0.4399
	Liposarcoma	49 (36.6%)	42 (31.8%)	91 (34.2%)	
Histopathological grade**	G1: Well differentiated	13 (9.7 %)	8 (6.1 %)	21 (7.8%)	0.4007
	G2: Moderately differentiated	21 (15.7 %)	28 (21.2 %)	49 (18.4%)	
	G3: Poorly differentiated	53 (39.6 %)	45 (34.1 %)	98 (36.9%)	
	Unknown***	47 (35.1 %)	51 (38.6 %)	98 (36.9%)	
Primary tumor site at initial diagnosis	Abdomen/pelvis, other	13 (9.7%)	19 (14.4%)	32 (12.0%)	0.8896 (Extremities vs. other)
	Abdominal/pelvic wall	8 (6.0%)	7 (5.3%)	15 (5.6%)	
	Chest wall	2 (1.5%)	3 (2.3%)	5 (1.9%)	
	Chest, other	3 (2.2%)	2 (1.5%)	5 (1.9%)	
	Face	3 (2.2%)	3 (2.3%)	6 (2.3%)	
	Gastrointestinal tract	3 (2.2%)	5 (3.8%)	8 (3.0%)	
	Intrathoracic	4 (3.0%)	.	4 (1.5%)	
	Lower extremity	28 (20.9%)	29 (22%)	57 (21.4%)	
	Neck	1 (0.7%)	.	1 (0.4%)	
	Retroperitoneal	33 (24.6%)	27 (20.5%)	60 (22.6%)	
	Upper extremity	8 (6.0%)	5 (3.8%)	13 (4.9%)	
	Uterus	28 (20.9%)	32 (24.2%)	60 (22.6%)	

Data shown are n (%).
* Fisher's exact test (for categorical variables) and Wilcoxon's test (for continuous variables) qwk 3-h *vs.* q3wk 24-h.
**Histological grade was not collected on the CRF. The grades reported here correspond to available data from the ongoing independent review.
***Including 67 no yet reviewed cases by the central pathology review.

Patients were enrolled in the US (n=181), Russia (n=26), Canada (n=24), France (n=17), Italy (n=8), Australia (n=4), Belgium (n=3) and Spain (n=3).

Numbers analysed

The "all-randomised" set was used for the primary analysis (n=266).

Outcomes and estimation

Results for the primary and main efficacy secondary endpoints are shown in the following tables and figures. For visual comparison, the data on L-sarcoma population treated with 24-h regimen q3wk for the initial phase II studies (ET-B-005—98, ET-B-008-98, ET-B-017-99) are also provided (N=100, see Supportive Studies in the section on Clinical Efficacy).

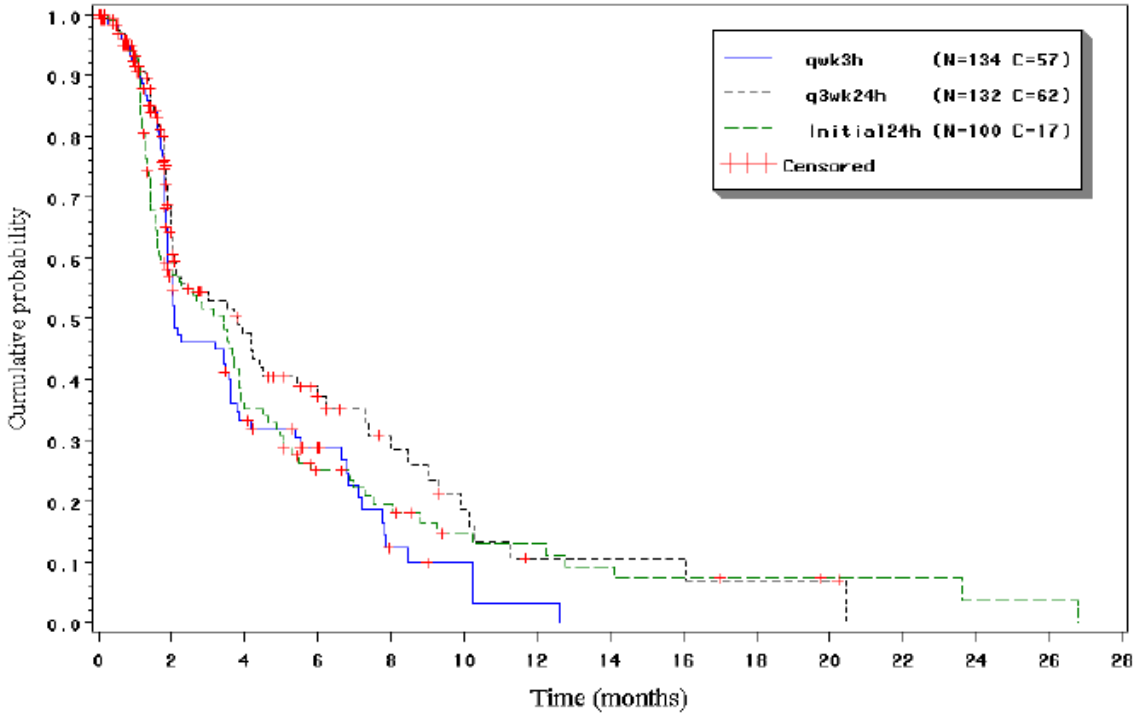
Time to Progression

Time to Progression (Integrated L-sarcoma Population)

Descriptive	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Events	77 (57.5%)	70 (53.0%)	83 (83.0%)
Censored	57 (42.5%)	62 (47.0%)	17 (17.0%)
Median	2.1 95% CI (1.9-3.6)	3.8 95% CI (2.1-5.4)	3.4 95% CI (1.7-3.9)
No PD at 3 months	46.1% 95% CI (35.9-56.4)	53.1% 95% CI (42.9-63.3)	51.7% 95% CI (41.6-61.8)
No PD at 6 months	28.9% 95% CI (19.0-38.7)	37.1% 95% CI (26.4-47.8)	25.0% 95% CI (16.1-33.9)
No PD at 12 months	3.3% 95% CI (0-9.2)	10.6% 95% CI (1.5-19.8)	12.9% 95% CI (5.2-20.6)

log rank test (p-value=0.1711)

Kaplan-Meier of Time to Progression (Integrated L-sarcoma Population)



Progression-Free Survival (Integrated L-sarcoma Population)

Descriptive	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Events	84 (62.7%)	78 (59.1%)	87 (87.0%)
Censored	50 (37.3%)	54 (40.9%)	13 (13.0%)
Median	2.1 95% CI (1.9-3.4)	3.5 95% CI (2.0-4.5)	2.7 95% CI (1.7-3.7)
PFS at 3 months	45.1% 95% CI (35.2-55.0)	50.2% 95% CI (40.3-60.1)	48.8% 95% CI (38.8-58.7)
PFS at 6 months	26.9% 95% CI (17.6-36.2)	34.6% 95% CI (24.5-44.7)	23.6% 95% CI (15.1-32.1)
PFS at 12 months	5.2% 95% CI (0-11.6)	11.5% 95% CI (2.8-20.2)	12.2% 95% CI (4.9-19.5)

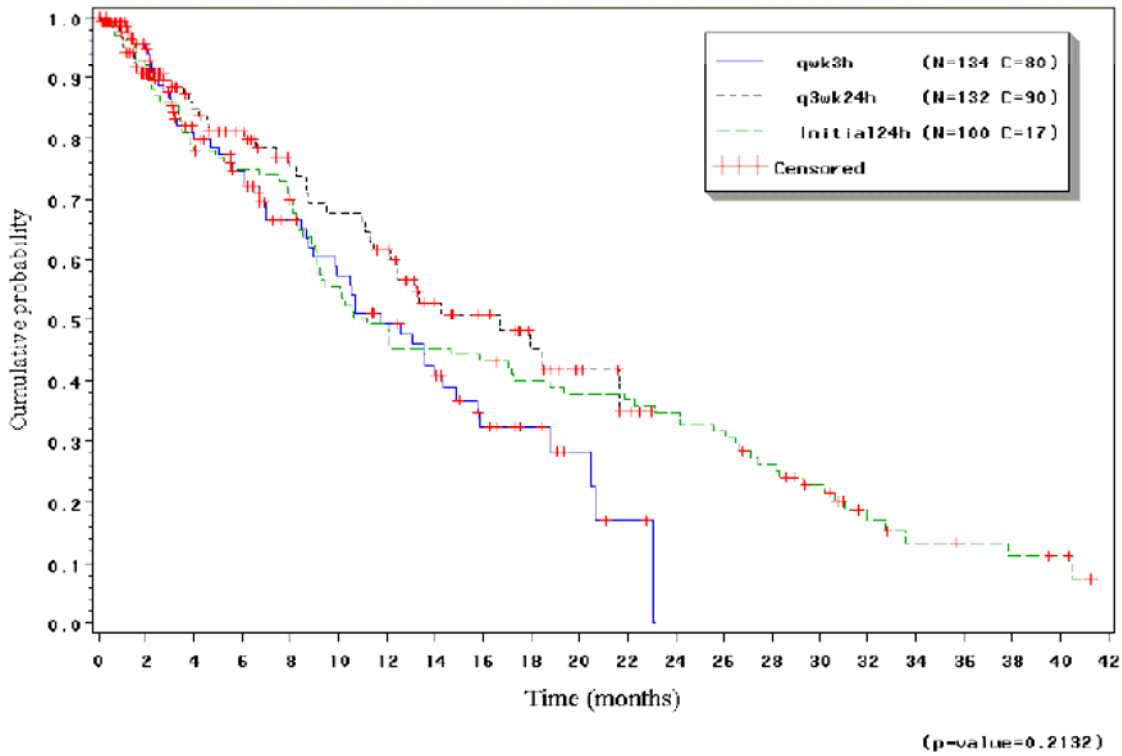
log rank test (p-value=0.2438)

