EU Risk Management Plan
for
Yondelis®
(trabectedin)

RMP version to be assessed as part of this application:	
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Summary of significant changes in this RMP:	No major changes have been made
Other RMP versions under evaluation:	
RMP Version number:	Not applicable
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QPPV Name(s):	Dr. Hervé Dhellot, MSc
QPPV Oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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Abbreviations

ADR	Adverse Drug Reactions
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
AP	Acute Pancreatitis/Alkaline Phosphatase
APC	Adenomatous Polyposis Coli
ASR	Age-Standardised Rate
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BBB	Blood-Brain Barrier
BRCA	BReast CAncer gene
CAS	Chemical Abstracts Service
CCDS	Company Core Data Sheet
CCI	Charlson's Comorbidity Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
Cmax	Maximum Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CYP	Cytochrome-P450
DNA	Deoxyribonucleic Acid
EAP	Expanded Access Programme
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EEA	European Economic Area
EMA	European Medicines Agency
EOC	Epithelial Ovarian Cancer
EORTC	European Organisation for the Research and Treatment of Cancer
EPAR	European Public Assessment Report
ESMO	European Society of Medical Oncology
EU	European Union
AURACAN	European Reference Network on Rare Adult Cancers
FIGO	International Federation of Gynaecology and Obstetrics
G	Grade
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumours
GLP	Good Laboratory Practice
HGSC	High Grade Serous Carcinoma
HR	Hazard Ratio
HRD	Homologous Recombination Deficiency

IIS	Investigator-Initiated Study
IND	Investigational New Drug
INN	International Non-proprietary Name
IPCT	Intraperitoneal Chemotherapy
IQR	Interquartile Range
ISA	Integrated Safety Analysis
ISS	Integrated Safety Summary
ITT	Intention-To-Treat
i.v.	Intravenous
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndrome(s)
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mechanism of Action
MPM	Malignant Pleural Mesothelioma
MTD	Maximum Tolerated Dose
NF	Neurofibromatosis
NOS	Not Otherwise Specified
NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotrophic Tyrosine Receptor Kinase
OS	Overall Survival
PARP	Poly ADP Ribose Polymerase
PFI	Progression-Free Interval
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PL	Patient Leaflet
PLD	Pegylated Liposomal Doxorubicin
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTC	Premature Termination Codon
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
ROC	Relapsed Ovarian Cancer
RRP	Recommended Regimen Population
SAE	Serious Adverse Event
SEER	Surveillance, Epidemiology, and End Results (SEER) Programme of the National Cancer Institute
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
STS	Soft Tissue Sarcoma
SXR	Steroid and Xenobiotic Receptor
TFI	Treatment-Free Interval
TNF	Tumour Necrosis Factor

TRS	Translocation-Related Sarcoma
TSC	Tuberous Sclerosis Complex
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VEGF	Vascular Endothelial Growth Factor
WRN	Werner syndrome gene

Part I: Product(s) Overview

Active substance(s) (INN or common name)	Trabectedin
Pharmacotherapeutic group(s) / (ATC Code)	Antineoplastic agent (L01CX01)
Marketing Authorisation Holder	Pharma Mar, S.A. Avda. de los Reyes 1, Pol. Ind. La Mina 28770 Colmenar Viejo (Madrid), Spain
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Yondelis®
Marketing Authorisation procedure	Centralised Procedure
Brief description of the product	**Chemical class:** Trabectedin (Yondelis®, R279741), formerly known as ecteinascidin 743 (ET-743), is a novel tetrahydroisoquinoline alkaloid compound with unique antitumour properties and mechanism of action. Trabectedin was originally obtained from the Caribbean tunicate *Ecteinascidia turbinata* and it is currently prepared synthetically. **Chemical name:** Chemical Abstracts Service (CAS) registry number: (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-5-(acetyloxy)- 3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16-epithiopropanoxymethano)-7,13-imino-12*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-19-one. **Molecular formula:** The molecular formula is $C_{39}H_{43}N_3O_{11}S$. **Molecular weight:** The molecular weight of trabectedin is 761.84 g/mol. **Solubility:** Trabectedin is hydrophobic and has a low solubility in water. Trabectedin solubility is enhanced in acidic media.
	Summary of mode of action: Trabectedin binds to the minor groove of deoxyribonucleic acid (DNA), bending the helix towards 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 also prevents the binding of translocation-related fusion proteins to DNA promoter regions thereby deregulating the expression of proteins known to impact tumour growth and progression. Additionally, trabectedin has been shown to influence the tumour microenvironment by targeting tumour-associated macrophages and histiocytes in both preclinical models and biopsy samples from trabectedin-treated soft tissue sarcoma (STS) patients. 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 cancer, non-small cell lung cancer, ovarian cancer and melanoma.
	Important information about its composition: **Formulation information:** Yondelis® is provided as a sterile powder for concentrate for solution for infusion in two strengths, 0.25 mg and 1 mg. Inactive ingredients are sucrose, potassium dihydrogen phosphate, phosphoric acid and potassium hydroxide. Each vial of trabectedin for injection is a single use vial. For full information about pharmaceutical particulars, see Yondelis® Summary of Product Characteristics

Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/yondelis-epar-product-information_en.pdf
Indication(s) in the EEA	**Current:** Yondelis® is indicated for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. Yondelis® in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with platinum sensitive relapsed ovarian cancer (ROC).
	Proposed: Not applicable.
Dosage in the EEA	**Current:** <u>Posology</u> For the treatment of STS, the recommended dose is 1.5 mg/m^2 body surface area, administered as an intravenous (i.v.) infusion over 24 hours with a 3-week interval between cycles. For the treatment of ROC, Yondelis® is administered every 3 weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. To minimise the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1-hour period. All patients must receive corticosteroids, e.g., 20 mg of dexamethasone i.v. 30 minutes prior to PLD (in combination therapy) or Yondelis® (in monotherapy) not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed. Dosage adjustments are required under the criteria specified in the Summary of Product Characteristics (SmPC). <u>Method of administration</u> Intravenous administration through a central venous line is strongly recommended (see sections 4.4 and 6.6 of SmPC). For instructions on reconstitution and dilution of the medicinal product before administration see section 6.6 of SmPC.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	**Current:** Powder for concentrate for solution for infusion. Vial containing 0.25 mg trabectedin. Vial containing 1mg trabectedin.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication: Soft tissue sarcoma (STS)/Relapsed ovarian cancer (ROC)

Yondelis® is indicated for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. Yondelis® in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with platinum-sensitive ROC.

Soft tissue sarcoma

Incidence and prevalence

Soft tissue sarcomas constitute a heterogeneous group of rare solid tumours that account for only 1-2% of all cancers in adults and 7% in children and adolescents (1). Considering all adult STS, the most common histotypes include liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma. Approximately 40% to 50% of STS occur in the extremities, and approximately 13% occur in the trunk (2).

In 2024, it is estimated that about 13,590 new STSs will be diagnosed (7,700 in males and 5,890 in females) and about 5,200 people (2,760 males and 2,440 females) are expected to die of STSs in the United States (US) (3). In Europe, STSs present an age-standardised rate (ASR) of 1.5-3.0/100,000/year, being moderately more frequent in males than females. The most common STS histotypes in Europe have been reported as leiomyosarcoma (19%), liposarcoma (16%), and sarcoma not otherwise specified (14%) (4).

Demographics of the population in the authorised indication and risk factors

STS can occur at any age and in any part of the body, but the incidence of the different histological subtypes varies with age: synovial sarcomas, rhabdomyosarcomas and Ewing's sarcomas are more likely to occur in young adults, whereas malignant fibrous histiocytoma and leiomyosarcomas are more frequent in the elderly, and liposarcomas are generally diagnosed in patients aged 40-50 years (5).

A retrospective study using data from 33,803 patients from the regional German cancer registries showed that median age of patients was 65 years (interquartile range [IQR] [Q1, Q3]: 51-75 years), with 26% of patients being aged 75 years or older. Overall, 15% of patients were diagnosed between age 18 and 44; 15% between 45 and 54; 18% between 55 and 64; 26% between 65 and 74; 26% from 75 and more years. All STS were evenly distributed between males and females. Overall, the most common histologic categories were leiomyosarcoma (19%), liposarcoma (16%), sarcoma not otherwise specified (NOS) (14%), fibroblastic/myofibroblastic (12%), fibrohistiocytic (10%), and tumours of uncertain differentiation (9%). The most common anatomic locations of primary tumour were lower extremity (20%), trunk (15%), head or neck (12%), miscellaneous (11%), and upper extremity (8%) (6). A population-based epidemiologic study in Austria of 5,333 patients from 1984 to 2004, reported the male-to-female ratio of 0.8 (2,317 males and 3,016 females). The age predilection revealed that STS in general are malignancies of the advanced age as an analysis of age distribution showed a peak incidence of STS around the age of 60 years and a second, modest peak in early childhood (0–5 years). The most common histotypes were sarcoma NOS (36%), leiomyosarcoma (24%), liposarcoma (12%), malignant fibrous histiocytoma (9%) and fibrosarcoma (5%) (5). A retrospective Italian study using data from 859 patients with STS and diagnosed from 2009 to 2012 reported similar median age of patients: 62 years (IQR: 42-74 years). As regards to site, STS arose mainly in the lower extremities (35.6%) and trunk (33.6%). Of the 859 STS diagnosed, 29.4% were sarcoma NOS, 22.2% were liposarcoma, 20.4% were fibrosarcoma, 16.1% were leiomyosarcoma, and 4.4% were rhabdomyosarcoma (4). Lastly, a retrospective registry study with data from 5,384 patients with STS from Switzerland between 1996 and

2015 also reported that the three most common STS subtypes were undifferentiated/unclassified sarcoma (22.3%), liposarcoma (20.6%) and leiomyosarcoma (20.6%) (7).

In the US soft tissue cancer represents 0.7% of all new cancer cases. Approximately 7.2% were diagnosed under age 20; 8.9% between 20 and 34; 8.5% between 35 and 44; 11.8% between 45 and 54; 18.1% between 55 and 64; 21.6% between 65 and 74; 15.9% between 75 and 84; and 7.9% from 85 and more years of age. The age-adjusted incidence rate was 3.4 per 100,000 men and women per year. These rates are based on cases diagnosed between 2017 and 2021 from 22 SEER (Surveillance, Epidemiology, and End Results Programme of the National Cancer Institute) geographic areas. The median age at death for cancer of the soft tissue including heart was 67 years old. Approximately 3.3% died under age 20; 5.4% between 20 and 34; 5.6% between 35 and 44; 10.2% between 45 and 54; 18.9% between 55 and 64; 24.0% between 65 and 74; 20.8% between 75 and 84; and 11.9% 85 and more years of age. The age-adjusted death rate was 1.3 per 100,000 men and women per year. These rates are based on patients who died between 2018 and 2022 in the US (8).

The risk of sporadic STSs is increased by prior radiation therapy and, in the case of lymphangiosarcoma, by chronic lymphedema. The chemicals thorotrast, vinyl chloride, and arsenic are also established as carcinogens for hepatic angiosarcomas. STSs occur with greater frequency in patients with the following inherited syndromes (9):

- → Nevoid basal cell carcinoma syndrome (Gorlin syndrome: premature termination codon [PTC] gene mutation).
- → Gardner syndrome (adenomatous polyposis coli [APC] mutation).
- → Li-Fraumeni syndrome (p53 mutation).
- → Tuberous sclerosis (Bourneville disease: tuberous sclerosis complex [TSC]1 or TSC2 mutation).
- → Von Recklinghausen disease (neurofibromatosis type [NF]1 mutation).
- → Werner syndrome (adult progeria: WRN gene mutation).

The main existing treatment options

Current treatment options for STS include surgery, radiotherapy and chemotherapy (2). Based on the current European Society of Medical Oncology (ESMO) Network for rare adult cancers (ESMO)–European Reference Network on Rare Adult Cancers (EURACAN) Clinical Practice Guidelines (10), surgery is the standard treatment of all patients with an adult type, localised STS. In advanced STS, doxorubicin-based regimens are standard first line chemotherapy. Options for second and later lines include trabectedin, ifosfamide, pazopanib, eribulin and gemcitabine-based regimens (11).

Localised disease: Surgery is the standard treatment of all patients with an adult type, localised STS. The standard surgical procedure is an en bloc excision with negative margins (absence of residual tumour, R0) (12).

The typical wide excision is followed by radiotherapy as the standard treatment of high-grade (G2–3) lesions. Radiotherapy should not be given in the case of a currently unusual, truly compartmental resection of a tumour entirely contained within the compartment (12).

Reexcision at reference centres must be considered in case of unplanned resections, if adequate margins can be achieved without major morbidity, and taking into account tumour extent and tumour biology. In the case of R2 surgery (macroscopic tumour at the margin), reoperation in reference centres is mandatory, possibly following preoperative treatments if adequate margins cannot be achieved, or if surgery is mutilating. When re-excision is not possible after R1-R2 resections, post-operative radiotherapy may be considered. Amputation may be the only option in certain cases. Options for limb-preserving surgery may include chemotherapy and/or radiotherapy, or isolated limb perfusion with tumour necrosis factor-a (TNF-a) plus melphalan. Perioperative regional hyperthermia combined with chemotherapy is another option (12).

Regional lymph node metastases should be distinguished from systemically arising metastases. These are rare and constitute an adverse prognostic factor in adult-type STSs. Surgery through wide excision may be coupled with adjuvant radiation therapy and adjuvant chemotherapy for sensitive histological types, as standard treatment of these presentations. Chemotherapy may be administered as preoperative treatment. Adjuvant chemotherapy is not standard treatment in adult-type STS and can be proposed as an option to the high-risk individual patient for shared decision making with the patient. Adjuvant chemotherapy is not used in histological subtypes known to be chemoresistant. If used, adjuvant chemotherapy should consist of the combination chemotherapy regimens proven to be most active in advanced disease. Radiation therapy should not delay the start of chemotherapy (12).

Advanced/metastatic disease: The decision making is complex, depending on diverse presentations and histologies, and should always be multidisciplinary. A summary of recommendations is presented (12):

- → Metachronous (disease-free interval ≥1 year), resectable lung metastases without extrapulmonary disease are managed with surgery as standard treatment if complete excision of all lesions is feasible.
- → Standard chemotherapy is based on anthracyclines as first-line treatment. Multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide or dacarbazine may be the treatment of choice; particularly in subtypes sensitive to ifosfamide or dacarbazine, when a tumour response is felt to be potentially advantageous and patient performance status is good.
- → Gemcitabine/docetaxel combination is not generally recommended as a first-line therapy for advanced STS patients.
- → Imatinib is standard medical therapy for patients with dermatofibrosarcoma protuberans.
- → Neurotrophic tyrosine receptor kinase (NTRK) inhibitors are standard treatment of patients with advanced NTRK-rearranged sarcomas. They can be considered also in the preoperative setting, when a cytoreduction can improve morbidity and function.
- → Trabectedin is an option for second line and beyond and is approved for advanced previously treated STS.
- → Pazopanib is an option in non-adipogenic STS in second and further lines of treatment.
- → Eribulin is an option in patients with liposarcomas.
- → The combination of dacarbazine and gemcitabine or gemcitabine/docetaxel is an option in doxorubicin-pre-treated patients.

Finally, best supportive care alone is an option for unfit patients with advanced STS, especially if further-line therapies have already been used. Radiation therapy should be used as a palliative resource in all cases as appropriate to the clinical need (13).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Despite available chemotherapy, the prognosis for patients with STS is very poor, with an estimated median survival of 8-14 months from the start of first-line anthracycline-based cytotoxic therapy, as shown in randomised trials performed over the last several decades (8, 14, 15). In the US , the annual mortality rate for STS is estimated to be 5,200 deaths per year in 2024 and the overall 5-year survival rate for STS is 65.9% (8).

Important co-morbidities:

van Herk-Sukel et al. conducted, in 2012, the first population-based study to report on the prevalence of concomitant diseases at STS diagnosis and the incidence of comorbidities after STS diagnosis and treatment. The authors showed that 33% of the patients with STS suffered from cardiovascular disease (including hypertension) at time of diagnosis, and 10% had evidence of respiratory disease. Diabetes,

anaemia, and depression occurred in 6-7% of the patients at time of diagnosis (9). These findings were supported by a previously performed study in The Netherlands (16).

In this study, STS patients were twice as likely to have any of the comorbidities prior to diagnosis compared with the cancer-free control group. This can likely be attributed to several risk factors that are both related to the development of the comorbidity and STS such as immunodeficiency, environmental factors, lifestyle factors, and genetic factors (9).

Cardiovascular diseases, anaemia, and depression were common incident comorbidities, especially in the first six months after STS diagnosis. These incidence rates decreased during follow-up, which suggests that cardiovascular diseases, anaemia and depression are comorbidities related to the cancer itself or its treatment. Also, the authors found that male gender and STS located in the abdomen or (retro)peritoneum significantly increased the risk of developing cardiovascular disease after correction for other risk factors (9).

In addition to risk factors for cardiovascular disease, a clear association was demonstrated between chemotherapy in the first six months after STS diagnosis and the risk of anaemia during follow-up. It is well recognized that anaemia might arise during or shortly after myelotoxic chemotherapy. Next to chemotherapy, radiation therapy may further negatively impact the severity and incidence of anaemia (9).

A population-based cohort study conducted by Maretty-Nielsen K, et al. in 2014, showed an overall prevalence of comorbidity of 25%. Overall prevalence of medical conditions was 3.9% for chronic pulmonary disease, 3.6% for both, myocardial infarct and cerebrovascular disease or 3.1% for ulcer disease (17).

A recent study conducted by Loong HH, et al. over a population-based soft-tissue and bone sarcoma cohort worldwide showed that comorbidities have significant negative prognostic impact on the survival of patients with sarcomas. Results showed that 33.7% of patients had at least one or more associated comorbidities defined within the Charlson's Comorbidity Index (CCI) in the 'connective and other soft-tissue' at time of sarcoma diagnosis. The mean CCI of the connective and soft-tissue group was 4.8. The most common comorbidity present at sarcoma diagnosis was diabetes mellitus, reported at 10.7% in connective and soft-tissue group. Other common comorbidities including both groups were cerebrovascular disease (4.8%), other chronic ischaemic heart disease (3.8%), chronic lung disease (2.9%), congestive heart failure (2.6%), liver disease (2.4%) and peptic ulcer disease (2.4%) (18).

Relapsed ovarian cancer

Incidence and prevalence of ROC

Ovarian cancer is the 8th most commonly occurring cancer in women worldwide, the 8th leading cause of cancer mortality and the 18th most common cancer overall. There were more than 324,000 new cases of ovarian cancer in 2022 which resulted in more than 206,000 deaths (19) (20). It is estimated that by 2035, the incidence of ovarian cancer will increase to 371,000 per year (55%), whereas death rates will increase by 67% reaching 254,000 deaths/year (21). The majority of malignant neoplasms of the ovary originate from the coelomic epithelium; less frequently, tumours originate from the germ cells (dysgerminomas and teratomas) and the follicular cells (granulosa cell tumours) (22). Epithelial ovarian cancer (EOC) is the most predominant pathologic subtype, with five major histotypes that differ in origination, pathogenesis, molecular alterations, risk factors, and prognosis (23). Non-epithelial (mainly germ cell) cancers have a relatively high incidence in young women and are highly treatable by chemotherapy, with major progress being observed over the last few decades, but account for less than 10% of all ovarian cancers (22).

The incidence of ovarian cancer has appreciable geographic variation; in 2020 the ASR of ovarian cancer incidence ranged from 4.4 to 10.7 per 100,000 women in Central Africa and Central and Eastern Europe respectively (24).

Europe in general has one of the highest incidences of ovarian cancer in the world with the rate of newly diagnosed cases of ovarian cancer in the whole Europe of 12.6 per 100,000 of the population (25, 26). The highest ASR was observed in Central and Eastern Europe, with 11.4 per 100,000 women in 2012, followed by the Northern America with 8.1 per 100,000 and Western Europe with 7.5 per 100,000 of ASR. Among the five most peopled European countries (the United Kingdom [UK], Germany, France, Spain and Italy), the UK has the highest incidence rate for ovarian cancer with 16 per 100,000 of the population (27).

Unfortunately, the mortality rate of ovarian cancer worldwide has not significantly changed within the last 50 years, with about 151,917 women dying annually due to this neoplastic disease, with approximately a third of these deaths occurring in Europe. In contrast, at all ages, EU mortality rates decreased from 5.8 to 5.2/100,000 (-9.9%) between 2002 and 2012; however, with significant cross-national variation across 28 Member States with declines ranging from 0.6% to 28% (28). The European five-year survival rate for ovarian cancer is 41% (26). Moreover, European cancer mortality predictions for the year 2020 in comparison with 2015 reported that the ovarian cancer rates are 4.2 per 100,000 (−11.5% fall since 2015). This is in agreement with the observation that ovarian cancer incidence rose until 1990 and then started to decline thereafter. The spread of oral contraceptive use across Europe largely influenced the declining trends in ovarian cancer, in the UK earlier and subsequently in other countries. The declining use of hormone replacement therapy and the role of improved diagnosis and treatment, though difficult to quantify, has also positively influenced trends for this cancer site (25).

