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 ($\geq$ 1/10), common ($\geq$ 1/100 to < 1/10) and uncommon ($\geq$ 1/1000 to < 1/100).

The table below displays the adverse reactions reported in $\geq$ 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)**
Rhabdomyolysis	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 separate 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 analyte	n (%)	Worst On-Treatment Toxicity Grade				
		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: $< 65, \geq 65$.
- 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) $\geq$ 1,500/mm^3
- Platelet count $\geq$ 100,000/mm^3
- Bilirubin $\leq$ upper limit of normal (ULN)
- Alkaline phosphatase $\leq$ 2.5 ULN (consider hepatic isoenzymes 5-nucleotidase or GGT, if the elevation could be osseous in origin).
- Albumin $\geq$ 25 g/l.
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) $\leq$ 2.5 x ULN
- Creatinine clearance $\geq$ 30 ml/min
- Creatine phosphokinase (CPK) $\leq$ 2.5 ULN
- Haemoglobin $\geq$ 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.