Overall Survival

Descriptive	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Events	54 (40.3%)	42 (31.8%)	83 (83.0%)
Censored	80 (59.7%)	90 (68.2%)	17 (17.0%)
Median	11.8 95% CI (8.9-14.9)	16.7 95% CI (12.2-n.r.)	11.2 95% CI (9.1-17.2)
OS at 6 months	74.8% 95% CI (65.9-83.7)	81.2% 95% CI (73.4-89.0)	75.0% 95% CI (66.5-83.5)
OS at 12 months	49.4% 95% CI (37.9-60.9)	61.6% 95% CI (50.5-72.6)	49.3% 95% CI (39.5-59.2)
OS at 24 months	-	-	34.7% 95% CI (25.3-44.2)

n.r. - upper limit not reached
log rank test (p-value=0.2132)

Kaplan-Meier of Overall Survival (Integrated L-sarcoma Population)



Overall Response Rate

There were no complete responses according to the independent review. Overall response rates were low whereas the SD rates were in the 30% - 50% range. The rate of PD as best response was consistently below 50% in all three set of patients. Of note, 95% confidence intervals for PR, SD and PD overlap.

Best Overall Response (Integrated L-sarcoma Population)

Response	Number of patients (%)		
	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Partial response	1 (0.7%) 95% CI (0-4.1)	4 (3.0%) 95% CI (0.8-7.6)	12 (12.0%) 95% CI (6.4-20)
Stable disease	46 (34.3%) 95% CI (26.3-43.0)	55 (41.7%) 95% CI (33.2-50.6)	42 (42.0%) 95% CI (32.2-52.3)
Progressive disease	53 (39.6%) 95% CI (31.2-48.4)	42 (31.8%) 95% CI (24.0-40.5)	43 (43.0%) 95% CI (33.1-53.3)
Not evaluable	34 (25.4%) 95% CI (18.3-33.6)	31 (23.5%) 95% CI (16.5-31.6)	3 (3.0%) 95% CI (0.6-8.5)
PR+SD	47 (35.1%) 95% CI (27.0-43.8)	59 (44.7%) 95% CI (36.0-53.6)	54 (54.0%) 95% CI (43.7-64.0)

Ancillary analyses

An Updated Clinical Study Report was submitted including a number of new statistical analyses. The key efficacy result of the ET743-STS-201 study, i.e., the final TTP primary analysis per independent review, assessed at **cut-off date 31 May 2006**, shows statistically significant differences favouring the q3wk 24-h regime (log-rank p=0.0302; significance level for 206 progression events after alpha spending adjustment foreseen in the Statistical Analysis Plan, p=0.0340). The results are summarised in Table XXX. Different TTP sensitivity analyses were conducted to assess the impact of different methods of adjudication of progression in case of missing evaluations (data not shown). These sensitivity analyses consistently showed similar relative risk reductions in each assessment for patients treated in the q3wk 24-h arm. The results were statistically significant in the primary, protocol-specified analysis of TTP as well as in the majority of sensitivity analyses.

Summary of final results for the primary efficacy endpoint: time to progression as per independent review (ET743-STS-201 study)

Efficacy variables	**qwk 3-h** (n=134)	**q3wk 24-h** (n=136)	**LR* (p-value) HR* (p-value)**
TTP, months (independent review) Number of events, n (%) Median (95% CI) No PD at 3 months, % (95% CI) No PD at 6 months, % (95% CI)	102 (76.1%) 2.3 (2.0-3.5) 45.1% (36.3-53.9%) 27.3% (19.0-35.6%)	104 (76.5%) 3.7 (2.1-5.4) 53.4% (44.6-62.2%) 37.2% (28.4-46.0%)	. LR: 4.698 (p=0.0302)** HR: 0.734 (p=0.0320) . .

Data for TTP are shown for all randomised patients. *Log rank and HR q3wk 24-h vs. qwk 3-h group. ** The level of significance (log-rank) to be reached for 206 events after alpha spending adjustment was =0.0340. CI, confidence interval; HR, hazard ratio; LR, log-rank; PD, progressive disease; TTP, time to progression.

In a multivariate analysis including all available variables, the known prognostic factors for metastatic STS emerged as independent prognostic factors. In a multivariate model, the statistically significant treatment effect was confirmed (HR=0.680; p=0.0174).

The results of the different time-to-event analyses (TTP, PFS and OS) conducted in the all randomised, all treated and confirmed L-sarcoma data sets demonstrated a consistent pattern of treatment benefit favouring the q3wk 24-h trabectedin regimen (data not shown).

There were no statistically significant differences in TTP outcomes pre-vs. post-amendment. The HRs reflecting the greater benefit associated with the q3wk 24-h regime over the qwk 3-h regime were virtually identical in both cohorts (0.729 vs. 0.738) and consistent with the HR of 0.734 obtained in the intention-to-treat (ITT) population of 270 randomised patients.

Tumour shrinkage of any magnitude assessed by independent review was achieved by 50.5% of patients treated with the trabectedin q3wk 24-h regime as compared to 32.4% of patients treated with trabectedin qwk 3-h.

The sponsor was asked to submit an updated exploratory survival analysis (including an analysis censoring patients at time of cross-over to the alternative regimen). At the most recent **cut-off date (25 May 2007),** a total of 206 deaths had been reported in all randomised patients (last death recorded on 19 April 2007): 106 deaths in the qwk 3-h arm and 100 deaths in the q3wk 24-h arm. The median follow-up was 30.0 months (95% CI, 25.0-36.6 months) in the q3wk 24-h arm and 27.9 months (95% CI, 23.6-37.3 months) in the qwk 3-h arm (p=0.7838). Forty-three patients (32.1%) crossed over from the qwk 3-h to the q3wk 24-h arm, most of them (29 patients) after progression of the disease. Only six patients (4.4%) crossed over from the q3wk 24-h to the qwk 3-h arm, all of them after disease progression. Additional OS analyses have been done by censoring patients at the time of crossover to the alternative trabectedin regime. Censoring of patients at time of crossover to the alternative regime increased the difference in overall survival between treatment arms (data not shown). The survival at 12 months was in the range of 48.5-51.4% in the qwk 3-h arm and in the range of 60.2-66.7% in the q3wk 24-h arm. In this exploratory analyses, an improvement in one year survival with trabectedin q3wk 24-h was observed in the "all randomised" population and the most important effect was found in the "all treated" and "confirmed L-sarcoma" populations (data not shown).