Demographics of the population in the authorised indication and risk factors

Globally of the total incidence rate of EOCs, 45% were serous carcinomas, followed by mucinous carcinomas (13%), endometrioid carcinomas (13%), “other” epithelial carcinomas (24%) and clear cell carcinomas (6%) (29, 30). Notably the incidence of clear cell carcinomas was higher in Asian countries relative to other regions, with rates of 15-20% compared with rates of ~5% in Europe and North America. With respect to non-EOC (germ cell and sex cord-stromal tumours), the incidence rates for all countries were much lower than the epithelial cancers (30).

Family history of breast/ovarian cancer is the single greatest risk factor, which explains 5% to 15% of cases of ovarian cancer (31) and personal history of breast cancer is associated with an increase in the risk of ovarian cancer (32).

A number of epidemiologic studies have evaluated a variety of risk factors for ovarian cancer. To date, these risk factors include: age; reproductive factors (menstrual-related factors, age of menarche and menopause, parity, pregnancy characteristics or age at childbirth), gynaecologic factors, hormonal factors such as the use of contraceptive methods, hormone replacement therapy or infertility treatments; genetic factors, lifestyle including diet, physical activity, obesity, smoking or the intake of alcohol or caffeine (32).

The main existing treatment options

Ovarian cancer is a chemosensitive disease and combination chemotherapy can result in complete remission in approximately 60-80% of patients. Despite this, ovarian cancer is still associated with high mortality, principally due to the delayed diagnosis (almost 75% of patients present International Federation of Gynaecology and Obstetrics [FIGO] stage III - IV disease at diagnosis) and the appearance of chemoresistant cell clones after initial response to chemotherapy (33).

The 5-year survival rate for early-stage disease is >80%, but for the 70% of patients with advanced disease at diagnosis, this is decreased to 25 - 35%. The standard primary treatment of ovarian cancer

includes cytoreductive surgery aimed at removing all the visible disease (residual tumour equal to 0 is at present considered the optimal goal of surgery), followed by carboplatin plus paclitaxel chemotherapy.

Extensive and largely retrospective experience has shown that optimum surgical debulking including total abdominal hysterectomy and bilateral salpingo-oophorectomy, leaving residual tumour deposits that are less than 1 cm in size is associated with improved patient outcomes. However, 75% of patients present with advanced (stage III or IV) disease and, although more than 80% of these women benefit from first-line therapy, tumour recurrence occurs in almost all these patients at a median of 15 months from diagnosis. Second-line treatments can improve survival and quality of life but are not curative (34).

Systemic therapy in first line:

Early stages:

The standard surgical approach in early-stage ovarian cancer is based on removal of both ovaries by open surgery with a staging procedure. Rupture of an intact tumour with spillage of cancer cells at the time of surgery must be avoided. The addition of adjuvant platinum-based chemotherapy to surgery is effective in significantly prolonging long-term overall survival (OS) and progression-free survival (PFS) in women with early-stage EOC. Albeit in a large cohort study (35) chemotherapy was associated with reduced mortality not only for high-risk patients but also for patients with stage IA/IB, grade 2 ovarian cancer, in general, women with a high-risk of recurrence (stage IA grade 3, IB or IC grade 2 or 3, any clear cell tumours) may benefit the most from adjuvant chemotherapy. For patients with early-stage disease requiring adjuvant chemotherapy, acceptable treatment regimens are carboplatin alone or carboplatin/paclitaxel. For patients receiving single-agent adjuvant carboplatin, 6 cycles are recommended, whereas for patients receiving carboplatin and paclitaxel, a minimum of 3 cycles is recommended except for the high-grade serous subgroup or stage IC (any histological type), for whom 6 cycles are recommended as well (33).

Advanced stages:

Complete resection of all macroscopic disease has been shown to be the single most important independent prognostic factor in advanced EOC and careful evaluation of patients before surgery is essential to defining the management plan (33, 34, 36). If resection of all macroscopic disease can be obtained based on pre-operative staging with an acceptable operative morbidity, upfront debulking surgery followed by carboplatin/paclitaxel is standard of care (37). Addition of bevacizumab should be considered, while maintenance antioestrogen therapy after chemotherapy can be considered in low-grade serous ovarian cancer. Neoadjuvant chemotherapy is still a controversial issue, and it is reserved for patients who cannot tolerate peritoneal drug administration and/or for whom optimal cytoreduction is not feasible after an adequate evaluation performed by a surgical team well trained on cytoreduction.

Intraperitoneal chemotherapy (IPCT):

IPCT has clinical and pharmacological advantages over intravenous chemotherapy in those post-surgical subjects with disease limited to the abdominal cavity, after optimal debulking surgery. Although three large, randomised studies found improvements in PFS and OS, they also demonstrated an increase in toxicity. As a consequence, IPCT may be an option only for selected patients at specialist centres (38).

Antiangiogenic therapy:

Two phase III trials have shown that bevacizumab (Avastin®) has beneficial effect when added to standard chemotherapy with paclitaxel and carboplatin in the first-line treatment of ovarian cancer (39, 40). Based on these data, bevacizumab is currently approved for its use:

- in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer,
- in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents,
- in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Bevacizumab is administered combined with chemotherapy for up to 6-10 cycles of treatment and the recommended dose of bevacizumab is between 10 and 15 mg per kilogram body weight every three weeks, depending on the type of cancer being treated.

Poly ADP ribose polymerase (PARP) inhibitors:

Three phase III trials (SOLO-1, PRIMA/ENGOT-OV26 and PAOLA-1/ENGOT-ov25) in newly diagnosed high-grade epithelial ovarian cancers (including fallopian tube and peritoneal) have investigated maintenance therapy with the PARP inhibitors olaparib or niraparib after surgery and chemotherapy (41-44). In another trial (VELIA/GOG-3005), veliparib was given with chemotherapy followed by maintenance. All four trials have demonstrated significant improvements in PFS (45).

The results of the SOLO1 trial showed the importance of the use of PARP inhibition after first-line chemotherapy in breast cancer gene (BRCA)-mutated patients (without the use of bevacizumab) (41). This phase III trial demonstrated a 70% risk reduction of disease progression or death with olaparib maintenance therapy compared with placebo after complete or partial response on first-line standard, platinum-based chemotherapy in patients with newly diagnosed, advanced BRCA-mutated ovarian cancer. Extended follow-up has demonstrated sustained long-term benefit, with 5-year follow-up showing a median PFS of 56 months with olaparib versus 14 months with placebo (hazard ratio [HR] 0.33, 95% CI 0.25-0.43). At 5 years, 48% of patients treated with olaparib remained progression-free compared with 21% in the placebo group (44).

PRIMA/ENGOT-OV26 evaluated niraparib as maintenance therapy for up to 3 years in patients with stage III-IV disease at high risk of treatment failure, with or without BRCA mutation. The study showed a significant improvement in PFS in the homologous recombination repair deficiency (HRD) population (HR 0.43, 95% CI 0.31-0.59, P<0.001) and in the overall population (HR 0.62, 95% CI 0.50-0.76, P<0.001). An exploratory subgroup analysis showed that the greatest benefit occurred in women with a BRCA mutation and a significant, but lesser, benefit in women who were BRCA wild type with HRD. There was also an increase of 2.7 months in the median PFS in the HRD-negative, sometimes termed homologous recombination proficient population (HR 0.68, 95% CI 0.49-0.94, P=0.020) (42).

In the PAOLA-1/ENGOT-ov25 trial, patients with stage III-IV ovarian cancer, with or without residual tumour after surgery, were treated with chemotherapy and bevacizumab, and after chemotherapy randomised to maintenance therapy with olaparib tablets or placebo for two years, as well as completing 15 months bevacizumab in both arms of the trial (43). Randomisation to olaparib or placebo was stratified based on tumour BRCA mutation status and response to first-line treatment. The primary analysis in the all-comer, ITT population showed a significant benefit in PFS in patients receiving olaparib and bevacizumab with a median PFS of 22.1 months compared with 16.6 months with placebo and bevacizumab (HR 0.59, 95% CI 0.49-0.72, P<0.001). Exploratory subgroup analyses showed the greatest benefit among women with a BRCA mutation (HR 0.31, 95% CI 0.20- 0.47) followed by HRD-

positive women including women with BRCA mutation (HR 0.33, 95% CI 0.25- 0.45) and HRD-positive women with BRCA wild-type (HR 0.43, 95% CI 0.28-0.66).

Rucaparib also has robust activity as single-agent therapy in relapsed BRCA-mutated high grade serous carcinoma (HGSC) (46), and the ARIEL2 study (47) demonstrated that tumours harbouring mutations in RAD51C alterations are BRCA-like (high genomic loss of heterozygosity) and responded to rucaparib at very similar rates to BRCA-mutated disease. The NOVA trial (48) with maintenance niraparib showed improved median PFS for both germline BRCA-mutated ovarian cancer and non-germline-mutated BRCA.

In the VELIA/GOG-3005 trial, standard chemotherapy in stage III-IV ovarian cancer was compared with veliparib given during chemotherapy and then as maintenance for up to 2 years, or with veliparib given only with chemotherapy (45). A hierarchical testing analysis showed the greatest reduction in the risk of progression or death of 56% among patients with a BRCA mutation (HR 0.44, 95% CI 0.28-0.68, P<0.001), followed by 43% in patients with HRD, using the Myriad Mychoice® cut off value of 33 (HR 0.57, 95% CI 0.43-0.76, P<0.001) and 32% in the intention-to-treat (ITT) population (HR 0.68, 95% CI 0.56-0.83, P<0.001). The median PFS in the ITT group was 23.5 and 17.3 months in the veliparib and control groups, respectively.

Therapy for ROC:

Approximately 70-80 % of patients diagnosed with EOC will suffer a relapse after receiving first-line chemotherapy based on platinum and taxane (38).

Appropriate salvage therapy is based on the timing and nature of the recurrence and the extent of prior chemotherapy. Surgical resection should be considered in platinum-sensitive patients with prolonged treatment free-interval (e.g., >24 months), especially with isolated recurrence and good performance status. In general, patients with disease progression during first-line treatment with platinum are considered to have 'platinum-refractory' disease. Patients who develop recurrence <6 months from the completion of first-line platinum chemotherapy are considered to have 'platinum-resistant' disease and those with an interval >6 months 'platinum-sensitive' disease.

Patients experiencing a durable response to platinum induction chemotherapy have a high probability of responding again to platinum-containing compounds. Although the accepted definition of platinum-sensitive EOC is disease that has recurred more than 6 months after the last platinum treatment, the likelihood that an individual patient tumour will respond to platinum retreatment is a continuum, with long platinum-free intervals associated with high response rates (34).

With increasing use of non-platinum and biological agents such as PARP inhibitors, angiogenesis inhibitors and immune checkpoint blockade in ROC, in the Ovarian Cancer Consensus Conference 2015 it was decided that clinical trial design needs to collect information evaluating the impact of these agents on disease biology and response to subsequent treatment (37). It was proposed that progression-free interval (PFI), which focuses on only one therapeutic class (platinum), should be replaced with the broader term of treatment-free interval (TFI). In addition to the TFI from last platinum dose (TFIp), the TFI from last non-platinum therapy (TFInp) as well as last biological agent (TFIb), when applicable, should be recorded prospectively.

Secondary cytoreduction may be appropriate in selected patients despite the lack of level 1 evidence demonstrating a survival advantage. For the majority of patients with recurrent EOC, the treatment is based only on systemic therapy. Several factors should be considered in the selection of second-line therapy in EOC (36, 38):

Factors depending on the treatment:

- Response to the last therapy and time since it finished.
- Activity and toxicity of available treatments.

- Ease of administration and cost.

→ Factors depending on the patient:

- Previous and residual toxicity experienced by the patient.
- Clinical condition and previous medical history.
- Preference of the patient.
- BRCA mutation status.

Platinum-refractory or resistant disease:

Single-agent therapy is considered the standard treatment in patients with refractory and resistant disease. Several antineoplastic agents (e.g., topotecan, PLD, paclitaxel, gemcitabine) produce clinical responses in 10–25% of women with platinum-resistant disease. In this setting, there are no robust randomised data to support one agent over another, and not all are licensed for this indication. The choice should be guided by patient preference and toxicity profile. Due to this low response rate it is believed that patients with resistant or refractory platinum disease should be strongly considered for inclusion in clinical trials (49, 50).

Platinum-sensitive disease:

Two phase 3 trials have shown that combination platinum-based chemotherapy with paclitaxel or gemcitabine improves progression-free survival compared with single-agent platinum or conventional platinum-based chemotherapy in women with recurrent platinum-sensitive disease (51, 52). A third phase 3 study (CALYPSO) showed an increase in PFS in favour of PLD and carboplatin over combination paclitaxel and carboplatin (46).

Treatment of patients with a PFI >12 months: patients with recurrent disease and a PFI over 12 months are considered fully platinum sensitive, as they use to respond to re-treatment with a platinum-based regimen. As there is no combination that can be considered superior in terms of efficacy, the selection between the different options should be based on their respective toxicity profiles (38).

Antiangiogenic therapy:

A phase III trial (OCEANS) has shown that bevacizumab (Avastin®) is beneficial when added to gemcitabine with paclitaxel and carboplatin in the treatment of platinum-sensitive ovarian cancer (53, 54). Based on these data bevacizumab was approved in October 2012 by the European Commission, in combination with carboplatin and gemcitabine for the treatment of adult patients with first recurrence of platinum-sensitive EOC who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents. Bevacizumab is administered in combination with carboplatin and gemcitabine for 6 and up to 10 cycles, followed by continued use of bevacizumab as single agent until disease progression. The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Partially sensitive patients (6–12 months):

The best treatment of patients with partially platinum-sensitive ovarian cancer is not clearly defined. Patients relapsing between 6 and 12 months after the last platinum-based chemotherapy are believed to have a lower response to platinum than those considered fully platinum sensitive (PFI >12 months) and also a shorter PFS and OS (50, 55).

For this reason, different strategies beyond carboplatin-based regimens are under investigation on this group of patients. One of these strategies is the use of non-platinum-based regimen, based on the results of the OVA-301 trial. This multinational, multicentre trial assessed the safety and efficacy of trabectedin plus PLD versus PLD alone in platinum-sensitive and platinum-resistant patients with ROC. A subgroup analysis showed that the group of patients with a PFI of 6-12 months obtained an improvement in OS when treated with trabectedin and PLD compared to PLD monotherapy. In this subpopulation, trabectedin + PLD induced a significant 36% reduction in the risk of death (HR=0.64; p=0.0027), with

a 6-month advantage in median survival relative to treatment with single-agent PLD. This difference was more evident when platinum was the next regimen used after the progression of the patient to the trial medication (HR: 0.58; p=0.0153). Based on the above-mentioned sub-analysis, the combination of trabectedin and PLD has been proposed as an alternative for patients with a PFI of 6-12 months (56-58).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Globally, ovarian cancer is the 8th most common malignancy diagnosed among women and 8th leading cause of cancer mortality. Worldwide in 2022, there were more than 324,000 new cases and more than 206,000 deaths due to ovarian cancer (19). Only 46% of ovarian cancer patients survive beyond 5 years. The high mortality associated with ovarian cancer is due to late diagnosis and resistance to treatment (59).

Important co-morbidities

A cross-sectional study carried out in France with patients over 18 years, diagnosed with advanced (stage IIIB–IV) or recurrent EOC showed that, among the 127 patients included, a total of 73 comorbidities were reported in 44 patients (34.6%). Vascular (10.2%), metabolic (7.1%), respiratory (5.5%), and psychiatric disorders (5.5%) were the most common types of comorbidities reported (60).

A characterization of the epidemiology of comorbid conditions in 5,087 US women with ovarian cancer age ≥66 years and matched cancer-free women showed that the prevalence of most conditions was similar between cancer and cancer-free patients, but exceptions included hypertension (51.8% and 43.5%, respectively), osteoarthritis (13.4% and 17.3%, respectively), and cerebrovascular disease (8.0% and 9.8%, respectively). In contrast, 3- and 12-month incidence rates (per 1,000 person years) of most conditions were significantly higher in cancer than in cancer-free patients: hypertension (177.3 and 47.4, respectively); thromboembolic event (145.3 and 5.5, respectively); congestive heart failure (113.3 and 28.6, respectively); infection (664.4 and 55.2, respectively); and anaemia (408.3 and 33.1, respectively) at 12 months (61).

Part II: Module SII – Non-clinical part of the safety specification

The non-clinical safety profile of trabectedin has been characterised by safety pharmacology studies both *in vivo* and *in vitro*, single and repeat-dose toxicity studies in mice, rats, dogs, rabbits, and/or cynomolgus monkeys, reproductive and developmental toxicity studies, mutagenicity studies, distribution studies, metabolism studies, excretion studies, local tolerance studies and interaction studies (both *in vivo* and *in vitro*).

The pharmacology studies showed that trabectedin is a potent cytotoxic product both *in vitro* and *in vivo*. Trabectedin also showed anti-proliferative activity in tumours resistant to classical chemotherapeutic agents as well as additive/synergistic activities with doxorubicin and cisplatin.

In vivo xenograft studies revealed that the best anti-tumour effects were obtained using an intermittent schedule at the maximum tolerated dose (MTD), even though a split dose approach was better tolerated. This was shown to be consistent with the clinical findings.

TOXICITY	
Key safety findings (from non-clinical studies)	**Relevance to human usage**
Single and repeat dose toxicity	
In **single-dose** toxicity studies, trabectedin was administered as either a single bolus, or as i.v. infusion for 3 or 24 hours. The MTD after single dose was 300 µg/m² (100 µg/kg) in male mice, 450 µg/m² (75 µg/kg) in male rats and 300 µg/m² (50 µg/kg) in female rats, 540 µg/m^2 (27 µg/kg) in male and female dogs and 1,050 µg/m² (87.5 µg/kg) in male and female cynomolgus monkeys. The duration of the i.v. administration (bolus, 3- or 24-h infusion) did not influence the MTD. **Repeat-dose** toxicity i.v. studies were performed in mice, rats and dogs. Repeated i.v. administration according to the clinical schedule, i.e., 3- and 24-h infusion of trabectedin once every 3 weeks, was studied in rats and monkeys with dosing for up to 9 and 24 weeks, respectively. In rats, the MTD was 150 µg/m² (25 µg/kg) in both genders. In monkeys, the MTD was 300 µg/m² (25 µg/kg) in both genders. **Toxicokinetic evaluations** were conducted in mice, rats and monkeys in support of the repeat-dose i.v. toxicology studies with trabectedin. In mice, rats, and monkeys, the trabectedin plasma concentration-time profile displayed multi-compartmental kinetics without notable gender differences. After i.v. dosing, plasma levels dropped rapidly, followed by a much slower decrease. The estimated systemic clearances in the species used in non-clinical studies were moderate to high when compared to the respective hepatic blood flows, and the values for apparent volume of distribution at steady state were many-fold those of the total body water, indicating extensive tissue distribution. At their respective MTD, the highest plasma exposure (as measured by area under the curve [AUC]) OF unbound trabectedin was found in humans, followed by monkeys, mice, and rats. None of these species displayed overt gender-related differences in maximum concentration (Cmax) and AUC of trabectedin. Notably, the clear gender-related differences in trabectedin metabolism and hepatobiliary excretion in the rat were not reflected in the plasma exposure to unchanged drug.	The key safety findings from non-clinical single and repeat-dose toxicity studies relevant to human usage are described below under the relevant toxicities.