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

The applicant provided a separate analysis, for patients with liposarcoma or leyomiosarcoma compared to patients with other kinds of STS. Comparison of efficacy data obtained in the ET743-STS-201 study *vs*. pooled data from three previous phase II trials with the q3wk 24-h trabectedin regime

	ET743-STS-201 (interim data 31-05-2006)			Pooled data previous phase II studies q3wk 24-h		
	qwk 3-h	**q3wk 24-h**	**Total**	**L-sarcomas**	**Non-L-sarcomas**	**Total**
n	134	132	266	100	83	183
TTP						
Median (months)	2.1	3.8	3.0	3.4	1.9	2.7
	(1.9-3.6)	(2.1-5.4)	(2.1-3.8)	(1.7-3.9)	(1.6-3.0)	(1.7-3.5)
No PD at 3 months (%)	46.1	53.1	49.7	51.7	40.0	46.5
	(35.9-56.4)	(42.9-63.3)	(42.5-56.9)	(41.6-61.8)	(29.0-51.0)	(39.0-53.9)
No PD at 6 months (%)	28.9	37.1	32.9	25.0	19.1	22.4
	(19.0-38.7)	(26.4-47.8)	(25.6-40.2)	(16.1-33.9)	(9.7-28.4)	(15.9-28.8)
PFS						
Median (months)	2.1	3.5	2.5	2.7	1.8	2.3
	(1.9-3.4)	(2.0-4.5)	(2.0-3.6)	(1.7-3.7)	(1.5-2.9)	(1.6-3.2)
PFS >3 months (%)	45.1	50.2	47.7	48.8	38.3	44.0
	(35.2-55.0)	(40.3-60.1)	(40.7-54.7)	(38.8-58.7)	(27.8-48.8)	(36.8-51.3)
PFS >6 months (%)	26.9	34.6	30.6	23.6	19.0	21.5
	(17.6-36.2)	(24.5-44.7)	(23.7-37.5)	(15.1-32.1)	(10.1-28.0)	(15.3-27.7)
OS						
Median (months)	11.8	16.7	13.4	11.2	8.7	10.3
	(8.9-14.9)	(12.2-nr)	(11.1-15.9)	(9.1-17.2)	(5.7-13.9)	(8.7-13.9)
% Alive at 12 months	49.4	61.6	55.4	49.3	45.2	47.5
	(37.9-60.9)	(50.5-72.6)	(47.4-63.5)	(39.5-59.2)	(34.4-56.0)	(40.2-54.8)
% Alive at 24 months	NA	NA	NA	34.7	22.8	29.3
				(25.3-44.2)	13.6-31.9	22.6-36.0
RR (%)	1.0	4.0	2.5	12.0	2.4	7.7
	(0.0-5.5)	(1.1-9.9)	(0.8-5.8)	(6.4-20.0)	(0.3-8.4)	(4.3-12.5)

Data shown are per independent review. In brackets, 95% confidence intervals (CI). nr, upper limit not reached. L-sarcomas, liposarcoma or leiomyosarcoma; NA, not available; RR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression..

- Clinical studies in special populations

No specific studies have been performed in special populations. Children were not included in the pivotal study. Twelve patients aged ≤ 16 were enrolled within two phase II studies.

Thirty-five (13.2%) patients over 65 were included in the pivotal trial. In the SPC it is stated that plasma clearance and distribution volume is not influenced by age, so the same initial dose should be recommended in elderly patients.

Conventional restrictions of liver function parameters were used in the pivotal trial. In addition, patients with active viral hepatitis, chronic liver disease or creatinine above the ULN were excluded

from the pivotal trial. Approximately 15% of patients in each treatment arm had hepatic metastasis at baseline.

- Supportive study(ies)

Results from phase II, non-comparative studies ET-B-005-98, ET-B-008-98 and ET-B-017-99 are provided as supportive evidence. These studies included STS patients with up to 2 prior treatments, measurable disease, WHO PS <2, adequate hematologic, hepatic and renal function. Trabectedin was administered with the same q3wk 24-h dose and regime and the population was similar in these three studies (patients with STS after failure of previous chemotherapy), although for study 017, PD was not a formal requirement for eligibility. Evaluations were performed every 6 weeks. The primary endpoint was RR according to the WHO criteria. In the provided analysis, patients with GIST and Ewing's sarcoma were excluded (6 patients). Results are summarised in the following table.

Results of phase II uncontrolled studies

	ET-B-005-98 (Group A)	ET-B-005-98 (Group C)	ET-B-008-98 (Group 1)	ET-B-008-98 (Group 2)	ET-B-017-99	Total (pooled data)
n	44	55	23	27	34	183
RR (%)	9.1 (2.5-21.7)	10.9 (4.1-22.3)	0 (0-14.8)	3.7 (0.9-19.0)	8.8 (1.9-23.7)	7.7 (4.3-12.5)
TTP						
Median (months)	3.1 (2.0-3.9)	2.9 (1.8-4.6)	1.9 (1.5-3.9)	2.2 (1.3-5.0)	1.6 (1.3-3.5)	2.7 (1.7-3.5)
No PD at 3 months (%)	52.6 (36.8-68.5)	49.7 (36.3-63.1)	47.6 (26.1-69.2)	44.4 (25.7-63.2)	34.6 (18.0-51.3)	46.5 (39.0-53.9)
No PD at 6 months (%)	20.5 (7.4-33.5)	23.7 (11.5-36.0)	26.5 (6.9-46.0)	25.9 (9.4-42.5)	16.2 (2.5-29.8)	22.4 (15.9-28.8)
PFS						
Median (months)	2.6 (1.4-3.7)	2.9 (1.8-4.6)	1.9 (1.5-3.9)	2.2 (1.3-5.0)	1.6 (1.3-2.8)	2.3 (1.6-3.2)
PFS >3 months (%)	45.5 (30.7-60.2)	49.7 (36.3-63.1)	41.4 (20.8-62.0)	44.4 (25.7-63.2)	33.8 (17.6-50.0)	44.0 (36.8-51.3)
PFS >6 months (%)	17.7 (6.2-29.1)	23.7 (11.5-36.0)	23.0 (5.4-40.7)	25.9 (9.4-42.5)	17.6 (4.2-30.9)	21.5 (15.3-27.7)
OS						
Median (months)	8.7 (5.5-11.7)	13.9 (8.9-19.4)	12.9 (6.9-26.6)	10.7 (4.2-17.2)	12.6 (8.1-24.2)	10.3 (8.7-13.9)
% Alive at 12 months	34.1 (20.1-48.1)	53.8 (40.5-67.1)	52.2 (31.8-72.6)	42.4 (23.1-61.6)	55.9 (39.2-72.6)	47.5 (40.2-54.8)
% Alive at 24 months	18.2 (6.8-29.6)	32.5 (19.8-45.2)	39.1 (19.2-59.1)	25.4 (8.1-42.7)	35.3 (19.2-51.4)	29.3 (22.6-36.0)

Data shown are per independent review. In brackets, 95% confidence intervals (CI). **005-A:** first cohort or pretreated STS patients in ET-B-005-98 study. **005-C:** second cohort or pretreated STS patients in the ET-B-005-98 study. **008(1):** moderately pre-treated STS patients (≤2 single agents or one combination regime) in ET-B-008-98 study. **008(2):** extensively pre-treated STS patients (≥3 different single agents or >1 combination regime, or one combination and one or more single agents) in ET-B-008-98 study. The final reports of these three phase II trials had a total of 189 patients. For the current analysis, six patients were excluded: four with GIST in ET-B-008-98 study (3 in arm 008(1) and one in arm 008(2), and 2 patients with Ewing's sarcoma in ET-B-017-99 study. RR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

- Discussion on clinical efficacy

The main study evaluated the efficacy and safety of trabectedin, administered by two 2 different treatment regimens in 266 patients with locally advanced or metastatic leiomyosarcoma or liposarcoma (L-sarcoma) whose disease had relapsed or become refractory after treatment with an anthracycline and ifosfamide that had been given either in combination or in sequence. The distributions of demographic characteristics were well balanced in the two study groups. The two study groups were well balanced regarding important prognostic variables e.g. age, ECOG performance status (PS score of 0 or 1), histology (liposarcoma or leimyosarcoma), histopathological tumor grade, presence of liver metastases, bulky disease and time from diagnosis to treatment.

The interim analysis presented showed a median TTP (according to the independent review) of 2.1 months (95% CI, 1.9-3.6 months) in the qwk 3-h group and 3.8 months (95% CI, 2.1-5.4 months) in the q3wk 24-h group (log-rank p=0.0382), which represents a clinically significant difference. These results were not statistically significant at the 5% level after considering the alpha spending adjustement. However, consistent trends were observed for other time-dependent variables (PFS and OS).

The updated analyses provided further evidence to support the existence of a significant difference in terms of TTP and PFS. The further analyses did not suggest significant effects on OS but this might be

due to cross-over, although some support came from exploratory analyses of OS censoring patients before cross-over.

The final study report confirms the conclusions from the interim analysis provided in the initial MAA. Trabectedin has a definite antitumour activity in patients with STS whether the qwk 3-h or the q3wk 24-h regimens are used. The latter regimen seems to be the optimal one supported by robust TTP and PFS data assessed by an independent review panel. The results of the study in these time dependent variable are regarded as strongly consistent across the different sensitivity analyses carried out by the Applicant as per the CHMP request and confirmed in the final study results.

There were a number of methodological deficiencies that hampered the assessment of the efficacy of trabectedin in the treatment of STS. Crucial aspects included the timing and sponsor's access to data at the time of protocol amendment leading to a change of the primary endpoint. Although the decision to amend to protocol was data-driven, sufficient reassurance is provided in the exploratory analyses presented to indicate that the conclusions as regards a clinically significant effect on TTP still hold.

Clinical safety

- Patient exposure

Following the most recent update, the assessment of the clinical safety of Yondelis is based on data from clinical trials of 569 patients treated up to April 2007 with the recommended treatment regimen in several cancer types including soft tissue sarcoma, breast cancer, osteosarcoma, ovarian cancer, GIST, melanoma and renal carcinoma. This database is used as the basis for the description of undesirable effects in the SPC. The assessment of clinical safety has also included the "integrated safety database" for the initial safety summary, consisting of a total of 1018 cancer patients receiving trabectedin in phase II clinical studies (511 of whom had received trabectedin at the proposed schedule). A larger series also described includes any patients with advanced malignancies that had been treated with trabectedin (as of 31 May 2005, 3087 patients). Updated safety databases have also been provided during the procedure (data not shown).

The median number of cycles initiated was 2 (range 1-38; mean 3.83) for patients receiving trabectedin in the integrated safety database. The median duration of exposure, was 8.4 weeks (range 2- 125.9; mean 14.31 weeks). The median cumulative trabectedin dose was 3.50 mg/m2 for patients in the integrated safety database and very similar (3.0 mg/m2) for patients receiving the q3wk 24-h regimen (Table 8). Median relative dose intensity was 90% for a treatment essentially administered in late-stage palliation. Single-agent trabectedin q3wk 24-h has been consistently administered across studies for 6 or more cycles in 24% of patients, 10 or more cycles in 6% of patients, and some patients receiving treatment for more than 2 years (the maximum treatment duration was 125.9 weeks in one patient treated with q3wk 24-h schedule).

- Adverse events

Concerning the 569 patients database, approximately 91% of patients can be expected to have adverse reactions of any grade. Around 40% of patients are expected to have adverse reactions of grade 3 or 4 severity. The most common adverse reactions of any severity grade were nausea, fatigue, vomiting, anorexia, neutropenia, and increases in AST/ALT.

Adverse reactions

The frequencies of the adverse reactions reported below are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

The table below displays the adverse reactions reported in ≥ 1% of patients according to the standard MedDRA system organ class. Both adverse events and laboratory values have been used to provide frequencies. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Most frequent adverse reactions

For Blood and Lymphatic system and Hepatobiliary disorders (see laboratory findings). Nausea, vomiting, diarrhoea and constipation: Nausea and vomiting were reported in 63 and 38.5% of patients respectively. Grade 3-4 nausea and vomiting were reported in 6% and 6.5% of patients, respectively. Grade 3-4 diarrhoea and constipation were reported in less than 1% of patients. Stomatitis: Grade 3-4

mucositis was reported in less than 1% of the patients. Fatigue/Asthenia: Grade 3-4 fatigue/asthenia occurred in 9 and 1% of patients respectively. Anorexia: Grade 3-4 anorexia occurred in less than 1% of the patients. Dyspnoea: Grade 3-4 dyspnoea reported as trabectedin related occurred in 2% of the patients. Alopecia: Alopecia was reported in approximately 3% of all patients, of which the majority was grade 1 alopecia.

System Organ Class	**Adverse reactions reported in ≥ 1% of patients in clinical trials at the recommended regime [1.5 mg/m^2, 24 hour infusion every 3 weeks (24-h q3wk)]**
Investigations	**Very Common** Blood creatine phosphokinase increased, Blood creatinine increased, Blood albumin decreased **Common** Weight decreased
Blood and Lymphatic System Disorders	**Very Common** Neutropenia, Thrombocytopenia, Anaemia, Leukopenia **Common** Febrile neutropenia
Nervous System Disorders	**Very Common** Headache **Common** Peripheral sensory neuropathy, Dysgeusia, Dizziness, Paraesthesia
Respiratory, Thoracic and Mediastinal Disorders	**Common** Dyspnoea, Cough
Gastrointestinal disorders	**Very Common** Vomiting , Nausea, Constipation **Common** Diarrhoea , Stomatitis, Abdominal pain, Dyspepsia, Upper abdominal pain
Skin and Subcutaneous Tissue Disorders	**Common** Alopecia
Musculoskeletal and Connective Tissue Disorders	**Common** Myalgia, Arthralgia, Back pain
Metabolism and Nutrition Disorders	**Very Common** Anorexia **Common** Dehydration, Decreased appetite, Hypokalaemia
Infections and Infestations	**Common** Infection
Vascular Disorders	**Common** Hypotension, Flushing
General Disorders and Administration Site Conditions	**Very Common** Fatigue, Asthenia **Common** Pyrexia, Oedema, Oedema peripheral, Injection site reaction
Hepatobiliary Disorders	**Very Common** Hyperbilirubinemia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased
Psychiatric Disorders	**Common** Insomnia

In the integrated safety database, between 49% and 57% of patients experienced Grade 3-4 AEs, of which approximately two-thirds were considered related to study drug. The most common AEs in all 3 groups were nausea, fatigue, vomiting, and constipation. The most frequent drug-related Grade 3-4

AEs in this category were neutropenia, transaminase elevations, nausea, fatigue, asthenia, vomiting, and thrombocytopenia.

Drug-related Grade 3 or 4 AEs in ≥1% of Patients in Either Treatment Group by Preferred Term (Integrated safety database)

SOC	Number (%) of patients				
Preferred term[a]	q3wk 24-h (N=368)	ET-B008[b] (N=143)	qwk 3-h (N=302)	q3wk 3-h (N=205)	Total (N=1018)
Patients with at least 1 drug-related Grade 3 or 4 AE	**137 (37)**	**43 (30)**	**109 (36)**	**84 (41)**	**373 (37)**
Gastrointestinal Disorders	**29 (8)**	**18 (13)**	**22 (7)**	**11 (5)**	**80 (8)**
Nausea	21 (6)	12 (8)	13 (4)	5 (2)	51 (5)
Vomiting	16 (4)	11 (8)	11 (4)	7 (3)	45 (4)
Abdominal pain	4 (1)	0 (0)	1 (<1)	0 (0)	5 (<1)
General Disorders and Administration Site Pain	**24 (7)**	**19 (13)**	**24 (8)**	**21 (10)**	**88 (9)**
Fatigue	20 (5)	18 (13)	14 (5)	15 (7)	67 (7)
Asthenia	3 (1)	0 (0)	4 (1)	7 (3)	14 (1)
Investigations	**57 (15)**	**2 (1)**	**46 (15)**	**44 (21)**	**149 (15)**
ALT increased	43 (12)	0 (0)	24 (8)	39 (19)	106 (10)
AST increased	29 (8)	1 (1)	7 (2)	6 (3)	43 (4)
Neutrophil Count Decreased	8 (2)	0 (0)	3 (1)	0 (0)	11 (1)
Transaminases Increased	3 (1)	1 (1)	4 (1)	1 (<1)	9 (1)
Blood CPK increased	2 (1)	0 (0)	7 (2)	1 (<1)	10 (1)
Blood and Lymphatic System Disorders	**49 (13)**	**15 (10)**	**26 (9)**	**25 (12)**	**115 (11)**
Neutropenia	45 (12)	5 (3)	19 (6)	17 (8)	86 (8)
Thrombocytopenia	11 (3)	5 (3)	5 (2)	5 (2)	26 (3)
Febrile Neutropenia	2 (1)	9 (6)	1 (<1)	5 (2)	17 (2)
Anaemia	1 (<1)	2 (1)	7 (2)	0 (0)	10 (1)
Respiratory, Thoracic and Mediastinal Disorders	**11 (3)**	**0 (0)**	**4 (1)**	**4 (2)**	**19 (2)**
Dyspnoea	8 (2)	0 (0)	4 (1)	3 (1)	15 (1)
Infections and infestations	9 (2)	2 (1)	6 (2)	1 (<1)	18 (2)
Infection	6 (2)	1 (1)	0 (0)	1 (<1)	8 (1)
Musculoskeletal and Connective Tissue Disorders	**4 (1)**	**3 (2)**	**3 (1)**	**4 (2)**	**14 (1)**
Rhabdomyolisis	0 (0)	3 (2)	0 (0)	2 (1)	5 (<1)

AE = treatment related adverse event; NOS = not otherwise specified

[a] If a patient had more than 1 occurrence of a specific event, that patient was counted only once for that preferred term.