Species and gender differences may be related to trabectedin's differential cytotoxicity sensitivity, but also to the differences in the metabolic profile, (hepatobiliary) excretion rate and differential body retention of trabectedin-related material, or a combination of these factors.	
Reproductive and developmental toxicity	
Reproductive toxicology studies: Teratogenicity: Placenta passage and foetal tissue exposure were confirmed in pregnant rats (demonstrated in study PBC040-101). Trabectedin was not embryotoxic or teratogenic in rats or rabbits. However, as doses used were considerably lower than the intended human clinical dose because of dose-limiting maternal toxicity, the results of these studies are unlikely to have much relevance to human pregnancy. **Male and female fertility, pre- and post-natal development:** No fertility and early development studies have been performed. However, despite limited histopathological changes in the gonads in the repeat dose toxicity studies (cellular debris in the epididymides, degeneration of germinal epithelium and presence of spermatid giant cells in male rats, some decreased cyclicity in female rats and immature testes in male monkeys), based on the nature of the compound (cytotoxic and mutagenic) trabectedin is likely to affect the reproductive capacity.	No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action (MoA), trabectedin may cause serious birth defects when administered during pregnancy. Women of childbearing potential must use effective contraception during treatment and 8 months thereafter and immediately inform the treating physician if a pregnancy occurs. Men in fertile age must use effective contraception during treatment and 5 months after treatment. 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.
Genotoxicity, cytotoxicity and binding to DNA (related to MoA) and carcinogenicity	
• Genotoxicity: Trabectedin was mutagenic in both *in vitro* and *in vivo* test systems. • Cytotoxicity and binding to DNA (related to MoA): Pharmacology studies show that trabectedin is a potent cytotoxic product both *in vitro* and *in vivo*. It binds to the minor groove of the DNA, bending the helix to the major groove. • Carcinogenicity: The specific exclusion of formal 2-year Good Laboratory Practice (GLP) mice and rat carcinogenicity studies complied with regulatory guidance and standard practice for the assessment of an anticancer agent.	The DNA binding as a MoA and genotoxicity results suggest a potential risk for a tumourigenic effect, e.g., secondary myelodysplasia and leukaemia. Acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) have been seen in clinical trials but metastatic STS and ROC target populations are already confounded by prior chemotherapy known to be associated with secondary malignancies. Therefore, AML/MDS is considered an Important potential risk.
Nephrotoxicity	
In monkeys, kidney tubular dilatations with flattened epithelium and epithelial degeneration or necrosis were seen in some animals at high doses. Minimal to moderate kidney tubular dilatation with slight epithelial degeneration or necrosis was seen in a few animals during chronic administration via peripheral veins. Unilateral, occasionally bilateral, marked interstitial inflammation with fibrosis and accompanied by tubular basophilia and pelvic dilatation were observed when trabectedin was injected through a central catheter. Dilatation of the ureters and hyperplasia of ureteral and renal pelvic transitional epithelium were considered associated events. However, these lesions were secondary to the severe thrombophlebitis noted in the cannulated vein, since they were mainly unilateral when the infusion was administered peripherally in the vena femoralis and located at the same site of infusion, or	Extrapolation of the monkey renal toxicological findings to human usage remains difficult. These findings were secondary to severe local intolerance at the administration site (i.e., catheter tip location), with severe damage of surrounding tissues (e.g., the kidneys) and therefore uncertainly attributable to trabectedin. Animal data do not provide enough intrinsic nephrotoxic data to further extrapolate to humans.

resulted from inflammation originating from the thrombophlebitis of the vena cava inferior when the catheter was placed in this central vein. Sporadic increase in creatinine kinase in monkeys is considered to be linked to the restraint measures needed for blood sampling and/or to muscular necrosis at the site of administration or pre-moribund status above the MTD. Histopathological changes in muscles distant from the injection site, which would suggest rhabdomyolysis, were not observed in rats or monkeys.	
Gastrointestinal toxicities	
In single-dose toxicity studies in the rat, epithelial necrosis and ulceration in the gastrointestinal (GI) tract were noted, in repeated-dose dose toxicity studies single cell necrosis, ulceration and epithelial atrophy were observed in the GI tract. Common clinical signs in the cynomolgus monkey single-dose studies included diarrhoea, emesis, lack of appetite, lethargy and loss of body weight. In repeat-dose toxicity studies, focal necrotic ulcerations of the colon/rectum were reported in sacrificed animals or those that died after the first cycle of treatment.	In general, based on the non-clinical observations across species, on the pharmacological activity of trabectedin, and on the available clinical data, GI toxicities were commonly reported.
Hepatotoxicity	
Trabectedin causes hepatoxicity in all species. However, the pattern of liver toxicity varies from durable and cumulative hepatocellular and hepatobiliary damage in rodents and dogs, to reversible transaminase increase with limited hepatic cellular damage in monkeys and patients. In rats, the severity of the clinical chemistry changes was pronounced and increased with successive treatments, particularly in females. Hepatobiliary histopathological alterations persisted, suggesting that hepatic and biliary damages are cumulative and irreversible in these species. In mice and dogs, both hepatic and biliary changes were observed. In mice, histopathological changes were reversible, but in dogs, clinical pathology alterations and some hepatic lesions were still present 36 days after dosing. In monkeys, transient increases in transaminases and slight focal hepatic necrosis (hepatocellular hypertrophy, without biliary damage) were observed mainly at or above the MTD, but only sporadically after repeated administration at lower doses, and not systematically in all studies. When elevated, transaminases tended to decrease with repeated cycles. Increases in alkaline phosphatase (ALP) above background variations were noted in one male and one female animal receiving 780 µg/m^2 (65 µg/kg) without correlating hepato-biliar histopathology. Hepatic findings in monkeys were clearly less pronounced than in rats, not systematically observed, and were found to be reversible, non-cumulative in nature and characterised by transient increases in transaminase levels, rare increases in ALP, hepatocellular hypertrophy, focal hepatocyte degeneration and necrosis, and mixed inflammatory cells in the sinusoids and portal tracts, without any biliary damage. Gender-related differences were not seen in monkeys.	The nature of trabectedin-induced hepatotoxicity is very different in the various species. In both monkey and man, trabectedin-induced hepatotoxicity was reversible, non-cumulative, with limited biliary damage, if any. In the rat, it was non-reversible and cumulative and included an important biliary component. In addition, overt gender differences in hepatotoxicity were evident in the rat with female animals being more sensitive. Such gender-related differences were not seen in either monkeys or in humans. The *in vivo* profile of hepatotoxicity together with the similarity in the *in vitro* hepatic metabolism, supports the selection of the cynomolgus monkey as the most relevant and predictive animal species to evaluate the human risk for hepatotoxicity of trabectedin. In patients, trabectedin was frequently associated with dose-dependent, intrinsic liver-related abnormalities (elevated transaminases and acute pancreatitis) indicative of a reversible and transient hepatocellular injury, with uncommon cholestasis. Hepatoxicity or hepatic injury associated with relevant impairment of liver function was rare (lower than 1 %).
Pancreatic toxicity	

Swollen pancreas corresponding histologically to an increase in apoptosis and acinar single cell atrophy, or necrosis was observed in rat and dog toxicology studies. In rats, intracytoplasmic zymogen accumulation was also noted in the peri-insular cells. These lesions were totally or partially reversible after 3 to 4 weeks. A reversible, pancreatic acinar degranulation was noted in monkeys, with dose-dependent increase in incidence and severity. However, trabectedin did not affect serum amylase levels in the monkey repeated-dose toxicity study using a 3-hour i.v. infusion administered once every 3 weeks for eight cycles.	Pancreatic findings were consistently observed across animal species and these animal findings could be relevant to man. Infrequent reports of pancreatitis-related adverse events have been reported. In the integrated safety dataset for sarcoma and for ovarian, <1% of patients experienced any pancreatitis, lipase and/or amylase increased treatment-emergent adverse events. In all these cases there was either insufficient information for meaningful assessment or robust confounding factors were reported. Until further information is available, this event is considered an important potential risk.
Retinal toxicity	
Focal retinal oedema outside the macula has been detected by ophthalmological examination in two of 28 animals (and of 54 bearing in mind other studies) in the cynomolgus monkey toxicity study when using a 3-hour i.v. infusion of trabectedin administered once every 3 weeks for 8 cycles. This lesion was observed before terminal sacrifice in one animal and remained present for 40 days in a second animal. No histopathological alterations were observed in the retina. Moreover, there was no dose-relationship, and animals treated by a higher dose for the same period of time in this study or in previous studies did not show ocular alterations. Since the two animals with retinal oedema showed some of the most severe systemic toxicity, with generalised oedema, these lesions could be secondary to the extensive oedema observed in the animals, as well as to hypoalbuminaemia and very poor general condition rather than to a primary effect of trabectedin on the retina. Retinal oedema appeared associated to general oedema and hypoalbuminaemia induced by local intolerance at the injection site in monkeys.	The retinal oedema findings in the monkey appear to be indirectly associated to general oedema and hypoalbuminaemia induced by local intolerance at the injection site. However, as the monkey retinal findings could indicate a risk for a rare effect in a critical organ, these animal findings could be relevant to man. A review of clinical and post-marketing data did not identify any relevant clinical findings for retinal toxicity.
Myelosuppression	
Myelosuppression was the main toxicity finding following single or repeated dosing in rats, dogs (single dose data only), and monkeys. In rats, following repeated dosing, myelosuppression (reduced bone marrow cellularity and diffuse atrophy of the lymphoid tissues) recovered at least partially after each treatment cycle. In monkeys, following repeated dosing, mortality during early cycles was related mainly to severe neutropenia. In surviving animals, myelosuppression (anaemia, neutropenia, thrombocytopenia, leukopenia associated with depletion in lymphoid organs and hypocellularity in bone marrow) recovered partially between treatment cycles.	Myelosuppression was consistently observed in repeat-dose animal toxicity studies and these animal findings are expected to be relevant to man. Myelosuppression has been confirmed as an adverse drug reaction (ADR) by clinical trials at all clinically relevant dose levels. In clinical trials, anaemia, thrombocytopenia and thrombocytopenia with bleeding, neutropenia and neutropenia with infections (including septic shock) were very commonly (>10%) observed. Leukopenia, observed in non-clinical studies, is a broad category of white cells with the subtype of neutropenia. Neutropenia and neutropenia with infections including septic shock is the more clinically relevant subcategory of leukopenia.
SAFETY PHARMACOLOGY	
Cardiovascular (including potential for QT interval prolongation)	
***In vitro*, trabectedin had no significant effect compared with solvent on the membrane** There was no effect on K^+ current (IKr) in hERG-transfected Human Embryonic Kidney Cell Line 293 cells up to a concentration of 3 µM (2.5 µg/mL). At the high concentration of 10 µM, only a marginal effect (about 10% reduction relative to solvent control) was observed. This	**Arrhythmogenic effect:** Animal studies indicate no arrhythmogenic effect. The arrhythmogenic potential of trabectedin was investigated in humans as well. These investigations confirmed that trabectedin does not induce arrhythmogenic effects. **Cardiac dysfunction:**

concentration is well above the plasma concentrations reached in patients (C_{max} of 1.8 ± 1.1 µg/mL for trabectedin 1,500 µg/m^2 q3wk 24-h). The effects *in vivo* of trabectedin on the cardiovascular system were also investigated in anaesthetised cynomolgus monkeys following the administration of trabectedin as a 1-hr i.v. infusion at 1,080 µg/m² (90 µg/kg). The drug did not induce any relevant effects on heart rate, lead II electrocardiogram (ECG) variables (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 plasma concentrations of trabectedin measured in this study (C_{max} of 10.6 ± 5.4 ng/mL) are similar to or higher than those reached in patients, as shown above. Moreover, no electrophysiological alterations were observed in the repeated dose monkey toxicity studies. In these repeated-dose monkey studies, as well as in repeated-dose rat toxicity studies, there was no evidence of trabectedin-induced myocardial toxicity based on histological examination of the heart. In conclusion, trabectedin had no relevant effect on the cardiovascular and respiratory systems at therapeutic exposures.	Animal studies indicate no induction of myocardial toxicity.
Central nervous system (CNS)	
Trabectedin had limited effect on the CNS at exposures below the therapeutic clinical range, in terms of AUC. In the multi-cycle toxicity studies in rats and monkeys, no CNS effects were observed.	There were no findings indicative of CNS toxicity in animal studies. Furthermore, in human no signal has been raised regarding nervous system toxicity.
MECHANISMS FOR DRUG INTERACTIONS	
Plasma protein binding	
No study has been conducted in which the potential of trabectedin was investigated to displace other compounds from their protein binding. However, trabectedin is not expected to displace other drugs from their plasma protein binding since the concentrations of trabectedin achieved in plasma are extremely low relative to the physiological concentrations of albumin and alpha-1 acid glycoprotein. The ability of various compounds to displace trabectedin from plasma proteins was investigated during *in vitro* studies. A wide variety of drugs that bind to different sites on albumin and to alpha-1 acid glycoprotein were examined. No drugs studied at clinically relevant concentrations impacted the protein binding of trabectedin to a significant degree including acetylsalicylic acid, ceftazidime, cloxacillin, diazepam, diclofenac, digitoxin, erythromycin, ethanol, ondansetron, paracetamol, phenytoin, propranolol, tamoxifen, valproic acid, and warfarin. Thus, clinically relevant drug interactions at the level of protein binding are very unlikely.	Based on the maximum trabectedin plasma levels reached versus the much higher physiological plasma concentrations of albumin and alpha-1 acid glycoprotein, trabectedin is not expected to displace other drugs from their plasma protein binding. Based on *in vitro* data it is very unlikely that co-medication would displace trabectedin from its plasma protein binding to a clinically relevant extent.

Cytochrome P 450 (CYP) inhibition by trabectedin: Trabectedin exhibited only limited inhibitory activity on human microsomal CYP enzymes 1A2, 2A6, 2B6, 2C8, 2C19, 2D6, or 2E1 at supra-therapeutic drug concentrations of up to 5 μM, using probe substrates indicative of specific CYP enzyme activity. At this concentration of trabectedin, CYP3A4 was inhibited by 41.2% to 73.9%, and CYP2C9 was inhibited by 47.8%. Mean maximum plasma concentrations of trabectedin in patients are much lower, ranging from 1.2 to 1.8 ng/mL (approximately 0.002 μM) following administration of 1.5 mg/m^2 as a 24 h infusion. These results confirmed those generated in an earlier study in which CYP activity was probed by means of fluorescent substrates. No appreciable inhibition of the main CYP enzymes was seen at concentrations up to 0.05 μM of trabectedin.	Based on *in vitro* CYP inhibition data combined with maximum plasma concentrations reached in the clinic, trabectedin is not expected to inhibit the CYP-dependent metabolism of co-administered drugs to a clinically relevant extent.
Effect of CYP3A4 inhibitor or inducers on trabectedin: Trabectedin is extensively metabolised in the liver by the CYP system. *In vitro* studies using human hepatic subcellular fractions and heterologously expressed CYPs have shown that, virtually, all major CYP isoforms are able to metabolise trabectedin. Further *in vitro* experiments were conducted specifically to identify the major CYP isoform(s) involved at clinically relevant concentrations of trabectedin. To that aim, 7.62 nM (corresponding to 10 ng/mL) trabectedin was incubated together with pooled human liver microsomes up to 20 minutes and the disappearance of unchanged drug from the incubation mixture was quantified by means of a sensitive LC-MS/MS method. Selective chemical inhibitors and inhibitory antibodies directed against CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 were used as diagnostic tools. Results from these experiments showed that trabectedin metabolism was completely abrogated by selective chemical CYP3A4 inhibitors (ketoconazole and troleandomycin) as well as selective inhibitory antibodies directed against CYP3A4. This strongly suggests that CYP3A4 is the predominant isoform implicated in the hepatic metabolism of trabectedin at clinically relevant trabectedin levels.	Based on *in vitro* data, CYP3A4 is the main CYP isoform responsible for the hepatic metabolism of trabectedin at clinically relevant concentrations. Trabectedin clearance being largely metabolic, the co-administration with potent inducers or inhibitors of CYP3A4 may reduce or increase, respectively, the plasma concentrations of trabectedin. This was confirmed in 2 formal human drug-drug interaction studies, with co-administration of the CYP3A4 inhibitor ketoconazole and the CYP3A4 inducer rifampin, respectively.
Trabectedin effect on xenobiotic receptor (SXR): Trabectedin inhibited drug-induced activation of CYP3A4 and MDR1 in human hepatocytes through SXR antagonism. This phenomenon was observed at concentrations achieved *in vivo* following therapeutically relevant doses. The clinical significance of the *in vitro* results is presently not understood.	The clinical relevance of the observed trabectedin SXR antagonism *in vitro* is unclear. Available pharmacokinetic data in cancer patients do not suggest appreciable effects of repeated cyclic dosing with trabectedin on *in vivo* enzymatic activity of CYP3A4, supporting the fact that the pharmacokinetics of trabectedin are consistent upon repeated dosing. Notably, weekly administration of 0.3 to 0.65 mg/m^2 of trabectedin as a 3-h infusion (with dexamethasone prophylaxis) to patients with cancer had minimal impact on the *in vivo* activity of the CYP3A4 enzyme. Based on these clinical pharmacokinetic data, it seems that the basal *in vivo* function of CYP3A4 (a well-known SXR target gene) is unaffected. Extending this conclusion to other SXR targets (e.g., UGT1A1, MRP1) a clinically relevant interaction based on trabectedin's SXR antagonism potential is unlikely.

CYP induction by trabectedin: Trabectedin has limited induction potential toward major human CYPs *in vitro*. No appreciable increase in any of the major CYP mRNAs (CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5) was seen upon incubation of human hepatocytes with up to 10 nM of trabectedin, except for CYP1A1 (ca 5-fold increase in mRNA levels). These results are supported by ex vivo studies in rats and monkeys and show that trabectedin is not a potent inducer of CYP activity when given as a cyclic regimen. Most CYPs displayed a concentration-dependent decrease in the rate of their transcription (*in vitro*) and translation (*ex vivo*). However, these data should be interpreted with reservation since the experimental design of the *in vitro* study was suboptimal and because systemic or hepatotoxic effects may have confounded the ex vivo findings.	Based on *in vitro* and preclinical ex vivo data, trabectedin shows limited potential to induce CYPs. No clinically relevant effects of trabectedin based on the metabolism and pharmacokinetics of other CYP substrates is expected. Furthermore, weekly administration of 0.3 to 0.65 mg/m^2 of trabectedin as a 3-h infusion (with dexamethasone prophylaxis) to patients with cancer had minimal impact on the *in vivo* activity of the CYP3A4 enzyme . Therefore, trabectedin is not expected to induce the CYP-dependent metabolism of co-administered drugs to a clinically relevant extent.
P-glycoprotein (P-gp): *In vitro* experiments clearly showed that trabectedin is a P-gp substrate. *In vivo* experiments with P-gp knock-out mice [mdr1a/1b (-/-)], showed that these animals displayed 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 intestines and heart. Parent drug levels were similar in the plasma and the liver of P-gp knock-out animals and wild type controls. These data suggest a role for P-gp in the tissue distribution of trabectedin and its metabolites, and concurrent treatment with P-gp modulators may potentially alter the body distribution of trabectedin and/or its metabolites. Specifically, enhanced brain penetration of trabectedin-related material due to inhibition of P-gp at the level of the blood-brain barrier (BBB) may be of special concern. However, data generated in P-gp knock-out mice do not quantitatively translate to humans: in patients free/unbound systemic levels of co-administered P-gp inhibitors rarely reach their P-gp transporter Ki, implying a clinically relevant effect on trabectedin brain distribution with P-gp inhibitor co-dosing is not expected. Cyclosporin A, the most potent P-gp inhibitor approved for clinical use to date, only modestly (up to 2-fold) increased the brain levels of verapamil, a P-gp model substrate. The role of P-gp in the (hepatobiliary) excretion of trabectedin and metabolites is considered of minor importance, given the fact that the excretion pattern of trabectedin was similar between the wild type and P-gp knock-out mice.	Since trabectedin is a P-gp substrate, its distribution to the brain could theoretically be increased by co-administered P-gp inhibitors. However, co-administered P-gp inhibitors rarely reach their P-gp transporter Ki systemically, and therefore a clinically relevant effect on trabectedin brain distribution with P-gp inhibitor co-dosing is not expected. The low likelihood for co-administration of trabectedin with potent P-gp inhibitors further reduces the concern for increased brain penetration of trabectedin-related material due to P-gp inhibition at the BBB. Therefore, the clinical relevance for treatment with trabectedin is considered limited. However, there are no clinical data investigating the potential drug-drug interaction and more specifically the effect on trabectedin brain distribution with co-dosed P-gp inhibitors.
OTHER TOXICITY RELATED INFORMATION	
Injection site reactions	

In mice, rats, rabbits and monkeys, dose-dependent local inflammation was regularly observed at the injection site after i.v. injection particularly after repeated cycles. In repeated dose toxicity studies in cynomolgus monkeys, severe thrombophlebitis with extensive perivascular inflammation and fibrosis generally with pronounced necrosis, also affecting surrounding tissues, was observed after the fourth cycle and led to premature sacrifice or death in some animals. These monkey adverse effects were observed when trabectedin was administered to animals less than 3 kg. Mortalities were seen at 0.42 mg/m^2 and above. Local intolerance at the injection site was fully or partially reversible after cessation of dosing. Local intolerance at the injection site in the animal studies is likely related to the small size of the animals and veins diameters.	Injection site reactions were consistently seen in rodents and, upon repeated dosing, in monkeys, and these animal findings are expected to be relevant to man. Injection site reactions have been reported in patients in clinical trials. There have been few reported cases of trabectedin extravasation, with subsequent tissue necrosis requiring debridement. Therefore, injection site reactions are considered an Important identified risk.

Part II: Module SIII - Clinical trial exposure

In September 2007, trabectedin received Marketing Authorisation in the EU under the trade name Yondelis®, for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. As of 17 September 2024, trabectedin is approved for the treatment of STS in 75 countries, including Europe, United States of America and Japan. The numbers take into account new approvals as well as withdrawals due to commercial reasons.

In October 2009, following submission of a type II variation, the European Commission approved Yondelis in a second indication, namely Yondelis® in combination with PLD for the treatment of patients with platinum-sensitive ROC.

As of 17 September 2024, trabectedin is approved for the treatment of patients with platinum-sensitive ROC in 64 countries. The numbers take into account new approvals as well as withdrawals due to commercial reasons.

Overall, 3,620 subjects with ovarian cancer, STS, or other cancers have been exposed to trabectedin in the clinical development programme (see Table 1). These cumulative total exposure data do not include Investigator-Initiated Studies (IIS), Expanded Access Programmes (EAP), compassionate use, or observational programmes.