[b] Study ET-B-008-98 is with the q3wk 24-h schedule for a total of 511 patients with this regimen. The AEs from this study are presented in a separte column since NCI CTC Version 1.0 was used for toxicity grading.

- Serious adverse event/deaths/other significant events

The overall frequency of patients with ≥1 SAE regardless of grade and causality attribution was 28% and was similar across regimens (27% - 29%). The most frequent SAEs were also similar for the 3 regimens: dyspnea, vomiting, nausea, pyrexia, and abdominal pain. Deep vein thrombosis had a frequency of 3% in the q3wk 24-h group but only 1% in the qwk 3-h group and none in the q3wk 3-h group. A total of 10% of patients had drug-related SAEs, with an incidence in the q3wk 24-h group (7%) which was about half that in the q3wk 3-h group (13%). Drug-related SAEs that occurred in more than one patient in the q3wk 24-h group were nausea (2%), vomiting (2%), neutropenia (1%), and pyrexia (1%). A total of 8% of patients had drug-related Grade 3-4 SAEs; the incidence was approximately 2-fold higher in the q3wk 3-h group (12%) compared to the qwk 3-h (7%) and q3wk 24-h (6%) groups.

Drug-related SAEs in ≥1% of Patients in any Dose Group by Preferred Term (Available data population)

Preferred term[a]	Number (%) of patients			
	q3wk 24-h (N=242)	qwk 3-h (N=302)	q3wk 3-h (N=205)	Total (N=749)[b]
Patients with at least 1 drug-related SAE	**17 (7)**	**30 (10)**	**27 (13)**	**74 (10)**
Nausea	5 (2)	11 (4)	4 (2)	20 (3)
Vomiting	5 (2)	10 (3)	6 (3)	21 (3)
Neutropenia	3 (1)	4 (1)	6 (3)	13 (2)
Thrombocytopenia	1 (<1)	0	4 (2)	5 (1)
Febrile Neutropenia	0	1 (<1)	4 (2)	5 (1)
Sepsis	0	3 (1)	0	3 (<1)
Pyrexia	2 (1)	3 (1)	3 (1)	8 (1)
Renal Failure	0	0	4 (2)	4 (1)

SAE = serious adverse event

[a] If a patient had multiple reports of an AE, that patient was counted only once in the preferred term.

[b] Excluding studies ET-B-008-98 (143 patients) and ET-B-005-98 (126 patients).

In the integrated database, of 1018 treated patients, 29 (3%) died in association with an AE occurring during treatment or within 30 days of the last dose of treatment. Similar percent of patients in each group (q3wk 24h 1.8%, qwk 3h 1.0%, q3wk 3h 1.5%) died in association with AEs that were assessed by the investigator to be related to study drug. In the 569 patients database, fatal adverse reactions have occurred in 1.9% of patients. They were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal failure and rhabdomyolysis.

- Laboratory findings

Hepatobiliary disorders

In the 569 patients database transient grade 3 increases of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed in 38% and 44% of the patients and grade 4 elevations in 3% and 7% of the patients, respectively. The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to grade 1 or resolved by day 14-15. Grade 3 elevations of AST and ALT occurred in 12% and 20% of cycles respectively. Grade 4 elevations of AST and ALT occurred in 1% and 2% of cycles respectively. Most transaminase elevations improved to grade 1 or to pre-retreatment levels within 15 days, and less than 2% of cycles had recovering times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time. Grades 1 to 2 bilirubin increases were observed in 23% of the patients. Grade 3 hyperbilirubinemia occurred in 1% of patients. Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset. Clinical manifestations of severe hepatic injury were uncommon with a lower than 1% incidence of individual signs and symptoms including jaundice, hepatomegaly or liver pain. Mortality in the presence of hepatic injury occurred in less than 1% of patients.

In a completed drug combination Phase I study (ET743-USA-11), 8 patients volunteered to undergo liver biopsies. All patients had been treated with a combination of pegylated liposomal doxorubicin and trabectedin 1.1 mg/m2 with dexamethasone prophylaxis. Biopsy findings were consistent with a non-alcoholic steatohepatitis, with severity ranging from minimal steatosis to moderate steatosis with fibrosis. Pre- and post treatment biopsies showed no changes in 3 cases. One patient had minimal post-treatment steatosis. No mitochondrial abnormalities or stellate cell activation were observed.

Hematological Toxicity

In the 569 patients database neutropenia occurred in 77% of patients. Grade 3 and 4 neutropenia occurred in 26% and 24% of patients respectively. The analysis per cycle showed that neutropenia of grade 3 and 4 occurred in approximately 19% and 8% of cycles respectively. Febrile neutropenia occurred in 2% of patients and in < 1% of cycles. Neutropenia followed a predictable pattern of rapid onset and reversibility, and was rarely associated with fever or infection. In the integrated safety database seven patients (1%) in the q3wk 24-h schedule had a grade 3-4 infectious episode concomitant with grade 3-4 neutropenia.

Grade 3 and 4 thrombocytopenia occurred in 11% and 2% of patients respectively. The analysis per cycle showed that thrombocytopenia of grade 3 and 4 occurred in approximately 3% and < 1% of cycles respectively. Bleeding events associated to thrombocytopenia occurred in < 1% of patients.

Anaemia occurred in 93% of patients although 46% of patients were anaemic at baseline. Grade 3 and 4 anaemia occurred in 10% and 3% of patients respectively. The analysis per cycle showed that anaemia of grade 3 and 4 occurred in approximately 3% and 1% of cycles respectively.

A summary of hematological toxicity in the integrated safety database is provided in the following table. Most patients in each group had hematological toxicities of some kind during trabectedin treatment. NCI CTC Grade 3-4 hematological toxicities were highest for neutrophils and WBC and were higher in the q3wk 24-h group than in the other 2 groups.

Hematological Tests by Worst On-treatment Toxicity Grade (Integrated safety database)

Laboratory		Worst On-Treatment Toxicity Grade				
analyte	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
q3wk 24-h (1.5 mg/m^2) (N=511)						
Hemoglobin	375 (73)	11 (3)	119 (32)	180 (48)	49 (13)	16 (4)
Neutrophils	506 (99)	117 (23)	51 (10)	89 (18)	136 (27)	113 (22)
Platelets	304 (59)	159 (52)	44 (14)	30 (10)	60 (20)	11 (4)
WBC	313 (61)	18 (6)	26 (8)	104 (33)	121 (39)	44 (14)
qwk 3-h (0.58 mg/m^2) (N = 302)						
Hemoglobin	297 (98)	57 (19)	163 (55)	60 (20)	13 (4)	4 (1)
Neutrophils	296 (98)	153 (52)	53 (18)	63 (21)	24 (8)	3 (1)
Platelets	297 (98)	237 (80)	40 (13)	9 (3)	10 (3)	1 (<1)
WBC	14 (5)	1 (7)	4 (29)	6 (43)	3 (21)	0
q3wk 3-h (1.3 mg/m^2) (N=205)						
Hemoglobin	205 (100)	18 (9)	109 (53)	65 (32)	11 (5)	2 (1)
Neutrophils	205 (100)	63 (31)	27 (13)	44 (21)	35 (17)	36 (18)
Platelets	205 (100)	130 (63)	46 (22)	8 (4)	16 (8)	5 (2)
WBC	130 (63)	30 (23)	27 (21)	35 (27)	27 (21)	11 (8)
Total (N=1018)						
Hemoglobin	877 (86)	86 (10)	391 (45)	305 (35)	73 (8)	22 (3)
Neutrophils	1007 (99)	333 (33)	131 (13)	196 (19)	195 (19)	152 (15)
Platelets	806 (79)	526 (65)	130 (16)	47 (6)	86 (11)	17 (2)
WBC	457 (45)	49 (11)	57 (12)	145 (32)	151 (33)	55 (12)

CPK elevations of any grade were observed in 26% of patients. Grade 3 or 4 increases of CPK were observed in 4% of patients. CPK increases in association with rhabdomyolysis were reported in less than 1% of patients.

Secondary myelodysplasia and acute leukemia were observed in 3 patients with advanced malignancies that had been treated with trabectedin (as of 31 May 2005, 3087 patients). The diagnosis occurred after administration of 2, 12, and 14 trabectedin treatment cycles. All 3 patients who

developed acute myeloid leukemia had exposure to doxorubicin, and 2 of these patients had prior radiation therapy.