Table 1: Overall Clinical Exposure Data

Clinical Trials	Cumulative exposure up to 17 September 2024
Exposure to trabectedin sponsored clinical trials[a]	3,620
Expanded access program/Compassionate use[b]	5,892
Exposure to trabectedin from other sponsored clinical trials (IIS)[c]	2,913
Total Clinical Exposure	**12,425**

[a] Studies included are those sponsored by Pharma Mar S.A., Janssen and Taiho: ET-A-001; ET-A-002; ET-A-003; ET-A-004; ET-A-005; ET-A-006; ET-A-007; ET-A-009; ET-A-010; ET-A-012; ET-A-013; ET-A-015; ET-A-016; ET-A-017; ET-B-001; ET-B-002; ET-B-005; ET-B-008; ET-B-009; ET-B-010; ET-B-011; ET-B-013; ET-B-016; ET-B-017; ET-B-018; ET-B-019; ET-B-020; ET-B-021; ET-B-022; ET-B-023; ET-B-025; ET-B-026; ET-B-027; ET-B-028; ET-B-029; ET-B-031; ET-C-002-07; ET743-INT-11; ET743-INT-3; ET743-OVA-301; ET743-OVC-1001; ET743-OVC-1002; ET743-OVC-1003; ET743-OVC-1004; ET743-OVC-3006; ET743-SAR-1001; ET743-SAR-3006; ET743-SAR-3007; ET743-STS-201; ET743-USA-1; ET743-USA-11; ET743-USA-2; ET743-USA-3; ET743-USA-7; 10045020; 10045030; 10045040;10045050 and 10045060.

[b] ET743-INV-IND; ET743-NPP; ET743-SAR-3002; Pharma Mar Compassionate use and R279741SAR4004.

[c] Studies included are: AGO-OVAR 2.32; ATREUS; CSET 2014-2154 (TSAR)EORTC-1320; EORTC-1447; EORTC-62091/SARC-20/TRUSTS/ET-D-006-09; ET743-OVC-2002; ET743-SAR-2002; ET743-SAR-2004; ET743-SAR-2005; ET-A-008; ET-D-004-09 GEIS-20; ET-D-005-11/ CSET 1485; LMS-02; ET-D-008-09/T-DIS-1001; ET-D-009-10/Inovatyon; ET-D-013-10/PACT-18; ET-D-014-11/GISG-02; ET-D-015-11/ MITO-15; GEIS-37 (TRASTS); GEIS-75; Hyper-TET; IRFMN-OVA 6152; ISG-ARTICLE; ISG-STS 10-01/ ISG-GEIS-10-01; ISG-STS-TRAB-2012 (TRAVELL); JCOG1802; LMS04; MITO 23; MITO 26; MITO 30; NiTraSarC; OLATRAST; PIPER; PR Trab-PT; R279741SAR1005; R279741SAR2006; REPRAB-MITO 36; STRADA; TARMIC; TOMAS; TOMAS 2; TOP-ART; TR1US; TRAMANT; TRAMUNE; TRANSITION1 and MCS-ET-D-067-20.

Estimates of cumulative exposure to trabectedin in Pharma Mar Sponsored Clinical Trials, Janssen Products LP Sponsored Clinical Trials, Taiho Pharmaceutical Co. Ltd Sponsored Clinical Trials and IIS are provided in Table 2, Table 3, Table 4 and Table 5 respectively.

Table 2: Cumulative Subject Exposure to Trabectedin in Pharma Mar Sponsored Clinical Trials

Study	Short Title	Exposure
ET-A-001	Phase 1 dose escalation study to determine the safety of Yondelis® administered as a single intravenous infusion over 60 minutes or 3 hours every 21 days in subjects with solid tumors	72
ET-A-002	Phase 1 dose escalation study to determine the safety of Yondelis® administered as a continuous intravenous infusion over 24 hours q3wk in subjects with solid tumors	52
ET-A-003	Phase 1 dose escalation study to determine the safety of Yondelis® administered as a daily times five intravenous infusion q3wk in subjects with solid tumors	42
ET-A-004	Phase dose escalation study to determine the safety of Yondelis® administered as a 72 hour continuous intravenous infusion q3wk in subjects with advanced solid tumors	21
ET-A-005	Phase1 dose escalation study of Yondelis® administered as a 1-hour infusion weekly for 3 consecutive weeks every 4 weeks to subjects with advanced cancer	63
ET-A-006	Phase I with Yondelis® in 3hr infusions for subjects with advanced cancer and abnormal liver function	33
ET-A-007	Two part combination dose/sequence finding and evaluation of efficacy/antitumoral activity study of Yondelis® and doxorubicin in subjects with STS and advanced pre-treated, anthracycline-naive breast cancer subjects	38
ET-A-009	Dose finding study of a combination of Yondelis® and cisplatin in subjects with advanced pre-treated solid tumors, and therapeutic window study in previously untreated subjects with non small cell lung cancer (NSCLC)	49
ET-A-010	Clinical and pharmacokinetic dose finding study evaluating the combination of sequential paclitaxel and Yondelis® every 2 weeks in subjects with advanced solid tumors	27
ET-A-012	Clinical and pharmacokinetic dose finding study of Yondelis® and carboplatin in subjects with advanced solid tumors.	44
ET-A-013	Open-label, non randomized, mass balance and metabolism study of Yondelis® administered as a 3h or 24h intravenous infusion to subjects with advanced cancer	8
ET-A-015	Phase 1, dose finding study of a combination of Yondelis® and doxorubicin in subjects with advanced solid tumors	40
ET-A-016	Phase Ib and Pharmacokinetic study of Yondelis® administered in a 3-hour infusion days 1, 8, every 3 weeks in advanced sarcoma, ovarian cancer and breast cancer subjects	7
ET-A-017	Dose finding study of a combination of Yondelis® and cisplatin in patients with advanced solid tumors	12
ET-B-001	Open-label, single-arm, multicenter study to evaluate efficacy and safety in subjects with advanced or metastatic breast cancer	17
ET-B-002	Open-label, multicenter, 2- stage study to evaluate efficacy and safety in subjects with advanced or metastatic malignant melanoma	21
ET-B-005	An open-label non-randomized multicenter 3-group study of GIST, STS/single prior treatment, and STS/multiple prior treatments	126
ET-B-008	Open-label non-randomized, single-arm multicenter in advanced and/or metastatic breast carcinoma, malignant melanoma, renal carcinoma, and sarcoma subjects: Pre-treated soft tissue sarcoma carcinoma, malignant	143
ET-B-009	Open-label, uncontrolled multicenter 2-step study of Yondelis® as salvage treatment of subjects with advanced ovarian carcinoma failing platinum and taxane regimens	59
ET-B-010	Open-label, single-arm, multicenter study, with PK to assess influence of prophylactic dexamethasone in subjects with advanced stage and/or metastatic soft tissue sarcoma	41
ET-B-011	Phase 2 study of Yondelis® as second line therapy in subjects with advanced uterine carcinoma	1
ET-B-013	Open-label, single-arm, multicenter study of Yondelis® in subjects with previously treated advanced colorectal cancer	21
ET-B-016	Open-label single-arm, multicenter study of Yondelis® as first line therapy in advanced and/or metastatic soft tissue sarcoma subjects	36

Study	Short Title	Exposure
ET-B-017	Open-label non-randomized, multicenter single-arm study of Yondelis® as second or third line therapy in advanced and/or metastatic soft tissue sarcoma subjects	36
ET-B-018	Open-label single-arm, multicenter study of Yondelis® in advanced and/or metastatic gastrointestinal stromal tumors	20
ET-B-019	Open-label single-arm, multicenter study of Yondelis® as salvage therapy in metastatic osteosarcoma	25
ET-B-020	Unresectable Malignant Pleural Mesothelioma	4
ET-B-021	Open-label, non-randomized, multicenter, 2-group (previously treated or untreated) of Yondelis® as treatment of subjects with advanced non-small cell lung cancer (NSCLC)	30
ET-B-022	Open label, non-randomized, multicenter 2-group study (≤2 prior treatments and >2 prior treatments) of Yondelis® in subjects with advanced and/or metastatic soft tissue sarcoma previously treated with chemotherapy	68
ET-B-023	Open-label, uncontrolled, multicenter 2-step, study in pre-treated adult and pediatric subjects with advanced or recurrent sarcomas	75
ET-B-025	Study of efficacy and safety in men with androgen-independent advanced prostate carcinoma	58
ET-B-026	Open-label, randomized study of efficacy and safety in subjects with advanced ovarian cancer comparing 24-hr and 3-hr regimens of Yondelis®	107
ET-B-027	Phase II, multicenter, open-label, clinical trial of Yondelis® (Trabectedin) in Metastatic Breast Cancer Patients with triple negative profile (ER-, PR-, HER2-), HER2 overexpressing tumors and BRCA1 or BRCA2 mutation carriers	124
ET-B-028	A multicenter Phase II clinical trial of neoadjuvant trabectedin (Yondelis®) in patients with localized myxoid / round cell liposarcoma	29
ET-B-029	Phase II trial of trabectedin in patients with advanced NSCLC with XPG and/or ERCC1 Overexpression and BRCA1 Under-expression after progression on platinum based chemotx	18
ET-B-031	ET-B-031-10 Phase II advanced breast cancer Over/under expressing XPG	44
ET-C-002	A randomized multicenter Phase III trial of trabectedin (Yondelis®) vs Doxo-based chemotherapy as first line therapy in patients with translocation related sarcoma	61
Total		**1,672**

Key: STS= Soft Tissue Sarcoma; NSCLC= Non Small Cell Lung Cancer; GIST= Gastrointestinal Stromal Tumour; PK= Pharmacokinetics; XPG= Xeroderma Pigmentosum Complementation Group G

Table 3: Cumulative Subject Exposure to Trabectedin in Janssen Products LP Sponsored Clinical Trials

Study ID	Short Title	Exposure
ET743-INT-11	Study of efficacy and safety in subjects with advanced ovarian cancer (platinum sensitive and partially resistant)	147
ET743-INT-3	Study of efficacy and safety of 2 dosing regimens in subjects with advanced breast cancer	52
ET743-OVA-301	Study of efficacy and safety in subjects with advanced relapsed ovarian cancer	333
ET743-OVC-1001	A Single-blind, multicenter, placebo controlled, sequential design study evaluating the potential effects of a single-dose of trabectedin on the CHEMO intervals of the electrocardiogram	75
ET743-OVC-1002	DDI - rifampin	11
ET743-OVC-1003	DDI - ketoconazole	12
ET743-OVC-1004	Hepatic impairment	15
ET743-OVC-3006	Study of efficacy and safety in subjects with advanced relapsed ovarian cancer	286
ET743-SAR-1001	Phase 1 study to determine the dose of the combination of Yondelis® + doxorubicin at which neutropenia is manageable with the use of G-CSF in subjects with STS	41
ET743-SAR-3006	Local STS in China	18
ET743-SAR-3007	A randomized controlled study of Yondelis® or Dacarbazine for the treatment of advanced L sarcoma previously treated with Anthracycline & Ifosfamide	378

Study ID	Short Title	Exposure
ET743-STS-201	Study of efficacy and safety of 2 dosing regimens in subjects with L-sarcomas following treatment with an anthracycline with or without ifosfamide	260
ET743-USA-1	Study of efficacy and safety in subjects with persistent or relapsed endometrial cancer	50
ET743-USA-11	Phase1 to determine MTD of Yondelis® + DOXIL® in subjects with advanced malignancies	36
ET743-USA-2	Phase 1 to determine MTD of Yondelis® + docetaxel in subjects with advanced malignancies	49
ET743-USA-3	Phase 1 to determine MTD of Yondelis® + capecitabine in subjects with advanced malignancies	40
ET743-USA-7	Phase 1 to determine MTD of Yondelis® + gemcitabine in subjects with advanced malignancies	15
Total		**1,818**

Key: STS= Soft Tissue Sarcoma; CHEMO= Chemotherapy; DDI= Drug-Drug Interaction; G-CSF= Granulocyte Colony-Stimulating Factor; MTD= Maximum Tolerated Dose

Table 4: Cumulative Subject Exposure to Trabectedin in Taiho Pharmaceutical Co. Ltd Sponsored Clinical Trials

Study ID	Short Title	Exposure
10045020	A Phase I and pharmacokinetic study to assess the tolerability of ET-743 administered as a continuous intravenous infusion over 24 hours every 21 days in patients with soft tissue sarcoma	15
10045030	Phase II study of ET-743 in patients with translocation-related sarcomas	39
10045040	Safety study of ET-743 in patients with translocation-related sarcomas	30
10045050	Safety assessment study of ET-734 in patients with translation-related sarcoma	28
10045060	A phase 1 study of ET-743 in combination with pegylated liposomal doxorubicin (PLD) in patients with advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer	18
Total		**130**

Table 5: Cumulative Subject Exposure to Trabectedin in IIS

Study ID	Short Title	Exposure
AGO-OVAR 2.32	Trabectedin/PLD versus continuation of platinum-based chemotherapy in patients with disease stabilization and no symptom benefit under platinum-based chemotherapy for recurrent ovarian cancer	9
ATREUS	A phase II study on the activity of trabectedin in pre-treated epithelioid or biphasic/carcomatoid malignant pleural mesothelioma (MPM)	136
CSET 2014-2154 (TSAR)	Phase 3 randomized study comparing trabectedin to the best supportive care in patients with advanced soft tissue sarcoma	101
EORTC-1320	Trabectedin for recurrent grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group	90
EORTC-1447	Maintenance therapy with trabectedin versus observation after first line treatment with doxorubicin of patients with advanced or metastatic soft tissue sarcoma	6
EORTC-62091/ SARC-20/ TRUSTS/ ET-D-006-09	phase IIb/III multicenter study comparing the efficacy of Trabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in pts with advanced or metastatic Untreated STS	90
ET743-OVC-2002	Recurrent or persistent ovarian, fallopian tube or primary peritoneal	71
ET743-SAR-2002	IIS study in subjects with advanced, persistent or recurrent uterine leiomyosarcoma	20
ET743-SAR-2004	IIS A phase 1 trial and pharmacokinetic study of trabectedin in children and adolescent with relapsed or refractory solid tumors	12
ET743-SAR-2005	IIS pediatric study in subjects with STS, weight > 16 kg	50
ET-A-008	A phase 1 study of ET-743 in paediatric refractory solid tumors	12

Study ID	Short Title	Exposure
ET-D-004-09 GEIS-20	Randomized, open, multicenter, prospective, Phase II clinical trial of doxorubicin vs trabectedin plus doxorubicin in the first line treatment of patients with advanced non operable/metastatic soft tissue sarcomas	55
ET-D-005-11/ CSET 1485, LMS-02	Phase II multicentre study to determine the efficacy of doxorubicin in combination with trabectedin (Yondelis®) as a first-line treatment for patients presenting with metastatic leiomyosarcoma (uterine or soft tissue) and/or inoperable relapse	110
ET-D-008-09/ T-DIS-1001	Phase II, randomized trial to evaluate two strategies: Continuing versus intermittent (drug-holiday) trabectedin-regimen in patients with advanced STS experiencing response or stable disease after the 6th cycle	53
ET-D-009-10/ Inovatyon	Phase III international, randomized study of Trabectedin plus PLD versus Carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum	311
ET-D-013-10/ PACT-18	Single arm salvage study in subjects with metastatic pancreatic adenocarcinoma	25
ET-D-014-11/ GISG-02	Phase I dose escalating trial evaluating the combination of Gemcitabine and Trabectedin in patients with advanced and/or metastatic leiomyosarcoma or liposarcoma	5
ET-D-015-11/ MITO-15	Phase II study with trabectedin in BRCA1 and BRCA2 mutation carrier and BRCAness phenotype advanced ovarian cancer patients	100
GEIS-37 (TRASTS)	Phase I-II prospective trial, multicenter, open label, exploring the combination of trabectedin plus Radiotherapy in Soft Tissue Sarcoma patients	163
GEIS-75	Phase II multicohort trial of trabectedin and low-dose radiation therapy in advanced/metastatic sarcomas	61
Hyper-TET	Trabectedin combined with Regional Hyperthermia as second line treatment for adult patients with advanced soft-tissue sarcoma	120
IRFMN-OVA 6152	Multicenter, randomized, non-comparative, open label phase II trial on the efficacy and safety of the combination of bevacizumab and trabectedin with or without carboplatin in adult women with platinum partially sensitive recurring ovarian cancer	71
ISG-ARTICLE	A Randomized & Observational phase II trial assessing the activity of A Randomized & Observational phase II trial assessing the activity of Trabectedin vs gemCitabine in patients with metastatic or locally advanced LEiomyosarcoma pretreated with conventional hemotherapy	56
ISG-STS 10-01/ ISG-GEIS-10-01	Localized high-risk STS of the extremities and trunk wall in adults: an integrating approach comprising standard vs histotype-tailored neoadyuvant chemotherapy	45
ISG-STS-TRAB-2012 (TRAVELL)	A phase II study on trabectedin in advanced retroperitoneal leiomyosarcoma and well differentiated/dedifferentiated liposarcoma	105
JCOG1802	A randomized phase II trial of 2nd line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin and pazopanib (2ND-STEP)	41
LMS04	Randomised phase III multicentric study comparing efficacy of doxorubicin with trabectedin followed by trabectedin in non-progressive patients versus doxorubicin alone as first-line therapy in patients with metastatic or unresectable leiomyosarcoma (uterine or soft tissue)	74
MITO 23	Randomized phase III trial on Trabectedin (ET-743) vs clinician's choice chemotherapy in recurrent ovarian, primary peritoneal or fallopian tube cancers of BRCA mutated or BRCAness phenotype patients	122
MITO 26	Phase II on trabectedin in the treatment of advanced uterine and ovarian carcinoma	47
MITO 30	Phase II study on the combination of Trabectedin and Olaparib for advanced, platinum- resistant ovarian cancer	31
NiTraSarC	Combined treatment with Nivolumab and Trabectedin in patients with metastatic or inoperable soft tissue Sarcomas - The NiTraSarc Phase II Trial	92
OLATRAST	Phase-I clinical trial of Olaratumab plus Trabectedin in patients with soft-tissue sarcoma	17

Study ID	Short Title	Exposure
PIPER	Prospective identification of predictive biomarkers of trabectedin efficacy in non-l soft-tissue sarcoma patients	29
PR Trab-PT	Reintroduction of platinum-based therapy after trabectedin treatment in platinum-resistant relapsed ovarian cancer patients	10
R279741SAR1005	A Phase I Study to Evaluate the Safety of Trabectedin Administered as a 1-Hour Infusion in Ewing Sarcoma Patients in Combination with Low Dose Irinotecan and3'-Deoxy-3'-18F Fluorothymidine (18F-FLT)	31
R279741SAR2006	Phase II Multi-Center Trial of Trabectedin in Combination with Olaparib in Advanced Unresectable or Metastatic Sarcoma	29
REPRAB-MITO 36	Rechallenge with pegylated liposomal doxorubicin added to trabectedin in recurrent ovarian cancer: a multicenter prospective trial	43
STRADA	Solitary fibrous tumor: phase II study on TRabectedin versus Adriamycin plus DAcarbazine in advanced patients (STRADA)	24
TARMIC	Targeting Microenvironment and Cellular Immunity in Sarcomas Weekly trabectedin combined with Metronomic Cyclophosphamide in Patients with Advanced Pre-treated Soft-tissue Sarcomas. A Phase I/II study	50
TOMAS	A phase Ib study on the combination of trabectedin and olaparib in unresectable advanced/metastatic sarcomas after failure of standard therapies	50
TOMAS 2	Phase 2 randomized trial of trabectedin + olaparib vs trabectedin in advanced, metastatic or unresectable soft tissue sarcoma after failure of standard treatments	130
TOP-ART	Randomized Phase-II Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumours Harboring DNA Repair Deficiencies/ TOP-ART	61
TR1US	Safety and activity of trabectedin as first line in advanced STS patients unfit to receive standard chemotherapy: a prospective phase II study with clinical and molecular correlates	24
TRAMANT	Maintenance therapy with Trabectedin after combination therapy Liposomal Doxorubicin plus Trabectedin vs Liposomal Doxorubicin plus Trabectedin in patients affected by relapsed ovarian cancer recurring between 6 and 12 months after platinum-based chemotherapy	69
TRAMUNE	Trabectedin combined with durvalumab (MEDI4736) in patients with advanced pre-treated soft-tissue sarcomas and ovarian carcinomas. A Phase Ib study	40
TRANSITION1	A Phase 2, prospective study to evaluate the activity and efficacy of trabectedin treatment in patients with partially platinum-sensitive, recurrent ovarian cancer.	18
MCS-ET-D-067-20	Phase II study on Trabectedin in advanced rearranged Mesenchymal chondrosarcoma	4
Total		**2,913**

Key: BRCA= breast cancer gene; PLD= Pegylated Liposomal Doxorubicin; MPM= Malignant Pleural Mesothelioma; STS= Soft Tissue Sarcoma

Trabectedin has algo been administered to patients in EAPs or individual compassionate use, the cumulative exposure is presented in Table 6:

Table 6: Cumulative Subject Exposure to Trabectedin in EAPs/Compassionate Use

Study ID	Short Title	Exposure
ET743-INV-IND	Expanded access Single patient IND	609
ET743-NPP	Named Patient Program (Compassionate Use)	242
ET743-SAR-3002	Expanded access study to replace single patient IND access for subjects with relapsed or refractory STS, limited to USA, Canada and Israel	3,253
PhM Compassionate use	Compassionate Use Program for STS patients in Europe	1,787
R279741SAR4004	Yondelis Access Program	1
Total		**5,892**

Key: ID=Identification; IND=Investigational New Drug; STS=Soft Tissue Sarcoma; USA=United States of America

In this Risk Management Plan (RMP), the population mainly used for the characterization of the safety concerns corresponds to patients enrolled in the following completed clinical trials:

Completed randomised trials:

ET743-SAR-3007, the pivotal phase 3 study for L-types sarcoma US New Drug Application, a randomised controlled study of trabectedin versus dacarbazine for the treatment of advanced liposarcoma or leiomyosarcoma which enrolled 378 patients treated with trabectedin monotherapy at 1.5 mg/m^2 every q3wk 24-h in drug arm and 172 patients treated with dacarbazine at 1gr/m^2 in the control arm as of 05 January 2015 (this study is included in the integrated safety summary [ISS]-25).

ET743-STS-201, the pivotal phase 2 study for sarcoma supporting EU and rest of the world marketing authorisation application (MAA), a randomised, multicentre, open-label study of trabectedin 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 which enrolled 260 patients treated with trabectedin as of 03 December 2010. Among those patients, 130 received trabectedin at 1.5 mg every q3wk 24-h in drug arm and 130 received trabectedin at 0.58 mg every qwk 3-h in control arm (this study is included in ISS-25).

ET-C-002-07, a randomised phase 3 trial of trabectedin versus doxorubicin-based chemotherapy First-Line Therapy in patients with translocation-related sarcomas (TRS), designed and conducted to address the post-authorisation commitment (SOB001) requested by the Committee for Medicinal Products for Human Use (62) at the time of trabectedin MAA in the EU which enrolled 61 were treated with trabectedin monotherapy at 1.5 mg/m^2 every q3wk 24-h in drug arm, and 57 with doxorubicin-based chemotherapy (36 with doxorubicin as single-agent, and 21 with doxorubicin and ifosfamide in combination) in the control arm with a safety data cut-off-date of 20 August 2012 (this study is not included in ISS-25).

ET743-OVA-301, the pivotal study for the treatment of patients with platinum-sensitive ROC with a safety data cut-off-date of 01 May 2009 and a cut-off-date for efficacy data of 12 November 2010. In total, 633 patients were enrolled in this study; 333 patients received trabectedin at 1.5 mg/m^2 every q3wk 24-h plus PLD in drug arm and 330 received PLD in control arm (this study is not included in ISS-25).

ET743-OVC-3006, a randomized phase 3 trial of trabectedin and Doxil®/Caelyx® with Doxil®/Caelyx® monotherapy treatment of advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer. Five hundred seventy-six subjects were randomized, 289 subjects in the trabectedin+PLD arm and 287 subjects in the PLD arm. Eight subjects did not receive study drug (3 subjects in the trabectedin+ PLD arm and 5 subjects in the PLD monotherapy arm) due to worsening of health status (5 subjects) or withdrawal of subject consent (3 subjects). The remaining 568 subjects received at least 1 dose of study medication (286 subjects received trabectedin+ PLD and 282 received PLD alone (this study is included in ISS-25).

All clinical trials including open extensions:

These clinical trials include data of 1,719 patients treated with trabectedin from ISS-25 as well as 61 patients from study ET-C-002-07, 333 patients from study ET473-OVA-301 and 1,803 subjects from the EAP (ET743-SAR-3002 up to the clinical study report [CSR] cut-off date of 01 October 2010).

ISS-25 set comprises pooled data from 24 trabectedin single agent in various tumour types, including 23 Phase 2 studies and 1 Phase 3 study (ISS-25) with a cut-off-date of 05 January 2015.

ISS 25 include data from 2,005 patients from the following clinical trials:

- 1,040 patients from ISS for sarcoma which includes, among other, data for ET743-STS-201 and ET743-SAR-3007, the 2 pivotal randomised studies for sarcoma and other clinical trials as shown in Table 7

- 581 patients from ISS for ovarian, a pooled data from Phase 2 trials of trabectedin as a single agent in women in platinum-sensitive ROC and 1 Phase 3 trial of trabectedin and Doxil®/Caelyx® with Doxil®/Caelyx® monotherapy treatment of advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer
- 384 patients from ISS for other cancers as shown in Table 7

Data from 1,803 patients treated in the EAP at the time of the CSR cut-off-date of 01 October 2010 is also included in this RMP.

In total, data from 4,202 (2,005 from ISS 25, 1,803 from EAP ET743-SAR-3002, 333 from ET743-OVA-301 and 61 patients from ET-C-002-07) patients treated with trabectedin are included in the analysis of this RMP.

During the development of trabectedin, the following regimens were used:

- Q3wk 24-h: 24-h infusion every 3 weeks (Day 1 of a 3-week cycle), at a starting dose of 1.5 mg/m^2 (the most extensively evaluated regimen in STS patients).
- Q1wk 3-h: 3-h infusion weekly for the first 3 of every 4 weeks (Days 1, 8, and 15 of a 4-week cycle), at a starting dose of 0.58 mg/m^2.
- Q3wk 3-h: 3-h infusion every 3 weeks (Day 1 of a 3-week cycle), at a starting dose of 1.3 mg/m^2.
- Q3wk 24-h (24-h infusion every 3 weeks at a starting dose of 1.5 mg/m^2) and q3wk 3-h (3-h infusion every 3 weeks at a starting dose of 1.1 mg/m^2) ae both approved trabectedin regimens respectively in both indications STS and platinum-sensitive ROC.

Table 7 shows all randomised trials for STS (ET743-SAR-3007, ET743-STS-201, ET-C-002-07) and ROC (ET743-OVA-301 and ET743-OVC-3006) as well as all clinical trials including ISS-25 (that does not include 2 of the 4 randomised studies: ET743-OVA-301 with 333 patients, ET-C-002-07 study with 61 patients exposed) and the EAP ET743-SAR-3002 (1,803 subjects treated up to the CSR cut-off date of 01 October 2010).

Table 7: SIII Clinical Trial Exposure

Yondelis® studies / Description	**Number of patients treated**
Randomised trials **ET743-STS-201** Pivotal study for SOFT TISSUE SARCOMA (EU and Rest of the World) Cut-off-date: 03 December 2010	
Trabectedin 1.5 mg/m^2 q3wk 24-h (drug arm)	130
Trabectedin 0.58 mg/m^2 q1wk 3-h (control arm)	130
ET743-SAR-3007- Pivotal study for SOFT TISSUE SARCOMA (US) Cut-off-date: 05 January 2015	
Trabectedin 1.5 mg/m^2 q3wk 24-h (drug arm)	378
Dacarbazine (control arm)	172
ET-C-002-07 First-Line Therapy -Translocation-Related Sarcomas (TRS)- CHMP post-authorisation commitment SOB001* Cut-off-date: 20 August 2012	
Trabectedin 1.5 mg/m^2 q3wk 24-h (drug arm)	61
Doxorubicin-based chemotherapy - doxorubicin alone or doxorubicin plus ifosfamide (control arm)	57
TOTAL Sarcomas	928
Trabectedin monotherapy arm	**699**
Non-trabectedin containing arm	229
ET743-OVA- 301 – Pivotal study for ROC* Cut-off-date: Safety 01 May 2009 (12 November 2010 FU OS CSR/ report in 2011)	
Trabectedin 1.1 mg q3wk 3-h + PLD (drug arm)	**333**
PLD (control arm)	330
ET743-OVC-3006- Pivotal study for ROC*	
Trabectedin 1.1 mg q3wk 3-h + PLD (drug arm)	**286**

Yondelis® studies / Description			Number of patients treated
PLD (control arm)			282
TOTAL (RELAPSED OVARIAN CANCER)			1,231
Trabectedin monotherapy arm			619
Non-trabectedin containing arm			612
All clinical trials Integrated safety summary (ISS-25) – Phase II and III single agent Cut-off-date: 05 January 2015			
SUBSETS			
ISS FOR SARCOMA			
Study	**Regimen**	**Cancer type**	**Number of patients treated**
ETB00598	q3wk; 24-h (1.5mg/m^2)	STS	126
ETB00898	q3wk; 24-h (1.5mg/m^2)	STS	84
ETB01099	q3wk; 3-h (1.3 mg/m^2)	STS	8
ETB01699	q3wk; 24-h (1.5mg/m^2)	STS	36
ETB01799	q3wk; 24-h (1.5mg/m^2)	STS	36
ETB01899	q3wk; 24-h (1.5mg/m^2)	STS	20
ETB01999	q3wk; 24-h (1.5mg/m^2)	STS	25
ETB02200	q3wk; 3-h (1.3 mg/m^2)	STS	4
ETB02300	q3wk; 3-h (1.3 mg/m^2)	STS	34
ETB02806	q3wk; 24-h (1.5mg/m^2)	STS	29
ET743STS201	q3wk; 24-h (1.5mg/m^2)	STS	130
ET743SAR3007	q1wk; 3-h (0.58 mg/m^2) q3wk; 24-h (1.5mg/m^2)	STS STS	130 378
ISS for SARCOMA SUBTOTAL			**1,040**
ISS FOR OVARIAN			
Study	**Regimen**	**Cancer type**	**Number of patients included**
ETB00999	q3wk; 3-h(1.3mg/m^2)	Ovarian	41
ET743INT11	q wk; 3-h(0.58mg/m^2)	Ovarian	147
ETB02603	q3wk; 24-h(1.5mg/m^2)	Ovarian	54
	q3wk; 3-h(1.3mg/m^2)	Ovarian	53
ET743OVC3006	q3wk; 3-h (1.1 mg/m^2)/Doxil®	Ovarian	286
ISS for RELAPSING PLATINUM-SENSITIVE OVARIAN CANCER SUBTOTAL			**581**
TOTAL (SARCOMA+ OVARIAN)			**1,621**
ISS FOR OTHER CANCERS			
Study	**Regimen**	**Cancer type**	**Number of patients treated**
ETB00199	q3wk; 3-h (1.3 mg/m^2)	Breast	1
ETB00299	q3wk; 3-h (1.3 mg/m^2)	Melanoma	2
ETB00898	q3wk; 24-h (1.5mg/m^2)	Breast	26
	q3wk; 24-h (1.5mg/m^2)	Melanoma	12
	q3wk; 24-h (1.5mg/m^2)	Renal	21
ETB01399	q3wk; 3-h (1.3 mg/m^2)	Colorectal	10
ETB02100	q3wk; 3-h (1.3 mg/m^2)	Lung	30
ETB02502	q3wk; 24-h (1.5mg/m^2)	Prostate	5
	q wk; 3-h (0.58 mg/m2)	Prostate	33
ETB02706	q3wk; 3-h (1.3 mg/m^2)	Breast	124
ETB02907	q3wk; 3-h (1.3 mg/m^2)	Lung	18
ET743INT3	q wk; 3-h (0.58 mg/m^2)	Breast	27
	q wk; 3-h (1.3 mg/m^2)	Breast	25
ET743USA1	q3wk; 3-h (1.3 mg/m^2)	Endometrial	50
ISS for OTHER CANCERS SUBTOTAL			**384**
TOTAL ISS 25			**2,005**

Yondelis® studies / Description		Number of patients treated
EAP ET743-SAR-3002– Expanded access programme- **AS PART OF THE ALL CLINICAL TRIALS SARCOMA ONLY INDICATION **** Cut-off-date: CSR 01 October 2010		
EAP SAR3002	q3wk; 24-h (1.5 mg/m^2)	1,803
TOTAL TRABECTEDIN TREATED PATIENTS (ISS 25, ET-C-002-07* and ET743-OVA-301* + ET743-SAR-3002*)		**4,202**

* Studies not included in the ISS (ISS-25 included 23 phase 2 studies and 2 phase 3 study)

** Since the Clinical Study Report cut-off-date the study clinical database was closed, and only serious adverse event (SAE) have been collected in the Global Safety database for Yondelis®.

Table 8: SIII DURATION OF EXPOSURE (by Indication) (The Randomised, Blinded Clinical Trials Population)

Duration of Exposure (at least)	Patients	Person-Months
Indication: Soft Tissue Sarcoma (ET743-STS-201, ET-C-002-07 and ET743-SAR-3007)		
Q3wk 24-h	(N=569)	
>0 month and <1month	53	36.5
≥1 month	516	3,090.6
≥3month	296	2,687.0
≥6 month	172	2,128.6
≥9 month	116	1,710.8
≥12 month	59	1,110.7
≥15 month	41	866.1
≥18 month	23	571.6
≥21 month	13	381.1
≥24 month	8	267.0
Total person-months	**569**	**3,127.2**
Qwk 3-h	(N=130)	
>0 month and <1month	19	17.0
≥1 month	111	496.0
≥3month	61	397.5
≥6 month	27	245.1
≥9 month	9	107.2
≥12 month	2	34.4
≥15 month	1	20.6
≥18 month	1	20.6
≥21 month	0	0
≥24 month	0	0
Total person-months	**130**	**513.0**
Subtotal (STS-201, ET-C002-07 and SAR3007)	(N=699)	
>0 month and <1month	72	53.6
≥1 month	627	3,586.6
≥3month	357	3,084.5
≥6 month	199	2,373.7
≥9 month	125	1,818.0
≥12 month	61	1,145.0
≥15 month	42	886.6
≥18 month	24	592.2
≥21 month	13	381.1
≥24 month	8	267.0
Total person-months	**699**	**3,640.2**
Indication: ROC (ET743-OVA-301 and ET743-OVA-3006)	(N=619)	
Q3wk 3-h		
>0 month and <1month	49	33.9
≥1 month	570	3,286.1
≥3month	417	2,980.3

Duration of Exposure (at least)	Patients	Person-Months
≥6 month	198	1,972.9
≥9 month	103	1,285.1
≥12 month	40	637.6
≥15 month	17	325.9
≥18 month	11	230.9
≥21 month	5	115.3
≥24 month	2	48.9
Total person-months	**619**	**3,320.0**

Table 9: SIII DURATION OF EXPOSURE (Totals) (The Randomised, Blinded Clinical Trials Population)

Duration of Exposure (at least)	Patients	Person-Months
Indication: Soft Tissue Sarcoma and Relapsed platinum-sensitive ovarian cancer	(N=1,318)	
>0 month and <1month	121	87.5
≥1 month	1,197	6,872.7
≥3month	774	6,064.8
≥6 month	397	4,346.5
≥9 month	228	3,103.1
≥12 month	101	1,782.6
≥15 month	59	1,212.5
≥18 month	35	823.0
≥21 month	18	496.4
≥24 month	10	315.9
Total person-months	1,318	6,960.2

Table 10: SIII DOSE OF EXPOSURE (by Indication) (The Randomised, Blinded Clinical Trials Population)

Dose of Exposure	Patients	Person-Months
Indication: Soft Tissue Sarcoma (ET743-STS-201, ET-C-002-07 and ET743-SAR-3007)	(N=699)	
Q3wk 24-h		
1.5 mg/m^2	569	3,127.2
Qwk 3-h		
0.58 mg/m^2	130	513.0
Total	**699**	**3,640.2**
Indication: Relapsed platinum-sensitive ovarian cancer (ET743-OVA-301 + ET743-OVA-3006)	(N=619)	
Q3wk 3-h		
1.1 mg/m^2	619	3,320.0
Total	**619**	**3,320.0**

Table 11: SIII DOSE OF EXPOSURE (Totals) (The Randomised, Blinded Clinical Trials Population)

Dose of Exposure	Patients (N=1,318)	Person-Months
0.58 mg/m^2	130 (9.9%)	513.0
1.1 mg/m^2	619 (47%)	3,320
1.5 mg/m^2	569 (43.2%)	3,127.2
Total	**1,318**	**6,960.2**

Table 12: SIII Exposure by AGE GROUP AND GENDER (by indication) (the Randomised, Blinded Clinical Trials Population)

	Men[a]		Women	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
Indication: Soft Tissue Sarcoma (ET743-STS-201, ET-C-002-07 and ET743-SAR-3007)				

	Men[a]		Women	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
	(N=253)		(N=446)	
Q3wk 24-h				
<18 years	0	0	0	0
18 – 54 years	92	528.7	189	962.8
55 – 64 years	55	274.8	118	674.6
65 – 74 years	45	263.5	49	286.9
≥75 years	7	44.7	14	91.1
Total	**199**	**1,111.7**	**370**	**2,015.5**
Qwk 3-h				
<18 years	0	0	0	0
18 – 54 years	30	103.8	38	122.1
55 – 64 years	16	80.3	27	107.0
65 – 74 years	6	37.9	11	51.3
≥75 years	2	10.6	0	0
Total	**54**	**232.6**	**76**	**280.4**
All regimens				
<18 years	0	0	0	0
18 – 54 years	122	632.5	227	1,084.9
55 – 64 years	71	355.1	145	781.6
65 – 74 years	51	301.4	60	338.2
≥75 years	9	55.3	14	91.1
Total	**253**	**1,344.3**	**446**	**2,295.9**
Indication: Relapsed platinum-sensitive ovarian cancer (ET743-OVA- 301 + ET743-OVA-3006)				
	NA[a]	NA[a]	(N=619)	
<18 years			0	0
18 – 54 years			233	1,368.7
55 – 64 years			198	1,105.1
65 – 74 years			151	673.3
≥75 years			37	173.0
Total			**619**	**3,320.0**

[a] Males are not represented in the ET743-OVA- 301 and ET743-OVA-3006 trials

Table 13: SIII Exposure by AGE GROUP and GENDER (Totals) (the Randomised, Blinded Clinical Trials Population)

	Men (N=253)[a]		Women (N=1,065)	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
Both indications (STS and Relapsed platinum-sensitive ovarian cancer)				
<18 years	0	0	0	0
18 – 54 years	122	632.5	460	2,453.6
55 – 64 years	71	355.1	343	1,886.7
65 – 74 years	51	301.4	211	1,011.5
≥75 years	9	55.3	51	264.1
Total	**253**	**1,344.3**	**1,065**	**5,615.9**

[a] Males are not represented in the ET743-OVA- 301 and ET743-OVA-3006 trials

Table 14: SIII Exposure by ETHNIC or RACIAL ORIGIN (by Indication) (the Randomised, Blinded Clinical Trials Population)

Race	**Patients**	**Person-Months**
Indication: Soft Tissue Sarcoma	**(N=699)**	
Q3wk 24-h		
White	464	2,656.0
Black or African American	59	292.9
Asian	16	51.7

Race	Patients	Person-Months
Other[a]	10	41.8
Unknown[b]	20	84.7
Total	**569**	**3,127.2**
Qwk 3-h		
White	121	478.6
Black or African American	4	20.5
Asian	3	9.2
Other[a]	2	4.6
Total	**130**	**513.0**
Both regimens		
White	585	3,134.5
Black or African American	63	313.5
Asian	19	61.0
Other[a]	12	46.5
Unknown[b]	20	84.7
Total	**699**	**3,640.2**
Indication: Relapsed platinum-sensitive ovarian cancer	(N=619)	
White	520	2,906.4
Black or African American	5	14.3
Asian	80	318.0
Other[a]	10	62.1
Unknown[b]	4	19.2
Total	**619**	**3,320.0**

[a] "Other" From the Maghreb, Hispanic or Mixed race
[b] Information not collected

Table 15: SIII Exposure by ETHNIC ORIGIN (Totals) (the Randomised, Blinded Clinical Trials Population)

Race	Patients	Person-Months
Indication: Soft Tissue Sarcoma and Relapsed platinum-sensitive ovarian cancer	(N=1,318)	
White	1,105	6,040.9
Black or African American	68	327.7
Asian	99	379.0
Other[a]	22	108.6
Unknown[b]	24	103.9
Total	**1,318**	**6,960.2**

[a] "Other" From the Maghreb, Hispanic or Mixed race
[b] Information not collected

Exposure in All Clinical Trials Including Open Extensions

As described previously, all clinical trials include data of 4,202 patients treated with trabectedin from the ISS, those from the EAP (ET743-SAR-3002), ET743-OVA-301, ET-C-002-07 and ET743-OVC-3006 studies.