- Safety in special populations

There were no clinically relevant differences in the incidence of AEs, drug-related AEs, AEs leading to discontinuation, or deaths across the following groups:

- Type of Cancer: L-sarcoma, non-L-sarcoma, Other cancers (q3wk 24-h only)
- Age: < 65, ≥ 65.
- Gender: Male, Female.
- Race, Region (US, Canada, Europe), Others, BMI, ECOG.

The safety of trabectedin in pregnant or lactating women has not been established. Whether trabectedin is secreted in milk has not been determined in animals nor in humans.

One pregnancy occurred in a 22-year-old woman with osteosarcoma who was receiving trabectedin 1.3 mg/m2 as a 24-h infusion every 3 weeks under compassionate-use. Study medication was discontinued after 4 cycles of treatment, and the pregnancy was terminated at 20 weeks' gestation. Upon autopsy, the fetus' pathology was normal.

- Safety related to drug-drug interactions and other interactions

No formal analyses of drug-drug or drug-disease interactions were conducted.

- Discontinuation due to adverse events

In the q3wk 24-h group, 67% patients did not require any dose reduction, while 7% had 1 dose reduction, 22% had 2 dose reductions, and 4% had 3 or more dose reductions. The qwk 3-h and the q3wk 3-h regimens required more dose reductions. Most dose reductions were the result of nonhematologic toxicity, whereas hematologic toxicity represented only 2% to 9% and the combination of both toxicities only 1%. In the q3wk 24-h group 56% of patients required 1 (25%), 2 (8%), or 3 or more (24%) treatment cycle delays of any length. Most of those delays were the result of hematologic toxicity (35%), 10% were due to nonhematologic toxicity, and 10% were due to other reasons. The most common reason for discontinuation was disease progression (66%); 8% of patients discontinued treatment in association with AEs. There were no clinically noteworthy differences between treatment groups with respect to reasons for discontinuation.

- Post marketing experience

None available.

- Discussion on clinical safety

Significant hematological and hepatic toxicity has been observed, although toxicity was usually reversible and cumulative toxicity has not been observed. The proposed posology clearly causes a higher incidence of hematologic and hepatic toxicity than the other treatment regimen. The most common Grade 3-4 AEs in the q3wk 24-h dose group were increased ALT (12%), neutropenia (12%), increased AST (8%), and dyspnea, fatigue, nausea, and vomiting (7% each). The most frequent SAEs were dyspnea, vomiting, nausea, pyrexia, and abdominal pain. Liver toxicity usually presenting as transaminitis and neutropenia are considered to be the two dose limiting toxicities. Mortality associated with hepatic injury has been rare (<1%).

The development of rhabdomyolysis (associated with death in 5 patients (0.5%), in the integrated safety database) is of concern and the adherence to the treatment criteria in part 4.2 of the SPC is essential.

The results regarding dose reductions, cycle delays and treatment discontinuations confirm that the proposed posology is close to the threshold where a majority of patients would experience dose limiting toxicity.

The Applicant has provided updated safety data with a cut-off date of April 30th, 2007 (original cut-off date May 31st 2005). Overall, the safety database has been increased with data from 1403 additional patients, whilst the integrated safety database (patients included in clinical trials receiving trabectedin at doses and schedules considered most relevant by the applicant), has been updated with 146 new patients. The updated safety data provided appeared to be consistent with those provided in the initial application (data not shown).

It can be considered that the safety profile has been reasonably characterised. Altogether available safety data showed that despite being manageable, the toxicity of trabectedin is undoubtedly significant. Trabectedin's safety profile appears to be similar to other antineoplastic (i.e. severe and frequent AE, in the context of a life-threatening disease), especially regarding general state conditions (asthenia, anorexia), nausea and vomiting, or haematological toxicity. Updates on hepatotoxic data have been provided. Hepatotoxicity appears to be one of trabectedin's most relevant AE and occurs more frequently with the q3wk 24-h arm. The exact mechanism of injury is still not clear. Considerable increases in liver enzymes are very frequent, are apparently transient, non-cumulative and, especially taking into account the severity of the disease, adequately managed by dose. For the time being, a low incidence of symptomatic hepatic disease with frank liver injury is reported. Hepatotoxicity and rhabdomyolysis appear to be manageable by restrictions, monitoring and dose adjustments. Some of these AE will need to be closely followed by pharmacovigilance activities during post-marketing.

Adequate information is provided in the SPC about posology and method of administration (see SPC section 4.2) and instructions on reconstitution and dilution of the medicinal product before administration (see the SPC section 6.6).

All patients should receive 20 mg of dexamethasone intravenously 30 minutes prior to Yondelis; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

The following criteria are required to allow treatment with Yondelis:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Bilirubin ≤ upper limit of normal (ULN)
- Alkaline phosphatase ≤ 2.5 ULN (consider hepatic isoenzymes 5-nucleotidase or GGT, if the elevation could be osseous in origin).
- Albumin ≥ 25 g/l.
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 2.5 x ULN
- Creatinine clearance ≥ 30 ml/min
- Creatine phosphokinase (CPK) ≤ 2.5 ULN
- Haemoglobin ≥ 9 g/dl

The same criteria as above should be met prior to re-treatment. Otherwise treatment should be delayed for up to 3 weeks until the criteria are met.

Additional monitoring of haematological parameters bilirubin, alkaline phosphatase and aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

The same dose should be given for all cycles provided that no grade 3-4 toxicities are seen and that the patient fulfils the re-treatment criteria.

Prior to re-treatment, patients should fulfil the baseline criteria defined above. If any of the following events occur at any time between cycles, the dose must be reduced to 1.2 mg/m^2 for subsequent cycles:

- Neutropenia < 500/mm3 lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia < 25,000/mm3

- Increase of bilirubin > ULN and/or alkaline phosphatase> 2.5 x ULN
- Increase of aminotransferases (AST or ALT) > 2.5 x ULN which has not recovered by day 21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced to 1 mg/m^2. In the event that further dose reductions are necessary, treatment discontinuation should be considered.

In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted. Trabectedin has been administered for 6 or more cycles in 24% of patients treated with the proposed dose and schedule. This regime has been used for up to 38 cycles. No cumulative toxicities have been observed in patients treated with multiple cycles.

Paediatric patients

The safety and efficacy of trabectedin in paediatric patients has not yet been established. Therefore, this medicinal product should not be used in children and adolescents until further data become available.

Elderly patients

No specific studies in elderly patients have been performed. Overall 18% of the 1018 patients in the integrated safety analysis were over 65 years. No relevant differences in the safety profile were seen in this patient population. It seems that plasma clearance and distribution volume of trabectedin are not influenced by age. Therefore, dose adjustments based uniquely on age criteria are not routinely recommended.

Patients with impaired hepatic function

No studies with the proposed regime have been conducted in patients with liver dysfunction. Thus, data are not available to recommend a lower starting dose in patients with hepatic impairment. However special caution is advised and dose adjustments might be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin should not be treated with Yondelis (see section 4.4).

Patients with impaired renal function

Studies including patients with severe renal insufficiency (creatinine clearance < 30 ml/min) have not been conducted and therefore Yondelis should not be used in this patient population (see section 4.4). Considering the pharmacokinetic characteristics of trabectedin (see section 5.2), no dose adjustments are warranted in patients with mild or moderate renal impairment.