Table 16: SIII DURATION OF EXPOSURE (by Indication) (All Clinical Trials Population Including Open Extensions)

Duration of Exposure (at least)	Patients	Person-Months
Indication: Soft Tissue Sarcoma		
Q3wk 24-h	(N=2,728)	
EAP ET743-SAR-3002		
>0 month and <1month	292	201.5
≥1 month	1,511	7,570.0
≥3month	722	6,117.6

Duration of Exposure (at least)	Patients	Person-Months
≥6 month	388	4,656.1
≥9 month	229	3,468.3
≥12 month	130	2,440.0
≥15 month	83	1,810.3
≥18 month	45	1,184.3
≥21 month	31	912.2
≥24 month	22	709.5
Total	**1,803**	**7,771.5**
ISS studies for SARCOMA		
>0 month and <1month	109	75.2
≥1 month	816	4,232.2
≥3month	433	3,556.2
≥6 month	216	2,583.0
≥9 month	136	1,994.1
≥12 month	71	1,310.7
≥15 month	46	970.1
≥18 month	26	642.0
≥21 month	15	432.1
≥24 month	9	296.0
Total	**925**	**4,307.4**
Qwk 3-h	(N=130)	
ISS studies for SARCOMA		
>0 month and <1month	19	17.0
≥1 month	111	496.0
≥3month	61	397.5
≥6 month	27	245.1
≥9 month	9	107.2
≥12 month	2	34.4
≥15 month	1	20.6
≥18 month	1	20.6
≥21 month	0	0
≥24 month	0	0
Total	**130**	**513.0**
Q3wk 3-h (1.3 mg/m^2)	(N=46)	
ISS studies for SARCOMA		
>0 month and <1month	13	9.0
≥1 month	33	85.0
≥3month	9	43.7
≥6 month	2	15.6
≥9 month	0	0
≥12 month	0	0
≥15 month	0	0
≥18 month	0	0
≥21 month	0	0
≥24 month	0	0
Total	**46**	**93.9**
ISS studies for SARCOMA (all regimens) + EAP ET743-SAR-3002	(N=2,904)	
>0 month and <1month	433	302.6
≥1 month	2,471	12,383.2
≥3month	1,225	10,115
≥6 month	633	7,499.8
≥9 month	374	5,569.6
≥12 month	203	3,785.1
≥15 month	130	2,801
≥18 month	72	1,846.9

Duration of Exposure (at least)	Patients	Person-Months
≥21 month	46	1,344.3
≥24 month	31	1,005.5
Total	**2,904**	**12,685.8**
Indication: Relapsed platinum-sensitive ovarian cancer		
Q3wk 3-h Doxil® (1.1 mg/m²)	(N=286)	
>0 month and <1month	25	17.3
≥1 month	261	1,566.4
≥3month	190	1,423.5
≥6 month	97	995.4
≥9 month	49	646.3
≥12 month	24	388.1
≥15 month	12	230.8
≥18 month	8	169.2
≥21 month	4	90.7
≥24 month	1	24.3
Total	**286**	**1,583.7**
Q3wk 3-h PLD (1.1 mg/m²)	(N=333)	
>0 month and <1month	24	16.6
≥1 month	309	1,719.7
≥3month	227	1,556.8
≥6 month	101	977.5
≥9 month	54	638.8
≥12 month	16	249.5
≥15 month	5	95.1
≥18 month	3	61.7
≥21 month	1	24.7
≥24 month	1	24.7
Total	**333**	**1,736.3**
Q3wk 3-h Sub total (1.1 mg/m²)	(N=619)	
>0 month and <1month	49	33.9
≥1 month	570	3,286.1
≥3month	417	2,980.3
≥6 month	198	1,972.9
≥9 month	103	1,285.1
≥12 month	40	637.6
≥15 month	17	325.9
≥18 month	11	230.9
≥21 month	5	115.3
≥24 month	2	48.9
Total	**619**	**3,320.0**
Q3wk 24-h	(N=54)	
>0 month and <1month	4	2.8
≥1 month	50	243.3
≥3month	34	208.8
≥6 month	11	107.4
≥9 month	5	62.8
≥12 month	4	53.6
≥15 month	0	0
≥18 month	0	0
≥21 month	0	0
≥24 month	0	0
Total	**54**	**246.1**
Qwk 3-h	(N=147)	
>0 month and <1month	21	19.3

Duration of Exposure (at least)	Patients	Person-Months
≥1 month	126	562.6
≥3month	69	445.6
≥6 month	28	249.1
≥9 month	5	77.3
≥12 month	3	57.8
≥15 month	3	57.8
≥18 month	1	22.6
≥21 month	1	22.6
≥24 month	0	0
Total	**147**	**582.0**
Q3wk 3-h (1.3 mg/m^2)	(N=94)	
>0 month and <1month	4	2.8
≥1 month	90	402.8
≥3month	57	336.1
≥6 month	19	161.7
≥9 month	3	44.6
≥12 month	2	33.2
≥15 month	1	21.0
≥18 month	1	21.0
≥21 month	0	0
≥24 month	0	0
Total	**94**	**405.5**
All regimens		
>0 month and <1month	78	58.8
≥1 month	836	4,494.8
≥3month	577	3,970.7
≥6 month	256	2,491.1
≥9 month	116	1,469.8
≥12 month	49	782.1
≥15 month	21	404.6
≥18 month	13	274.4
≥21 month	6	137.9
≥24 month	2	48.9
Total	**914**	**4,553.6**
Indication: Other types of cancer		
Q3wk 24-h	(N=64)	
>0 month and <1month	10	6.9
≥1 month	54	166.6
≥3month	20	102.4
≥6 month	5	44.7
≥9 month	2	21.7
≥12 month	0	0
≥15 month	0	0
≥18 month	0	0
≥21 month	0	0
≥24 month	0	0
Total	**64**	**173.6**
Qwk 3-h	(N=60)	
>0 month and <1month	10	9.2
≥1 month	50	178.8
≥3month	18	110.9
≥6 month	6	58.3
≥9 month	2	27.9
≥12 month	1	18.4
≥15 month	1	18.4

Duration of Exposure (at least)	Patients	Person-Months
≥18 month	1	18.4
≥21 month	0	0
≥24 month	0	0
Total	**60**	**188.0**
Q3wk 3-h (1.3 mg/m^2)	(N=260)	
>0 month and <1month	78	44.3
≥1 month	182	613.2
≥3month	72	407.7
≥6 month	19	182.3
≥9 month	6	85.1
≥12 month	5	75.4
≥15 month	2	36.2
≥18 month	1	19.8
≥21 month	0	0
≥24 month	0	0
Total	**260**	**657.5**
All regimens		
>0 month and <1month	98	60.4
≥1 month	286	958.7
≥3month	110	621.0
≥6 month	30	285.3
≥9 month	10	134.7
≥12 month	6	93.8
≥15 month	3	54.6
≥18 month	2	38.3
≥21 month	0	0
≥24 month	0	0
Total	**384**	**1,019.1**

Table 17: SIII DURATION OF EXPOSURE (Totals) (All Clinical Trials Population Including Open Extensions)

Duration of Exposure (at least)	Patients	Person-Months
All indications	(N=4,202)	
>0 month and <1month	609	1,874.4
≥1 month	3,593	16,384.2
≥3month	1,912	14,706.7
≥6 month	919	10,276.3
≥9 month	500	7,174.1
≥12 month	258	4,661.1
≥15 month	154	3,260.3
≥18 month	87	2,159.5
≥21 month	52	1,482.2
≥24 month	33	1,054.4
Total	**4,202**	**18,258.6**

Table 18: SIII DOSE OF EXPOSURE (by Indication) (All Clinical Trials Population Including Open Extensions)

Dose of Exposure	Patients	Person-Months
Indication: STS (ISS for Sarcoma + EAP ET743-SAR-3002)	(N=2,904)	
Q3wk 24-h - 1.5 mg/m^2	2,728	16,386.3
Qwk 3-h - 0.58 mg/m^2	130	513.0
Q3wk 3-h - 1.3 mg/m^2	46	93.9
Total	**2,904**	**16,993.2**
Indication: Relapsed platinum-sensitive ovarian cancer	(N=914)	

Dose of Exposure	Patients	Person-Months
PLD Q3wk 3-h - 1.1 mg/m^2	333	1,736.3
Doxil® Q3wk 3-h 1.1 mg/m^2	286	1,583.7
Q3wk 24-h - 1.5 mg/m^2	54	246.1
Qwk 3-h - 0.58 mg/m^2	147	582.0
Q3wk 3-h - 1.3 mg/m^2	94	405.5
Total	**914**	**4,553.6**
Indication: OTHER TYPES OF CANCER	(N=384)	
Q3wk 24-h - 1.5 mg/m^2	64	173.6
Qwk 3-h - 0.58 mg/m^2	60	188.0
Q3wk 3-h - 1.3 mg/m^2	260	657.5
Total	**384**	**1,019.1**

Table 19: SIII DOSE OF EXPOSURE (Totals) (All Clinical Trials Population Including Open Extensions)

Dose of Exposure	Patients (N=4,202)	Person-Months
All indications		
Q3wk 24-h - 1.5 mg/m^2	2,846	12,498.6
Qwk 3-h - 0.58 mg/m^2	337	1,283.0
Q3wk 3-h - 1.3 mg/m^2	400	1,157.0
PLD (only for platinum-sensitive ROC) Q3wk 3-h – 1.1 mg/m^2	333	1,736.3
Doxil® Q3wk 3-h - 1.1 mg/m^2	286	1,583.7
Total	**4,202**	**18,258.5**

Table 20: SIII Exposure by AGE GROUP AND GENDER (by Indication) (All Clinical Trials Population Including Open Extensions)

	Men[a]		Women[b]	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
Indication: Soft Tissue Sarcoma				
	(N=1,217)		(N=1,687)	
Q3wk 24-h				
EAP ET743-SAR-3002				
<18 years	1	0.7	0	0.0
18 – 54 years	392	1,683.4	550	2,378.5
55 – 64 years	192	746.3	318	1,502.9
65 – 74 years	120	547.9	154	670.3
≥75 years	43	121.8	33	119.7
Total	**748**	**3,100.1**	**1,055**	**4,671.3**
ISS for Sarcomas				
<18 years	9	12.9	2	2.1
18 – 54 years	208	894.2	293	1,381.4
55 – 64 years	94	393.1	154	789.0
65 – 74 years	65	311.0	69	363.3
≥75 years	12	56.3	19	104.0
Total	**388**	**1667.5**	**537**	**2,639.9**
Qwk 3-h				
<18 years	0	0	0	0
18 – 54 years	30	103.8	38	122.1
55 – 64 years	16	80.3	27	107.0
65 – 74 years	6	37.9	11	51.3
≥75 years	2	10.6	0	0
Total	**54**	**232.6**	**76**	**280.4**
Q3wk 3-h (1.3 mg/m^2)				
<18 years	4	5.9	2	5.3
18 – 54 years	20	45.2	13	24.4

	Men[a]		Women[b]	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
55 – 64 years	2	2.1	2	2.4
65 – 74 years	1	1.6	0	0
≥75 years	0	0	2	6.9
Total	**27**	**54.9**	**19**	**39.0**
All regimens (ISS for Sarcoma + EAP ET743-SAR-3002)				
<18 years	14	19.5	4	7.4
18 – 54 years	650	2,726.6	894	3,906.5
55 – 64 years	304	1,221.8	501	2,401.3
65 – 74 years	192	898.4	234	1,084.9
≥75 years	57	188.7	54	230.7
Total	**1,217**	**5,055.1**	**1,687**	**7,630.7**
Indication: Relapsed platinum-sensitive ovarian cancer (ET743-OVA-301 + ISS trials)				
PLD Q3wk 3-h (1.1 mg/m^2)				
<18 years			0	0
18 – 54 years			146	817.7
55 – 64 years			108	552.2
65 – 74 years			59	264.9
≥75 years			20	101.4
Total			**333**	**1,736.3**
Doxil® Q3wk 3-h (1.1 mg/m^2)				
<18 years			0	0
18 – 54 years			87	551.0
55 – 64 years			90	552.8
65 – 74 years			92	408.5
≥75 years			17	71.5
Total			**286**	**1,583.8**
Q3wk 24-h (1.5 mg/m^2)				
<18 years			0	0
18 – 54 years			28	150.2
55 – 64 years			16	52.7
65 – 74 years			8	33.0
≥75 years			2	10.3
Total			**54**	**246.1**
Qwk 3-h				
<18 years			0	0
18 – 54 years			40	176.1
55 – 64 years			66	258.2
65 – 74 years			29	107.3
≥75 years			12	40.4
Total			**147**	**582.0**
Q3wk 3-h (1.3 mg/m^2)				
<18 years			0	0
18 – 54 years			34	151.2
55 – 64 years			33	138.6
65 – 74 years			21	90.4
≥75 years			6	25.3
Total			**94**	**405.5**
All regimens				
<18 years			0	0
18 – 54 years			335	1,846.1
55 – 64 years			313	1,554.5
65 – 74 years			209	904.0
≥75 years			57	248.9

	Men[a]		Women[b]	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
Total			**914**	**4,553.6**
Indication: Other types of cancer				
Q3wk 24-h (1.5 mg/m^2)				
<18 years	0	0	0	0
18 – 54 years	9	21.2	21	60.4
55 – 64 years	9	20.0	12	32.5
65 – 74 years	5	7.1	6	27.6
≥75 years	2	4.8	0	0
Total	**25**	**53.1**	**39**	**120.5**
Qwk 3-h				
<18 years	0	0	0	0
18 – 54 years	4	11.3	19	57.4
55 – 64 years	7	34.3	5	17.7
65 – 74 years	11	36.6	3	7.5
≥75 years	11	23.3	0	0
Total	**33**	**105.5**	**27**	**82.6**
Q3wk 3-h (1.3 mg/m^2)				
<18 years	0	0	0	0
18 – 54 years	8	11.3	111	292.3
55 – 64 years	18	36.7	53	139.2
65 – 74 years	18	25.1	40	134.4
≥75 years	3	2.9	9	15.5
Total	**47**	**76.2**	**213**	**581.4**
All regimens				
<18 years	0	0	0	0
18 – 54 years	21	43.8	151	410.1
55 – 64 years	34	91	70	189.5
65 – 74 years	34	68.8	49	169.4
≥75 years	16	31	9	15.5
Total	**105**	**234.6**	**279**	**784.4**

[a] Males are not represented in the platinum-sensitive ROC randomised and ISS-24 trials (OVA-301, ET-B-009-99, ET743-INT-11 and ET-B-026-03), breast trial (ET-B-001 and ET-B-008), and endometrial trial (ET743-USA-1).
[b] Females are not represented in the prostate ISS-24 trial (some patients of ET-B-025 trial).

Table 21: SIII Exposure by AGE GROUP AND GENDER (Totals) (All Clinical Trials Population Including Open Extensions)

	Men[a]		Women[b]	
Age Group	**Patients**	**Person-Months**	**Patients**	**Person-Months**
All indications				
<18 years	14	19.5	4	7.4
18 – 54 years	671	2,770.4	1,380	6,162.7
55 – 64 years	338	1,312.8	884	4,145.3
65 – 74 years	226	967.3	492	2,158.3
≥75 years	73	219.6	120	495.1
Total	**1,322**	**5,289.7**	**2,880**	**12,968.7**

[a] Males are not represented in the platinum-sensitive ROC randomised and ISS trials (ET743-OVA-301, ET-B-009-99, ET743-INT-11, ET743-OVC-3006 and ET-B-026-03), breast trial (ET-B-001 and ET-B-008), and endometrial trial (ET743-USA-1).
[b] Females are not represented in the prostate ISS trial (some patients of ET-B-025 trial).

Table 22: SIII Exposure by ETHNIC ORIGIN (by Indication) (All Clinical Trials Population Including Open Extensions).

Race	Patients	Person-Months
Indication: Soft Tissue Sarcoma	(N= 2,904)	
Q3wk 24-h		
ISS for Sarcoma		
White	492	2,766
Black or African American	59	292.9
Asian	16	51.7
Other[a]	11	47.2
Unknown[b]	347	1,149.5
Total	**925**	**4,307.4**
EAP ET743-SAR-3002		
White	1,578	6,941.1
Black or African American	100	434.7
Asian	53	169.5
Other[a]	72	226.5
Total	**1,803**	**7,771.5**
Qwk 3-h		
ISS for Sarcoma		
White	121	478.6
Black or African American	4	20.5
Asian	3	8.2
Other[a]	2	4.6
Total	**130**	**513.0**
Q3wk 3-h (1.3 mg/m^2)		
ISS for Sarcoma		
White	38	82.0
Black or African American	0	0
Asian	0	0
Other[a]	0	0
Unknown[b]	8	11.9
Total	**46**	**93.9**
All regimens		
White	2,229	10,267.7
Black or African American	163	748.2
Asian	72	230.5
Other[a]	85	278.4
Unknown[b]	355	1161.4
Total	**2,904**	**12,685.9**
Indication: Relapsed platinum-sensitive ovarian cancer	(N=914)	
PLD Q3wk 3-h (1.1 mg/m^2)		
White	262	1,439.3
Black or African American	2	3.1
Asian	65	271.1
Other[a]	4	22.7
Total	**333**	**1,736.3**
Doxil® Q3wk 3-h (1.1 mg/m^2)		
White	258	1,467.0
Black or African American	3	11.2
Asian	15	46.9
Other[a]	6	39.4
Unknown	4	19.2
Total	**286**	**1,583.7**
Q3wk 24-h		

Race	Patients	Person-Months
White	54	246.1
Black or African American	0	0
Asian	0	0
Other[a]	0	0
Total	**54**	**246.1**
Qwk 3-h		
White	137	554.6
Black or African American	6	18.2
Asian	1	1.8
Other[a]	3	7.4
Total	**147**	**582.0**
Q3wk 3-h (1.3 mg/m^2)		
White	93	400.1
Black or African American	0	0
Asian	0	0
Other[a]	0	0
Unknown[b]	1	5.5
Total	**94**	**405.5**
All regimens		
White	804	4,107.1
Black or African American	11	32.5
Asian	81	319.9
Other[a]	13	69.5
Unknown[b]	5	34.7
Total	**914**	**4,553.6**
Indication: Other types of cancer	**(N=384)**	
Q3wk 24-h (1.5 mg/m^2)		
White	4	6.6
Black or African American	1	2.3
Asian	0	0
Other[a]	0	0
Unknown[b]	59	164.7
Total	**64**	**173.6**
Qwk 3-h		
White	57	166.6
Black or African American	2	20.5
Asian	1	0.9
Other[a]	0	0
Total	**60**	**188.0**
Q3wk 3-h (1.3 mg/m^2)		
White	226	587.6
Black or African American	16	28.1
Asian	3	4.9
Other[a]	5	16.5
Unknown[b]	10	20.5
Total	**260**	**657.5**
All regimens		
White	287	760.8
Black or African American	19	50.9
Asian	4	5.8
Other[a]	5	16.5
Unknown[b]	69	185.1
Total	**384**	**1,019.1**

[a] "Other" From the Maghreb, Hispanic or Mixed race

Race	Patients	Person-Months

[b] Information not collected

Table 23: SIII Exposure by ETHNIC or RACIAL ORIGINS (Totals) (All Clinical Trials Population Including Open Extensions)

Race	Patients	Person-Months
All indications	(N=4,202)	
White	3,320	15,135.6
Black or African American	193	831.5
Asian	157	556.2
Other[a]	93	364.4
Unknown[b]	429	1,371.2
Total	**4,202**	**18,259.2**

[a] "Other" From the Maghreb, Hispanic or Mixed race

[b] Information not collected

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria from Yondelis® monotherapy in advanced STS and in combination with PLD for platinum sensitive ROC are discussed below.

Exclusion criterion: Hypersensitivity

Reason for exclusion: To minimise the potential risk in patients.

Is it considered to be included as missing information? No.

Rationale: Hypersensitivity is classified as an identified risk.

Exclusion criterion: Concurrent serious or uncontrolled infection

Reason for exclusion: As trabectedin may cause myelosuppression, there is an increased risk of infection. Hence, patients meeting the above criteria were excluded to avoid confounders due to pre-existing infection.

Is it considered to be included as missing information? No.

Rationale: The reference safety information warns about the risk of bone marrow suppression and infections.

Exclusion criterion: Breast-feeding

Reason for exclusion: To minimise the potential risk in patients as trabectedin can have genotoxic effects.

Is it considered to be included as missing information? No.

Rationale: This safety concern is adequately reflected within the product information.

Exclusion criterion: Combination with yellow fever vaccine

Reason for exclusion: Yellow fever vaccine is contraindicated in immunosuppressed patients, including patients with malignant neoplasms.

Is it considered to be included as missing information? No

Rationale: No clear evidence of a safety concern.

Exclusion criterion: Pregnant women or male or female patients who were not employing adequate contraception

Reason for exclusion: Ethical issue and to minimise the potential risk to foetus.

Is it considered to be included as missing information? No.

Rationale: This safety concern is adequately reflected within the product information.

Exclusion criterion: Known CNS metastasis. Patients with clinical signs of brain and/or leptomeningeal tumour involvement.

Reason for exclusion: To minimise the potential risk in patients and to avoid confounding factors during the assessment of the safety of trabectedin.

Is it considered to be included as missing information? No.

Rationale: The analysis of the safety profile of trabectedin in patients with medical history of CNS metastasis treated with trabectedin seems not to be different from the safety profile in patients without medical history of CNS metastasis at baseline.

Exclusion criterion: Unstable cardiac condition, including congestive heart failure or angina pectoris, myocardial infarction within one year before enrollment, uncontrolled arterial hypertension or arrhythmias.

Reason for exclusion: To minimise the potential risk in patients and to avoid confounding factors during the assessment of the safety of trabectedin.

Is it considered to be included as missing information? No.

Rationale: Cardiac Dysfunction is classified as important potential risk.

Exclusion criterion: History of another neoplastic disease (except basal cell carcinoma or cervical carcinoma in situ adequately treated) unless in remission for 5 years or more.

Reason for exclusion: To minimise the potential risk in patients and to avoid confounding factors during the assessment of the safety of trabectedin.

Is it considered to be included as missing information? No.

Rationale: No clear evidence of a safety concern.

Exclusion criterion: Patients with a clinically significant chronic liver disease, such as cirrhosis or active hepatitis.

Reason for exclusion: To minimise the potential risk in patients and to avoid confounding factors during the assessment of the safety of trabectedin.

Is it considered to be included as missing information? No.

Rationale: The completed clinical trial (ET743-OVC-1004), which investigated trabectedin administration to patients with hepatic dysfunction, indicated that hepatic impairment is associated with increased trabectedin dose-normalised exposure compared with subjects with normal hepatic function.

The product information includes the following: Patients must meet specific criteria on hepatic function parameters to start treatment with trabectedin. Since systemic exposure to trabectedin is increased due to hepatic impairment, and therefore the risk of hepatotoxicity might be increased, patients with clinically relevant liver diseases should be closely monitored and the dose adjusted if needed. Patients with elevated bilirubin at the time of initiation of a new treatment cycle must not be treated with trabectedin.