Yondelis is contraindicated (see SPC section 4.3) in patients with hypersensitivity to trabectedin or to any of the excipients, concurrent serious or uncontrolled infection, in patients who are breastfeeding (see section SPC 4.6), or in combination with yellow fever vaccine (see SPC section 4.4)

Adequate warnings are provided in the SPC section 4.4. Patients must meet specific criteria on hepatic function parameters to start treatment with Yondelis. Since systemic exposure to trabectedin is probably increased due to hepatic impairment and because the risk of hepatotoxicity might be increased, patients with clinically relevant liver diseases, such as active chronic hepatitis, must be closely monitored. Dose adjustment may be necessary. Patients with elevated bilirubin should not be treated with trabectedin (see SPC section 4.2). Creatinine clearance must be monitored prior to and during treatment. Trabectedin should not be used in patients with creatinine clearance < 30 ml/min (see SPC section 4.2). Grades 3 or 4 neutropenia and thrombocytopenia associated with trabectedin therapy have been very commonly reported. A full blood cell count including differential and platelet count should be performed at baseline, weekly for the first two cycles and then once between cycles (see SPC section 4.2). Patients who develop fever should promptly seek medical attention. If this occurs, active supportive therapy should be started immediately. Anti-emetic prophylaxis with dexamethasone should be administered to all patients (see SPC section 4.2). Trabectedin should not be used in patients with CPK > 2.5 ULN (see SPC section 4.2). Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities and/or

renal failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinization and dialysis should be promptly established, as indicated. Treatment with Yondelis should be discontinued until full recovery. Reversible acute increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been reported in most patients. Yondelis should not be used in patients with elevated bilirubin. Patients with increases in AST, ALT and alkaline phosphatase between cycles may necessitate dose reduction (see SPC section 4.2). The use of central venous access is strongly recommended (see SPC section 4.2). Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line. Co-administration of Yondelis with potent inhibitors of the enzyme CYP3A4 should be avoided (see SPC section 4.5). If this is not possible, close monitoring of toxicities are required and dose reductions of trabectedin should be considered. Caution should be taken if active substances associated with hepatotoxicity or rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of these toxicities may be increased. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended (see SPC section 4.3).

The concomitant use of trabectedin with alcohol should be avoided (see SPC section 4.5). Men in fertile age and women of childbearing potential must use effective contraception during treatment and 3 months thereafter for women and immediately inform the treating physician if a pregnancy occurs, and 5 months after treatment for men (see SPC section 4.6).

Interactions with other medicinal products and other forms of interaction are adequately described in the SPC (see SPC section 4.5). *In vivo* interaction studies have not been performed. Since trabectedin is metabolised mainly by CYP3A4, co-administration of substances that inhibit this isoenzyme e.g. ketoconazole, fluconazole ritonavir or clarithromycin could decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required (see SPC section 4.4). Likewise co-administration with potent inducers of this enzyme (e.g. rifampicin, phenorbarbital, Saint John's Wort) may decrease the systemic exposure to trabectedin.

Alcohol consumption should be avoided during treatment with trabectedin due to the hepatotoxicity of the product (see SPC section 4.4). Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of Pgp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. CNS toxicity has not been established. Caution should be taken in such situations.

Adequate information has been included in the SPC concerning pregancy and lactation (see SPC section 4.6). No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action, trabectedin may cause serious birth defects when administered during pregnancy. Trabectedin should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus (see SPC section 5.3) and be monitored carefully. If trabectedin is used at the end of pregnancy, potential adverse reactions should be monitored carefully in the newborns. Men in fertile age and women of childbearing potential must use effective contraception during treatment and 3 months thereafter for women and immediately inform the treating physician if a pregnancy occurs (see SPC section 5.3) and 5 months after treatment for men (see SPC section 4.4). Trabectedin can have genotoxic effects. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Yondelis. If pregnancy occurs during treatment the possibility of genetic counselling should be considered. Genetic counselling is also recommended for patients wishing to have children after therapy. It is not known whether trabectedin is excreted in human milk. The excretion of trabectedin in milk has not been studied in animals. Breast-feeding is contraindicated during treatment and 3 months thereafter (see SPC section 4.3).

No studies on the effects of the ability to drive and to use machines have been performed. However, fatigue and/or asthenia have been reported in patients receiving trabectedin. Patients who experience any of these events during therapy should not drive or operate machines (see SPC section 4.7).

There is limited data on the effects of trabectedin overdose. The major anticipated toxicities are gastrointestinal, bone marrow suppression and hepatic toxicity. There is no specific antidote for trabectedin currently available. In the event of an overdose, patients should be closely monitored and symptomatic supportive care measures instituted as required (see SPC section 4.9).

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management plan

The MAA submitted a risk management plan (RMP). The updated version of the RMP is in accordance with the EU-RMP template in most relevant aspects. Information on patient exposure has been updated. Data on most relevant identified risks, including hepatoxicity, CPK elevations/rhabdomyolysis, neutropenia, thrombocytopenia, anaemia, infections, myelodysplasia and AML, emesis and local infusions has been updated. Newly identified potential risks which arose during the procedure, including pancreatic, renal, retinal and cardiovascular toxicities have been added. No additional measures for these potential risks are deemed necessary at this stage other than those proposed by the applicant (routine pharmacovigilance measures and monitoring of currently ongoing clinical data).

Safety and efficacy of trabectedin in patients under 18 has not been established. The MAH addressed the potential risk of off-label use, which is considered low by the applicant due to the control cytotoxics are exposed to. This matter is reflected in the SPC.

Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potential risk in off-label paediatric use.	Routine Pharmacovigilance	Risk minimisation by SPC. Yondelis is not indicated for paediatric use (SPC section 4.2).
Risk of accidental Exposure to trabectedin in uterus.	Routine Pharmacovigilance	Risk minimisation by SPC. Patients of both genders are to avoid conception (4.6). Contraindication: Breast-feeding (4.3).
Risk in patients with severe renal impairment.	Routine Pharmacovigilance	Risk minimisation by SPC. Not recommended in patients with severe renal impairment (4.2). Treatment criteria includes renal function test (4.2). Warning (4.4). Renal events are labelled as uncommon (4.8).
Risk in patients with hepatic impairment.	Routine Pharmacovigilance	Risk minimisation by SPC. Strict treatment criteria include evaluation of LFTs. Regular monitoring of LFTS is required. Dose adjustment guidelines provided in case of LFTs abnormalities (4.2). Special caution recommended for patients with impaired hepatic function in section 4.2. Warning: treatment should not be given if bilirubin is elevated (4.4). Hepatic events labelled in section 4.8.
Hepatic reactions	Routine Pharmacovigilance	Risk minimisation by SPC. Strict treatment criteria include evaluation of LFTs. Regular monitoring of LFTS is required. Dose adjustment guidelines provided in case of LFTs abnormalities (4.2). Special caution in patients with impaired liver function (4.2). Warnings: AST/ALT elevations, treatment should not be given if bilirubin is elevated (4.4). Hepatic events labelled in section 4.8.
Neutropenia and infection	Routine Pharmacovigilance	Risk minimisation by SPC. Strict treatment criteria include neutrophil test. Regular monitoring required. Dose adjustment guidelines provided in case of haematology abnormalities (4.2). Contraindication: Ongoing serious or uncontrolled infection (4.3). Warning of neutropenia and advice if fever occurs (4.4). Neutropenia and neutropenic fever events are labelled as expected (4.8).
Thrombocytopenia/bleeding	Routine Pharmacovigilance	Risk minimisation by SPC. Strict treatment criteria include platelets tests. Regular monitoring required. Dose adjustment guidelines provided in case of haematology abnormalities (4.2). Warning of thrombocytopenia (4.4). Thrombocytopenia is labelled as expected (4.8).
Anaemia	Routine Pharmacovigilance	Risk minimisation by SPC. Strict treatment criteria include haemoglobin test. Regular monitoring required. Dose adjustment guidelines provided in case of haematology abnormalities (4.2). Anaemia is labelled as expected (4.8).
CPK elevations/ Rhabdomyolysis	Routine Pharmacovigilance	Risk minimisation by SPC. Strict treatment criteria include CPK test (4.2). Warning of rhabdomyolysis and severe CPK elevations. Clinical context in which it appears and recommendations for clinical measures are provided (4.4). CPK increases and rhabdomyolysis are labelled as expected (4.8).
Emesis	Routine Pharmacovigilance	Risk minimisation by SPC. Preventive anti-emetic prophylaxis is required (4.2). Nausea and vomiting are labelled as expected (4.8).
Dyspnoea	Routine Pharmacovigilance	Risk minimisation by SPC. Dyspnoea is labelled as expected (4.8).