Exclusion criterion: Any unstable medical conditions, such as uncontrolled diabetes and newly developed deep vein thrombosis requiring i.v. or subcutaneous therapeutic anticoagulant therapy.

Reason for exclusion: It is common clinical practice to exclude subjects with unstable medical conditions because they may potentially confound the interpretation of safety data.

Is it considered to be included as missing information? No.

Rationale: No clear evidence of a safety concern.

Exclusion criterion: Patients with uncontrolled psychiatric disorder/social situation

Reason for exclusion: It is common clinical practice to exclude subjects with unstable medical conditions because they may potentially confound the interpretation of safety data.

Is it considered to be included as missing information? No.

Rationale: No clear evidence of a safety concern.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Events which are rare	3,916 patients were exposed over the clinical trial programme (phase 2 to phase 3) where the lowest ADR frequency was 1/1,305 patients.	The ADR frequency was 1/1,305 patients and could be detected without background incidence. This frequency is within the uncommon Council for International Organisations of Medical Sciences (CIOMS) threshold.
Due to prolonged exposure	The number of patients with 12 months or more of exposure to trabectedin was	There is a limited ability to observe effects due to prolonged exposure since patients whose

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
	low (6%) therefore there was a limited ability to observe effects due to prolonged exposure.	treatment exposure was 12 months or more are limited based on the nature of the disease.
Due to cumulative effects	The pharmacokinetic profile of trabectedin is consistent with a multiple compartment disposition model, including a terminal half-life in plasma of 175 hours. The concentration of trabectedin in plasma does not accumulate when administered every 3 weeks at doses up to and including 1.8 mg/m^2.	The lack of accumulation of trabectedin in plasma when administered every 3 weeks limits the ability to determine its cumulative effects.
Which have a long latency	The number of patients that survived longer than 3 years after trabectedin treatment was low; therefore, there was a limited ability to observe effects of trabectedin due to a long latency period.	Long term exposure will continue to be monitored through post-marketing experience which will provide additional safety information on long term latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 24: SIV.3 Exposure of special populations included or not in clinical trial development programmes (The Randomised, Blinded Clinical Trials Population: ET 743-STS-201, ET743-SAR-3007, ET-C-002-07, ET743-OVA-301 and ET743-OVC-3006)

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Patients with relevant comorbidities:	

Patients with hepatic impairment:

Parameter	All indications		Ovarian Cancer		Soft Tissue Sarcoma	
	Patients	Person-months	Patients	Person-months	Patients	Person-months
Alanine aminotransferase (ALT)						
≤ Upper limit of normal (ULN)	1,219	6,478.3	574	3,100.6	645	3,377.7
>ULN and ≤2.5 ULN	94	458.8	41	204.0	53	254.8
>2.5 ULN and ≤5 ULN	2	7.9	2	7.9	0	0
Missing	3	15.2	2	7.4	1	7.7
Aspartate aminotransferase (AST)						
≤ULN	1,181	6,318.0	551	3,012.8	630	3,305.2
>ULN and ≤2.5 ULN	131	623.1	62	288.1	69	335.0
>2.5 ULN and ≤5 ULN	1	3.3	1	3.3	0	0

>5 ULN and ≤20 ULN	1	4.7	1	4.7	0	0
Missing	4	11.2	4	11.2	0	0
Alkaline phosphatase (AP)						
≤ULN	1,087	5,909.6	535	2,895.4	552	3,014.2
>ULN and ≤2.5 ULN	223	1,016.5	79	399.1	144	617.5
>2.5 ULN and≤ 5 ULN	3	8.5	0	0	3	8.5
Missing	5	25.6	5	25.6	0	0
Bilirubin						
≤ULN	1,302	6,863.1	613	3,291.8	689	3,571.3
>ULN and ≤1.5 ULN	13	81.1	4	23.6	9	57.6
>1.5 ULN and ≤3 ULN	1	11.3	0	0	1	11.3
Missing	2	4.7	2	4.7	0	0
Total	**5,272**	**27,840.9**	**2,476**	**13,280.2**	**2,796**	**14,560.8**

Patients with renal impairment:

Parameter	**All indications**		**Ovarian Cancer**		**Soft Tissue Sarcoma**	
	Patients	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**
Creatinine clearance (CrCl)						
Normal (≥80 mL/min)	797	4,278.4	301	1,741.7	496	2,536.6
Mild (CrCl >60 to <80 mL/min)	324	1,689.9	198	1,017.8	126	672.1
Moderate (CrCl >30 to ≤60 mL/min)	192	975.8	116	545.1	76	430.7
Severe (CrCl ≤30 mL/min)	1	0.7	1	0.7	0	0
Missing	4	15.4	3	14.7	1	0.7
Total	**1,318**	**6,960.2**	**619**	**3,320.0**	**699**	**3,640.2**

Patients with cardiac impairment:

Parameter	**All indications**		**Ovarian Cancer**		**Soft Tissue Sarcoma**	
	Patients	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**
No	1,316	6,956.8	618	3,318.3	698	3,638.5
Yes	2	3.4	1	1.7	1	1.7
Total	**1,318**	**6,960.2**	**619**	**3,320.0**	**699**	**3,640.2**

Immunocompromised patients. Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme

Population with relevant different ethnic origin	Refer to section Part II Module SIII Clinical trial exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

Table 25: SIV.3 Exposure of special populations included or not in clinical trial development programmes (All Clinical Trials Population Including Open Extensions: ISS, the EAP [ET743-SAR-3002], ET743-OVA-301, ET-C-002-07 and ET743-OVC-3006)

Type of special population			**Exposure**					
Pregnant women			not included in the clinical development programme					
Patients with relevant comorbidities:								
Patients with hepatic impairment:								
Parameter	All indications		Ovarian Cancer		Soft Tissue Sarcoma		Other	
	Patients	Person-months	Patients	Person-months	Patients	Person-months	Patients	Person-months
ALT								
≤ULN	2,220	9,723.5	849	4,202.1	1,016	4,577.9	355	943.5
>ULN and ≤2.5 ULN	171	730.1	60	331.9	83	324.7	28	73.5
>2.5 ULN and ≤5 ULN	3	10.1	2	7.9	0	0	1	2.1
Missing	5	23.4	3	11.7	2	11.7	0	0
AST								
≤ULN	2,157	9,545.6	830	4,195.5	1,001	4,474.3	326	875.8
>ULN and ≤2.5 ULN	231	899.2	76	331.0	98	425.0	57	143.2
>2.5 ULN and ≤5 ULN	3	10.7	2	10.6	0	0	1	0.0
>5 ULN and ≤20 ULN	1	4.7	1	4.7	0	0	0	0
Missing	7	27.0	5	11.9	2	15.1	0	0
AP								
≤ULN	1,977	8,906.7	796	3,957.3	879	4,104.9	302	844.6
>ULN and ≤2.5 ULN	385	1,491.8	113	570.8	203	776.9	69	144.1
>2.5 ULN and≤ 5 ULN	20	41.6	0	0	11	19.3	9	22.3
>5 ULN and ≤20 ULN	8	16.5	0	0	5	9.2	3	7.3
>20 ULN	2	2.1	0	0	2	2.1	0	0
Missing	7	28.3	5	25.6	1	2.1	1	0.7
Bilirubin								
≤ULN	2,365	10,324.7	908	4,525.4	1,079	4,805.2	378	994.2
>ULN and ≤1.5 ULN	29	143.3	4	23.6	20	97.2	5	22.5

>1.5 ULN and ≤3 ULN	2	12.0	0	0	2	12.0	0	0
Missing	3	7.1	2	4.7	0	0	1	2.4
Total	**7,376**	**32,224.9**	**2,807**	**14,012.6**	**3,388**	**15,079.7**	**1,536**	**4,076.2**
Patients with renal impairment:								
Parameter	**All indications**		**Ovarian Cancer**		**Soft Tissue Sarcoma**		**Other**	
	Patients	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**
Creatinine clearance								
Normal (≥80 mL/min)	1,455	6,399.3	447	2,351.3	783	3,438.4	225	609.6
Mild (CrCl >60 to <80 mL/min)	610	2,673.7	300	1,459.4	208	929.1	102	285.2
Moderate (CrCl >30 to ≤60 mL/min)	326	1,388.5	163	727.5	107	538.6	56	122.4
Severe (CrCl ≤30 mL/min)	1	0.7	1	0.7	0	0	0	0
Missing	7	24.9	3	14.7	3	8.3	1	1.8
Total	**2,399**	**10,487.1**	**914**	**4,553.6**	**1,101**	**4,914.4**	**384**	**1,019.1**
Patients with cardiac impairment:								
Parameter	**All indications**		**Ovarian Cancer**		**Soft Tissue Sarcoma**		**Other**	
	Patients	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**	**Patients**	**Person-months**
No	2389	10,458.3	913	4,551.9	1,093	4,888.7	383	1,017.7
Yes	10	28.8	1	1.7	8	25.6	1	1.4
Total	**2,399**	**10,487.1**	**914**	**4,553.6**	**1,101**	**4,914.4**	**384**	**1,019.1**

Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Population with relevant different ethnic origin	Refer to section Part II Module SIII Clinical trial exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV. 1.1 Method used to calculate exposure

Post-approval (non-clinical trial) exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of reporting frequencies of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

It is of note that, according to internal Company conventions, exposure in observational studies is considered part of post-marketing exposure data.

Patient exposure (person-time)

Patient exposure was estimated by calculation from Company and partner distribution data. Estimates of exposure are based upon finished product. The recommended starting dose for trabectedin is 1.5 mg/m^2 body surface area, administered as an i.v. infusion over 24 hours with 3-week interval between cycles.

Assuming an average body surface area of 1.8 m^2[1], this corresponds to 2.7 mg per treatment course or cycle. The algorithm is based on the STS indication; the assumptions for the ROC indication might be lower.

An internal assessment showed that the total number of patients for the ROC indication are less than 3% worldwide. Under the STS indication, 3 cycles are equivalent to 1 patient exposed. For further stratification of the post marketing exposure according to the 2 indications, below is the proportion of sales per indication:

- 33% of sales are related to ROC indication
- 67% of sales are related to STS indication

The estimates of exposure have been stratified based on the 2 indications, along with the region. The exposure for the current and cumulative period are presented below in Table 26 and Table 27, respectively.

SV. 1.2 Exposure

Table 26: SV.1.2 Cumulative post-authorisation exposure by indication and region from launch to 30 September 2024

Region	Indications	Formulations	Number of Vials	Total mg	mg per Treatment	Number of Treatments (or Cycles)	Number of Patients Exposed
EU*	STS	1 mg Vial	449,113	449,113	2.7	166,338	55,446
		0.25 mg Vial	272,476	68,119	2.7	25,229	8,409
	STS Subtotal		721,590	517,232		191,567	63,856
	ROC	1 mg Vial	221,204	221,204	2.7	81,928	27,309
		0.25 mg Vial	134,204	33,551	2.7	12,427	4,142
	ROC Subtotal		355,407	254,755		94,354	31,451
EU Subtotal			**1,076,997**	**771,987**		**285,922**	**95,307**

[1] Based on the EMEA Scientific Discussion for this product

Region	Indications	Formulations	Number of Vials	Total mg	mg per Treatment	Number of Treatments (or Cycles)	Number of Patients Exposed
Non-EU	STS	1 mg Vial	212,779	212,779	2.7	78,807	26,269
		0.25 mg Vial	38,436	9,609	2.7	3,559	1,186
	STS Subtotal		251,215	222,388		82,366	27,455
	ROC	1 mg Vial	104,802	104,802	2.7	38,815	12,939
		0.25 mg Vial	18,932	4,732	2.7	1,753	584
	ROC Subtotal		123,734	109,534		40,568	13,523
Non-EU Subtotal			**374,949**	**331,923**		**122,933**	**40,978**
Worldwide Total			**1,451,946**	**1,103,911**		**408,854**	**136,285**

Key: EU=European Union; ROC=Relapsed Ovarian Cancer; STS=Soft Tissue Sarcoma.

* Exposure data corresponding to Switzerland and the United Kingdom are included in the EU Region

Based on the 1,103,911 milligrams of trabectedin distributed by the partner and Company from launch to 30 September 2024, the estimated exposure is 408,854 treatments (cycles) or 136,285 patients.

Additional stratifications for trabectedin:

Additional stratifications are provided using market research data where possible and appropriate. Information was collected in Europe (France, Spain, Germany and Italy) via IPSOS Patients Records Study Ovarian Cancer 2018 and IQVIA Soft Tissue Sarcoma Enhanced Tumour studies from 01 January 2018 to 31 December 2020 plus from 01 April 2021 to 30 June 2021 plus from 01 October 2021 to 31 December 2021 plus from 01 April 2022 to 30 December 2022. Data were collected from online surveys (Computer Assisted Web Interview) based on patient records. Further splits such as gender within age group are not available.

Table 27: Post-marketing (market research) Trabectedin Exposure by Age Group in the European Union (from 01 January 2018 to 31 December 2020 plus from 01 April 2021 to 30 June 2021 plus from 01 October 2021 to 31 December 2021 plus from 01 April 2022 to 30 December 2022)

Indication: Soft Tissue Sarcoma[a]					
Age Group	**Spain**	**Germany**	**Italy**	**France**	**Total**
0-50	107 (19%)	69 (12%)	72 (18%)	46 (15%)	294 (16%)
51-60	202 (36%)	123 (21%)	137 (35%)	65 (21%)	527 (28%)
61-70	217 (39%)	266 (45%)	152 (38%)	145 (47%)	780 (42%)
>70	31 (6%)	139 (23%)	36 (9%)	55 (18%)	261 (14%)
TOTAL	**557 (100%)**	**597 (100%)**	**397 (100%)**	**311 (100%)**	**1,862 (100%)**

a. Data are from IQVIA STS Enhanced Tumour Study

Table 28: Post-marketing (market research) Trabectedin Exposure by Age Group in the European Union (2018)

Indication: Ovarian Cancer[a]					
Age Group	**Spain**	**Germany**	**Italy**	**France**	**Total**
	% of Patients (N=80)	% of Patients (N=80)	% of Patients (N=80)	% of Patients (N=80)	% of Patients (N=320)
0-50 years	11	4	9	15	10
51-60 years	23	36	36	29	31
61-70 years	50	49	48	34	45
>70 years	16	11	7	22	14
TOTAL	**100**	**100**	**100**	**100**	**100**

a: Data are from IPSOS Patients Records Study Ovarian Cancer 2018

Table 29: Post-marketing (market research) Trabectedin Exposure by Gender in the European Union (from 01 January 2018 to 31 December 2020 plus from 01 April 2021 to 30 June 2021 plus from 01 October 2021 to 31 December 2021 plus from 01 April 2022 to 30 December 2022)

Indication: Soft Tissue Sarcoma[a,b]					
Gender	**Spain**	**Germany**	**Italy**	**France**	**EU**
FEMALE	226 (41%)	265 (44%)	159 (40%)	161 (52%)	811 (44%)
MALE	331 (59%)	332 (56%)	238 (60%)	150 (48%)	1,051 (56%)
TOTAL	**557 (100%)**	**597 (100%)**	**397 (100%)**	**311 (100%)**	**1,862 (100%)**

a. Data are only for STS as Males are not represented in Ovarian Cancer
b. Data are from IQVIA Soft Tissue Sarcoma Enhanced Tumour Study

In the US, the additional stratifications are provided using IQVIA (formerly IMS MIDAS™) data where possible and appropriate. Market research sources for non-study exposure data are unavailable for breakdowns such as: usage in pregnant or breast-feeding women, usage in hepatic impairment population, usage in renal impairment population.

Exposure by age and gender presented as a percentage of prescription sales:

Prescription sales (reported as absolute values) stratified by age and sex are presented below in Table 30.

Table 30: Number of Prescriptions Overall and Stratified by Age Range in the US (01 July 2021 to 30 June 2024)

Age Groups (Years)[a]	US[a] (2,480 Rx[b])
0 to 15	0.1%
16 to 35	4.8%
36 to 65	61.0%
≥66	34.1%

Key: Rx=Prescription; US=United States
a Regional Rx data by age were only available for the last 3 years ending June 2024. Data stratified by age were only available in the US.
b Included retail channels.

Table 31: Number of Prescriptions Overall and Stratified by Gender in the US (01 July 2021 to 30 June 2024)

Country	Females[a]	Males[a]
United States (2,480 Rx[b])	64.7%	35.3%

Key: Rx=Prescription; US=United States
[a] Regional Rx data by sex were only available for the last 3 years ending June 2024. Data were only available for the US.
[b] Included retail channels.

Patient exposure in observational studies is presented by duration of exposure (Table 32), by indication and dose (Table 33) and by indication, age group and gender (Table 34):

Table 32: SV.1.2 Exposure by Duration by Indication

Duration of Exposure (at least)[a]	Patients	Person-Months
Indication: Soft Tissue Sarcoma*		
Q3wk 24-h	(N=330[a])	
>0 m	30	20.7
>=1 m	300	1963.7
>=3 m	191	1760.8
>=6 m	122	1460.7
>=9 m	81	1162.7

Duration of Exposure (at least)[a]	Patients	Person-Months
>=12 m	49	828.7
>=15 m	18	421.3
>=18 m	8	255.0
>=21 m	7	236.6
>=24 m	7	236.6
Total person months	**330**	**1984.4**
Indication: Ovarian cancer**		
Q3wk 24-h	(N=297[b])	
>0 m	14	9.7
>=1 m	283	1,622.2
>=3 m	217	1,480.1
>=6 m	100	940.2
>=9 m	48	556.1
>=12 m	13	199.1
>=15 m	4	81.9
>=18 m	2	47.2
>=21 m	1	28.6
>=24 m	1	28.6
Total person months	**297**	**1,631.9**

*These data were extracted from three company sponsored non-interventional study (ET-D-007-09, ET-D-020-12 [Y-IMAGE] and ET-D-010-10).

**These data were extracted from two company sponsored non-interventional study (ET-D-031-14 [NIMES ROC] and ET-D-022-12 [OvaYond]).

[a] Treated patients; ET-D-007-09 (n=25), ET-D-020-12 (Y-IMAGE) (n=211) and ET-D-010-10 (n=94)

[b] Treated patients ; ET-D-031-14 (NIMES ROC) (n=220) and ET-D-022-12 (OvaYond) (n=77)

Table 33: SV.1.2 Exposure by Indication and Dose

Dose of Exposure	Patients	Person-Months
Indication: Soft Tissue Sarcoma*	(N=330[a])	
Q3wk 24-h		
1.5 mg/m^2	330	1984.4
Total	**330**	**1984.4**
Indication: Ovarian cancer **	(N=297[b])	
Q3wk 24-h		
1.1 mg/m^2	297	1,631.9
Total	**297**	**1,631.9**

* These data were extracted from a company sponsored non-interventional study (ET-D-007-09, ET-D-020-12 (Y-IMAGE) and ET-D-010-10)

**These data were extracted from two company sponsored non-interventional study (ET-D-031-14 [NIMES ROC] and ET-D-022-12 [OvaYond]).

[a] Treated patients; ET-D-007-09 (n=25), ET-D-020-12 (Y-IMAGE) (n=211) and ET-D-010-10 (n=94)

[b] Treated patients; ET-D-031-14 (NIMES ROC) (n=220) and ET-D-022-12(OvaYond) (n=77)

Table 34: SV.1.2 Exposure by Indication, Age Group and Gender

	Men		Women	
Age Group	**Person**	**Person-Months**	**People**	**Person-Months**
	(N=143[a])		(N=187[a])	
Indication: Soft Tissue Sarcoma*				
Q3wk 24-h				
<18 years	0	0	0	0
18 – 54 years	73	427.8	79	449.8
55 – 64 years	29	224.9	63	393.8
65 – 74 years	32	175.1	37	231.6
≥75 years	9	20.8	8	60.7
Total	**143**	**848.5**	**187**	**1135.9**

Indication: Ovarian Cancer**		(N=297[b])		
Q3wk 24-h				
<18 years			0	0
18 – 54 years			71	442.7
55 – 64 years			92	489.6
65 – 74 years			103	569.5
≥75 years			31	130.1
Total			**297**	**1,631.9**

*These data were extracted from a company sponsored non-interventional study (ET-D-007-09 ET-D-020-12 (Y-IMAGE) and ET-D-010-10)

**These data were extracted from two company sponsored non-interventional study (ET-D-031-14 [NIMES ROC] and ET-D-022-12 [OvaYond]).

[a] Treated patients; ET-D-007-09 (n=25), ET-D-020-12 (Y-IMAGE) (n=211) and ET-D-010-10 (n=94)

[b] Treated patients; ET-D-031-14 (NIMES ROC) (n=220) and ET-D-022-12(OvaYond) (n=77)

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Drug Abuse

No potential risk for drug abuse is expected. This is a cytotoxic agent administered as an i.v. infusion by specialised personnel.

Withdrawal and Rebound Effect

Cyclic regimens of trabectedin have been administered to a large number of patients enrolled in clinical trials and in the post-marketing setting. There is no evidence of a dependence related withdrawal effect following discontinuation of administration of trabectedin.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The safety concerns listed in the first approved version of the RMP (version 3.0, 17 September 2007) are presented below.