Local infusion reactions	Routine Pharmacovigilance	Risk minimisation by SPC. Administration via a central venous line is recommended in sections 4.2. Handling precautions given in section 6.6.
Myelodysplasia/AML	Routine Pharmacovigilance	Routine PV (particular attention will be paid to publication of this type of cases in the medical literature).
Renal toxicity	Routine Pharmacovigilance	Risk minimisation by SPC section 4.4 Creatinine clearance must be monitored prior to and during treatment. Trabectedin should not be used in patients with creatinine clearance < 30 ml/min (see section 4.2).
Pancreatic toxicity	Routine Pharmacovigilance	None
Cardiovascular toxicity	Routine Pharmacovigilance	None
Retinal toxicity	Routine Pharmacovigilance	None
Potential risk of interactions with other medicinal products.	Routine Pharmacovigilance	Risk minimisation by SPC section 4.4 and 4.5
Potential for medication error including overdose	Routine Pharmacovigilance	Risk minimisation by SPC. Posology, dosage adjustment and preparation instructions are provided in the SPC. Recommended measures in case of overdose are provided in section 4.9.
Potential for transmission of infectious agent	Routine Pharmacovigilance	Risk minimisation by SPC. The product is to be used by specialised personnel (4.2). Instructions for aseptic preparation of the iv infusion and for appropriate disposal are provided (6.6).
Potential for misuse	Routine Pharmacovigilance	The SPC sets the recommended use and disposal of the product.
Potential for off-label use	Routine Pharmacovigilance	The approved therapeutic indications are indicated in section 4.1. The product is to be used by specialized personnel (4.2) and is under prescription.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

Trabectedin was initially obtained by isolation from *Ecteinascidia turbinata* but was subsequently produced synthetically, which resulted in a decrease in the level of impurities. The excipients used in the preparation of the product were chosen based on the physico-chemical properties of the active substance and the intended route of administration (intravenous), which precluded the use of several excipients. The results showed that both the active substance and the finished product can be manufactured reproducibly. This indicates that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The Applicant gave a Letter of Undertaking and committed to resolve the Follow Up Measures after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology

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 sarcoma, breast, non-small cell lung, ovarian and melanoma.

Preclinical data indicate that trabectedin has limited effect on the cardiovascular, respiratory and central nervous system at exposures below the therapeutic clinical range, in terms of AUC.

The effects of trabectedin on cardiovascular and respiratory function have been investigated *in vivo* (anesthetised Cynomolgus monkeys). A 1 hour infusion schedule was selected to attain maximum plasma levels (C_{max} values) in the range of those observed in the clinic. The plasma trabectedin levels attained were 10.6 ± 5.4 (C_{max}), higher than those reached in patients after infusion of 1500 µg/m^2 for 24 (C_{max} of 1.8 ± 1.1 ng/ml) and similar to those reached after administration of the same dose by 3 hour infusion (C_{max} of 10.8 ± 3.7 ng/ml).

Myelosupression and hepatoxicity were identified as the primary toxicity for trabectedin. Findings observed included haematopoietic toxicity (severe leukopenia, anaemia, and lymphoid and bone marrow depletion) as well as increases in liver function tests, hepatocellular degeneration, intestinal

epithelial necrosis, and severe local reactions at the injection site. Renal toxicological findings were detected in multi-cycle toxicity studies conducted in monkeys. These findings were secondary to severe local reaction at the administration site, and therefore uncertainly attributable to trabectedin; however, caution must be guaranteed in the interpretation of these renal findings, and treatment-related toxicity cannot be excluded.

Trabectedin is genotoxic both *in vitro* and *in vivo*. Long-term carcinogenicity studies have not been performed.

Fertility studies with trabectedin were not performed but limited histopathological changes were observed in the gonads in the repeat dose toxicity studies. Considering the nature of the compound (cytotoxic and mutagenic), it is likely to affect the reproductive capacity.

Efficacy

The efficacy and safety of trabectedin is based in a randomised trial in patients with locally advanced or metastatic liposarcoma or leiomyosarcoma, whose disease had progressed or relapsed after treatment with at least anthracyclines and ifosfamide. In this trial trabectedin was administered either at 1.5 mg/m^2 as a 24-hour intravenous infusion every 3 weeks or at 0.58 mg/m^2 weekly as a 3-hour intravenous infusion for 3-weeks of a 4-week cycle. The protocol specified final time to progression (TTP) analysis showed a 26.6% reduction in the relative risk of progression for patients treated in the 24-h q3wk group (Hazard Ratio = 0.734 CI 0.554-0.974). Median TTP values were 3.7 months (CI: 2.1-5.4 m) in the 24-h q3wk group and 2.3 months (CI: 2.0-3.5 m) in the 3-h qwk group (p=0.0302). No significant differences were detected in overall survival (OS). Median OS with the 24-h q3wk regime was 13.9 months (CI: 12.5-18.6) and 60.2% of patients were alive at 1 year (CI: 52.0-68.5%). Additional efficacy data are available from 3 single-arm Phase II trials with similar populations treated with the same regime. These trials evaluated a total of 100 patients with lipo and leiomyosarcoma and 83 patients with other types of sarcoma.

Safety

The safety database is formed by 1018 patients, which constituted the "integrated safety database" for the initial safety summary. No further safety signals had been identified in the 2000 additionally exposed patients when the initial documents were submitted. Updates on renal, pancreatic, ophtalmological and cardiac, toxicity have been provided for the 1200 patients who have been exposed to trabectedin since then.

The most common AEs in all 3 treatment groups were nausea (60%), fatigue (50%), vomiting (35%), and constipation (18%). The most common (≥5%) Grade 3-4 AEs in the q3wk 24-h dose group were increased ALT (12%), neutropenia (12%), increased AST (8%), and dyspnea, fatigue, nausea, and vomiting (7% each). The incidence of increased ALT (12% vs.9%), neutropenia (12% vs. 6%) and increased AST (8% vs. 3%) was consistently higher in the proposed q3wk 24-h dose group.

Liver toxicity usually presenting as transaminitis and neutropenia are considered to be the two dose limiting toxicities. A considerably higher number of patients in the proposed q3wk 24-h regimen developed grade 3 (41% vs. 12%) and grade 4 (7% vs. 0%) liver toxicity (ALT-elevations) compared to the qwk 3-h arm of the pivotal study. A similar pattern of increased toxicity in the proposed q3wk 24-h treatment arm was observed for other liver function tests like AST and bilirubin.

Hematological toxicity was substantially and consistently higher in the q3wk 24-h group compared to the qwk 3-h group: grade 3/4 anemia (13% / 4% vs. 4% / 1%), grade 3/4 neutropenia (27% / 22% vs. 8% / 1%) and grade 3/4 platelets (20% / 4% vs. 3% / <1%). The incidence of grade 3/4 bleeding was rare (approximately 1 %).

4% of patients developed febrile neutropenia in the proposed q3wk 24-h regimen compared to less than 1% in the qwk 3-h group. The frequency was lower in Study ET743-STS-201, where it was 1.6% in each treatment arm.

CPK elevations of any grade based on laboratory values were observed in 20% of patients, regardless of the dosing regimen. The development of rhabdomyolysis (associated with death in 5 patients (0.5%), in the integrated safety database) is of concern.

From the safety database the adverse reactions reported in clinical trials have been appropriately described in the Summary of Product Characteristics. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

Readability testing has been conducted and the readability of the package leaflet is adequate. Some aspects regarding the understanding of the leaflet, however, will require confirmation through additional data and will be assessed as a follow-up measure.

Risk-benefit assessment

The pivotal study failed to formally demonstrate statistical significance in its primary objective at the interim analysis as defined in the original protocol but shows a difference between the two treatment arms favoring the proposed posology of q3wk 24-h. The difference was observed in terms of TTP, and despite methodological weaknesses in the trial design and conduct, a number of sensitivity analyses and updated analyses support this conclusion. Secondary endpoints, including PFS and overall survival, and previous phase II studies also support the demonstration of benefit in this indication.

Ideally, Yondelis should have been compared in an adequately designed and analysed randomised trial to best care or investigator's choice. Unfortunately, a direct comparison of the efficacy of trabectedin compared to best care or investigator's choice is not possible because no internal control arm has been used in the pivotal study. The applicant has claimed that a comparison to best supportive care is considered very difficult in this patient population.

Adequate exploratory data should be made available to identify patients that are most likely to respond. The population of soft tissue sarcoma patients after failure of anthracyclines and ifosfamide is considered to be heterogenous and clinical efficacy data for Yondelis are mainly based on L-sarcoma. Still, individual subpopulations are considered too rare for adequately powered randomized controlled trials to be conducted against best supportive care to explore factors associated with response to treatment within reasonable time. Thus, due to the rarity of the disease the CHMP has considered that the marketing authorisation could be granted under exceptional circumstances. The applicant has committed to explore further the population that might benefit most from the treatment as a specific obligation.

The available safety data showed that the toxicity of trabectedin is undoubtedly significant but manageable. A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Yondelis is not similar to Glivec or Sutent within the meaning of Article 3 of Commission Regulation (EC) No. 847/200, due to differences in the structure and mechanism of action.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Yondelis in the "treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents; efficacy data are based mainly on liposarcoma and leiomyosarcoma patients," was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.

And

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Yondelis not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Glivec or Sutent for the same therapeutic indication.