Important Identified Risks:

- Hepatic reactions
- Neutropenia and infection
- Thrombocytopenia/bleeding
- Anaemia
- Creatine phosphokinase (CPK) elevations/ Rhabdomyolysis
- Emesis
- Dyspnoea
- Local infusion reactions
- Myelodysplasia/AML

Important Potential Risks:

- Renal toxicity
- Pancreatic toxicity
- Cardiovascular toxicity
- Retinal toxicity
- Potential risk of interactions with other medicinal products

Missing information:

- Use in Children-Paediatric population
- Use in Pregnant and lactating women
- Use in patients with impaired renal function
- Use in patients with impaired hepatic function

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable. Risks not considered important for inclusion in the list of safety concerns in the RMP were not identified in the first approved version of the RMP (version 3.0, 17 September 2007) as per the legislative requirements at that time.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable. This section was not required in the first approved version of the RMP (version 3.0, 17 September 2007) as per the legislative requirements at that time.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There have been no re-classification or removal of safety concerns within the RMP update.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risks

- Injection site reaction

Important potential risks

- AML/ MDS
- Cardiac Dysfunction

- Pancreatitis, lipase and/or amylase increased

Important Identified Risk – Injection site reactions: *(Medical Dictionary for Regulatory Activities [MedDRA] preferred terms (PTs): Administration site discomfort, Administration site erythema, Administration site extravasation, Administration site induration, Administration site inflammation, Administration site irritation, Administration site oedema, Administration site pain, Administration site swelling, Catheter site erythema, Catheter site extravasation, Catheter site induration, Catheter site inflammation, Catheter site irritation, Catheter site necrosis, Catheter site oedema, Catheter site pain, Catheter site ulcer, Chemotherapy extravasation management, Device leakage, Extensive swelling of vaccinated limb, Extravasation, Implant site erosion, Implant site erythema, Implant site extravasation, Implant site induration, Implant site inflammation, Implant site irritation, Implant site mass, Implant site necrosis, Implant site oedema, Implant site pain, Implant site swelling, Implant site ulcer, Implant tissue necrosis, Induration, Infusion site erosion, Infusion site erythema, Infusion site eschar, Infusion site extravasation, Infusion site granuloma, Infusion site induration, Infusion site inflammation, Infusion site irritation, Infusion site joint effusion, Infusion site joint inflammation, Infusion site joint pain, Infusion site joint swelling, Infusion site mass, Infusion site necrosis, Infusion site nodule, Infusion site oedema, Infusion site pain, Infusion site swelling, Infusion site ulcer, Injection site erosion, Injection site erythema, Injection site extravasation, Injection site granuloma, Injection site induration, Injection site inflammation, Injection site irritation, Injection site joint effusion, Injection site joint erythema, Injection site joint pain, Injection site joint swelling, Injection site mass, Injection site necrosis, Injection site nodule, Injection site oedema, Injection site pain, Injection site swelling, Injection site ulcer, Instillation site erosion, Instillation site induration, Instillation site inflammation, Instillation site necrosis, Instillation site nodule, Instillation site oedema, Instillation site swelling, Instillation site ulcer, Localised oedema, Medical device site extravasation, Peripheral swelling, Puncture site erythema, Skin induration, Skin mass, Skin necrosis, Stoma site extravasation, Vascular access site erythema, Vascular access site extravasation, Vascular access site necrosis, Vascular access site oedema, Vascular access site swelling, Vascular access site ulcer, Vessel puncture site erythema, Application site haemorrhage, Application site erythema, Application site erosion, Application site irritation, Application site oedema, Application site pain, Thrombosis in device)*

Potential mechanisms:

Trabectedin extravasation may cause tissue necrosis. The mechanism of action of tissue necrosis is unknown but likely related to trabectedin DNA binding potential and its vesicant properties.

Evidence source(s) and strength of evidence:

- Periodic Safety Update Report (PSUR) 19 (cutoff date 17 September 2022)
- Investigator's Brochure v.15
- Clinical trials (Company Core Data Sheet [CCDS] v.16)
  - In patients with STS, in the integrated clinical trials phase 2 and 3, assigned to the recommended regimen [1.5 mg/m^2, 24-hour infusion every 3 weeks (24 h q3wk)], injection site reactions incidence was of 8.5%. In patients with ovarian cancer, in the integrated phase 3 clinical trials, assigned to combination therapy with trabectedin plus PLD, catheter site inflammation and catheter site pain incidence was of 1.6% and 2.4% respectively.
- Clinical trial and post-marketing (CCDS v.14 and SmPC)
  - During clinical studies and post-marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported. SmPC includes these ADRs as uncommon ADRs.

Characterisation of the risk:

In clinical trials, the Odds Ratio for any treatment-emergent event has been calculated for the two indications approved for Yondelis®

Table 35: SVII.3.1 Any Injection Site Reactions Treatment-Emergent Event

INDICATION: SOFT TISSUE SARCOMA					
	Any Treatment-Emergent Event, n (%)				
Trial	**Trabectedin Q3wk 24-h (1.5 mg/m²)**	**Trabectedin Qwk 3 h (0.58 mg/m²)**	**Dacarbazine Q3wk 20-min (1.0 g/m²)**	**Doxorubicin Q3wk-75 mg/m² or 60 mg/m² + Ifosfamide 6-9 g/m²**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL*					
ET743-STS-201	N=130	N=130	--	--	--
	13 (10%)	10 (7.7%)	--	--	1.33 (0.56-3.16)
ET743-SAR-3007	N=378	--	N=172	--	--
	54 (14.3%)	--	9 (5.2%)	--	3.02 (1.45-6.27)
ET-C-002-07	N=61	--	--	N=57	--
	12 (19.7%)	--	--	4 (7%)	3.24 (0.98-10.73)
ALL RANDOMISED TRIALS WITHOUT CONTROL**					
ISS-25 for STS	N=1,040	--	--	--	--
	106 (10.2%)	--	--	--	--
EAP ET743-SAR-3002	N=1,803	--	--	--	--
	20 (1.1%)	--	--	--	--

INDICATION: RELAPSED PLATINUM-SENSITIVE OVARIAN CANCER			
	Any Treatment-Emergent Event, n (%)		
Trial	**Trabectedin Q3wk 3-h (1.1 mg/m²) + Doxorubicin: Q3wk 90-min (30 mg/m²)**	**Doxorubicin: q4wk 90-min (50 mg/m²)**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL			
OVA-301	N=333	N=330	--
	32 (9.6%)	11 (3.3%)	3.08 (1.53-6.23)
OVC-3006	N=286	N=282	--
	23 (8%)	10 (3.5%)	2.38 (1.11-5.09)
OVA-301 + OVC-3006	N=619	N=612	--
	55 (8.9%)	21 (3.4%)	2.74 (1.64-4.6)
ALL RANDOMISED TRIALS WITHOUT CONTROL***			
ISS-25 for ovarian	N=295	--	--
	52 (17.6%)	--	--

Key: CI = confidence interval

[a] Odds ratio (95% CI) were based on Fisher's exact test.

* The 3 randomised trials (Phase 2 ET473-STS-201, Phase 3 ET743-SAR 3007 and Phase 3 ET-C-002-07) have not been integrated into 1 database due to differences in design. Therefore, the individual studies are presented separately.

** Integrated safety summary (ISS-25 trials) for sarcoma includes randomised trials ET473-STS-201 and the trabectedin arm of ET473-SAR-3007 but not the trabectedin arm of ETC-002-07 or the non-randomised EAP ET473-SAR-3002, therefore the latter is also presented separately

*** Integrated Safety Summary (3 trials: ET-B-009-99, ET743-INT-11 and ET-B-026-03) for ovarian excludes randomised Trial ET743-OVA-301 and ET743-OVC-3006. Trial ET743-OVA-301 and ET743-OVC-3006 could not be integrated due to differences in design.

Overall, the vast majority of reported adverse events (AEs) were mild to moderate in severity (grade 1 or 2) with a favourable outcome.

Risk factors and risk groups:

In one trial on the use of fosaprepitant, younger age (<50 years), low body mass index (<22) were both risk factors for injections site reactions (63). The potential for tissue damage is affected by the factors such as the drug concentration, high vesicant potential of drug and the unfiltered amount, tissue exposure and extravasated zone, repeated use of drugs having the vesicant characteristic. The risk factors affecting the formation of extravasation or making this formation easier involves patient characteristics (e.g., extreme age, patients with fragile veins, sedated or confused patients, etc.), diseases where patients are exposed to repeated treatment infusion requiring indwelling catheters such as cancer patients, issues related to the venous access line (such as peripheral i.v. particularly in areas such as antecubital fossa, on hand, on foot, wrist, thickness of the i.v. catheter tip, i.v. catheter length, placement of central catheter in the region instable to motion, bending or dislocation of the catheter, injection needle on the port not fully accessed, excessive back pressure around the needle, fibrin deposition or thrombosis at the catheter) or issues with the insertion line technique (such as inexperienced staff and insufficient information on the drug management) (64, 65).

Preventability:

The use of central venous access is strongly recommended. There is no specific antidote for extravasation of trabectedin. Extravasation should be managed by local standard practice.

Impact on the risk-benefit balance of the product:

The consequences of subcutaneous infiltration of cytotoxic vesicant agents may include significant tissue damage, altered limb function, pain, and impact on the quality of life for long term survivors.

Public health impact:

The public health impact of these events is expected to be low.

Important Potential Risk –AML/MDS: *(MedDRA PTs: Acute biphenotypic leukaemia, Acute leukaemia, Acute leukaemia in remission, Acute lymphocytic leukaemia, Acute lymphocytic leukaemia (in remission), Acute lymphocytic leukaemia recurrent, Acute megakaryocytic leukaemia, Acute megakaryocytic leukaemia (in remission), Acute monocytic leukaemia, Acute monocytic leukaemia (in remission), Acute myeloid leukaemia, Acute myeloid leukaemia (in remission), Acute myeloid leukaemia recurrent, Acute myelomonocytic leukaemia, Acute promyelocytic leukaemia, Acute undifferentiated leukaemia, B precursor type acute leukaemia, B-cell prolymphocytic leukaemia, B-cell type acute leukaemia, Bone marrow infiltration, Bone marrow metamyelocyte count increased, Bone marrow myelogram abnormal, Bone marrow reticulin fibrosis, Bone marrow transplant, Differential white blood cell count abnormal, Granulocytes maturation arrest, Immature granulocyte percentage increased, Leukaemia, Marrow hyperplasia, Metamyelocyte count increased, Metamyelocyte percentage increased, Myeloblast count increased, Myeloblast percentage increased, Myelocyte count increased, Myelocyte percentage increased, Myelocytosis, Myelodysplastic syndrome, Myelodysplastic syndrome transformation, Myelodysplastic syndrome unclassifiable, Myeloid leukaemia, Myeloid leukaemia in remission, Myeloid maturation arrest, Promyelocyte count increased)*

Potential mechanisms:

Trabectedin binds to DNA, is mutagenic and genotoxic and, prevents topoisomerase-I from opening the DNA causing failure of replication and disrupting the nucleotide excision repair system producing DNA double strands brakes.

Evidence sources and strength of evidence:

- PSUR 19 (cutoff date 17 September 2022)
- Investigator's Brochure v.15
- Secondary haematological malignancies Ad hoc report (23 September 2014):
    - The cumulative analysis identified 28 cases reporting haematological malignancies in patients who received trabectedin irrespective of causality. The source distribution of cases

was 22 cases from clinical trials and 6 spontaneous cases. Twelve (12) cases out of the 28 reported a fatal outcome, 9 due to AML and 3 due to other causes.

- Based on this cumulative review of clinical studies and spontaneous cases, the role of trabectedin in the occurrence of AML/MDS is yet to be determined. The majority of the reported cases adequately documented were heavily confounded, mainly by previous or concomitant chemotherapy or radiotherapy well known to induce secondary malignancies and specifically AML/MDS. Only 1 case was not considered to be confounded.

Characterisation of the risk:

In clinical trials, the Odds Ratio for any treatment-emergent event has been calculated for the two indications approved for Yondelis®.

Table 36: SVII.3.1 Any AML/MDS Treatment-Emergent Event

INDICATION: SOFT TISSUE SARCOMA					
	Any Treatment-Emergent Event, n (%)				
Trial	**Trabectedin Q3wk 24-h (1.5 mg/m²)**	**Trabectedin Qwk 3 h (0.58 mg/m²)**	**Dacarbazine Q3wk 20-min (1.0 g/m²)**	**Doxorubicin Q3wk-75 mg/m² or 60 mg/m² + Ifosfamide 6-9 g/m²**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL*					
ET743-STS-201	N=130	N=130	--	--	--
	1 (0.8%)	0 (0%)	--	--	
ET743-SAR-3007	N=378	--	N=172	--	--
	1 (0.3%)	--	0 (0%)	--	
ET-C-002-07	N=61	--	--	N=57	--
	2 (3.3%)	--	--	0 (0%)	
ALL RANDOMISED TRIALS WITHOUT CONTROL**					
ISS-25 for STS	N=1,040	--	--	--	--
	3 (0.3%)	--	--	--	--
EAP ET743-SAR-3002	N=1,803	--	--	--	--
	2 (0.1%)	--	--	--	--

INDICATION: RELAPSED PLATINUM-SENSITIVE OVARIAN CANCER			
	Any Treatment-Emergent Event, n (%)		
Trial	**Trabectedin Q3wk 3-h (1.1 mg/m²) + Doxorubicin: Q3wk 90-min (30 mg/m²)**	**Doxorubicin: q4wk 90-min (50 mg/m²)**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL			
OVA-301	N=333	N=330	--
	0 (0%)	0 (0%)	
OVC-3006	N=286	N=282	--
	2 (0.7%)	0 (0%)	
OVA-301 + OVC-3006	N=619	N=612	--
	2 (0.3%)	0 (0%)	
ALL RANDOMISED TRIALS WITHOUT CONTROL***			
ISS-25 for ovarian	N=295	--	--
	0 (0%)		

Key: CI = confidence interval

[a] Odds ratio (95% CI) were based on Fisher's exact test.

* The 3 randomised trials (Phase 2 ET473-STS-201, Phase 3 ET743-SAR 3007 and Phase 3 ET-C-002-07) have not been integrated into 1 database due to differences in design. Therefore, the individual studies are presented separately.
** Integrated safety summary (ISS-25 trials) for sarcoma includes randomised trials ET473-STS-201 and the Trabectedin arm of ET473-SAR-3007 but not the Trabectedin arm of ETC-002-07 or the non-randomised EAP ET473-SAR-3002, therefore the latter is also presented separately
*** Integrated Safety Summary (3 trials: ET-B-009-99, ET743-INT-11 and ET-B-026-03) for ovarian excludes randomised Trial ET743-OVA-301 and ET743-OVC-3006. Trial ET743-OVA-301 and ET743-OVC-3006 could not be integrated due to differences in design.

Overall, the incidence of the fatal AEs was less ≤0.8%, the remaining AEs were persisting or with outcome not provided. The vast majority of the AEs were reported with grade ≥4, only isolated grade 2 or grade 3 were reported.

Risk factors and risk groups:

Patients heavily pre-treated with chemotherapy and radiation. Among other cytotoxic drugs, PLD and alkylating agents such as ifosfamide have been associated with an increased risk for secondary AML and MDS. Other risk factors include smoking which can double or triple the risk of AML, genetics, blood disorders such as myelodysplastic syndrome, autoimmune conditions such as rheumatoid arthritis, and overweight.

Preventability:

Monitoring of patients with long term use administration.

Impact on the risk-benefit balance of the product:

Not determined yet, though AML/MDS are life threatening events which lead to death. Based on clinical trial data, the impact seems very low.

Public health impact:

The public health impact of these events is expected to be low, as these events are expected to be very low in incidence.

Important Potential Risk – Cardiac Dysfunction: (*MedDRA PTs: Acute left ventricular failure, Acute pulmonary oedema, Acute right ventricular failure, Cardiac asthma, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiogenic shock, Cardiopulmonary failure, Cardiorenal syndrome, Chronic left ventricular failure, Chronic right ventricular failure, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Ejection fraction decreased, Congestive hepatopathy, Hepatojugular reflux, Left ventricular failure, Low cardiac output syndrome, Neonatal cardiac failure, Obstructive shock, Pulmonary oedema, Pulmonary oedema neonatal, Radiation associated cardiac failure, Right ventricular failure, Ventricular failure, Cardiomyopathy*)

Potential mechanisms:

There is no known mechanism of trabectedin induced cardiotoxicity. The mechanism by which chemotherapies, such as the anthracyclines, induce cardiotoxicity is not fully understood but may be related to lipid peroxidation and generation of reactive oxygen species by the anthracyclines as the heart is particularly vulnerable to injury from free radicals that could eventually lead to cardiac failure.

Evidence sources and strength of evidence:

- PSUR 19 (cutoff date 17 September 2022)
- Investigator's Brochure v.15
- Yondelis® SmPC
- Cardiac Safety Report (28 Jun 2018):
  - This report summarizes the cardiac safety data from clinical studies and integrated data analysis sets for subjects with solid tumours who received trabectedin as a monotherapy or in combination with Doxil®. The specific clinical studies and integrated safety analysis sets

contributing to this report include: Three randomized, open-label, Phase 3 studies (SAR-3007, OVA-301, and OVC-3006). In Study SAR-3007, trabectedin was administered as a monotherapy and in the 2 other studies (OVA-301 and OVC-3006), trabectedin was administered in combination with Doxil®; Integrated safety data from 10 Phase 2 studies and 1 Phase 3 study (SAR-3007) in STS and other solid tumours where trabectedin was administered as a monotherapy at a dose of 1.5 mg/m^2 once every 3 weeks as a 24-h i.v. infusion (q3wk; 24-h); Integrated safety data from the 2 Phase 3 ovarian cancer studies (OVA-301 and OVC-3006) where trabectedin was administered in combination with Doxil®.

- The analysis confirmed the need for caution when administering trabectedin as monotherapy to patients with risk factors for developing cardiac related treatment emergent AEs or myocardial dysfunction (i.e., those patients with a left ventricular ejection fraction [LVEF] < lower limit of normal (LLN), a history of cardiovascular disease or prior cumulative anthracycline dose of ≥300 mg/m^2). If, after careful consideration of benefit versus risk, treatment with trabectedin is initiated in patients with risk factors for developing cardiac-related AEs or myocardial dysfunction, close monitoring for symptoms and signs of myocardial dysfunction, including but not limited to regular LVEF assessments, is strongly recommended. For subjects with a Grade 3 or 4 cardiac AEs or serious cardiac events indicative of cardiomyopathy or for subjects with an LVEF that decreases below the LLN, trabectedin should be discontinued. Additionally, the data suggested that administration of trabectedin concurrently with Doxil® is associated with an increased risk for cardiotoxicity compared with Doxil® monotherapy.

Characterisation of the risk:

In Trial ET743-SAR-3007, cardiac dysfunction occurred in 20 (5%) of 378 patients receiving trabectedin, 15 (4%) of whom developed Grade 3 or 4 cardiac dysfunction. One patient died of cardiac failure. In the dacarbazine group (n=172), cardiac dysfunction occurred in 4 (2.3%) patients, 2 (1.2%) of whom reported Grade 3 events. No cardiac dysfunction events in this treatment group were reported as Grade 4 event or as an event leading to death. Prior chemotherapy with an anthracycline was a criterion for inclusion in Trial ET743-SAR-3007. Median times from the last dose of an anthracycline were 6.8 months and 5.9 months for patients enrolled in the trabectedin and dacarbazine treatment groups, respectively. Therefore, all trial patients were at risk for anthracycline-related cardiotoxic effects, and patients with a reduced baseline LVEF were considered eligible if they were symptomatically stable. Despite randomisation, median cumulative prior exposures to an anthracycline were greater in the trabectedin group as compared with the dacarbazine group suggesting an increased baseline risk for cardiac events within the trabectedin treatment group. In addition, patients were randomised to the trabectedin and dacarbazine treatment groups in a 2:1 ratio, and the increase in treatment exposure within the trabectedin group (median 4 cycles within trabectedin group versus 2 cycles within the dacarbazine group,) may have led to an observation bias in regard to cardiac toxicity. Matched assessments of LVEF, using 2D-echocardiograms or multigated acquisition scans, were conducted at baseline and at the time of treatment discontinuation. These assessments were obtained in 251 (66.4%) patients receiving trabectedin and in 100 (58.1%) patients receiving dacarbazine. Despite the greater increase in overall exposure for the trabectedin group, absolute decreases of LVEF ≥15% at the end of treatment, or an absolute decrease of ≥5% if the ejection fraction was lower than the normal range, were similar for the trabectedin group (13.5%) and dacarbazine group (11%). This level of LVEF decline across both treatment groups, including the dacarbazine treatment group which has not been previously associated with cardiotoxicity, suggests significant potential confounding by previous anthracycline exposure (ET743-SAR-3007 CSR).

The Odds Ratio for any treatment-emergent event has been calculated for the two indications approved for Yondelis®.

Table 37: SVII.3.1 Any Cardiac Dysfunction Treatment-Emergent Event

INDICATION: SOFT TISSUE SARCOMA					
	Any Treatment-Emergent Event, n (%)				
Trial	**Trabectedin Q3wk 24-h (1.5 mg/m²)**	**Trabectedin Qwk 3 h (0.58 mg/m²)**	**Dacarbazine Q3wk 20-min (1.0 g/m²)**	**Doxorubicin Q3wk-75 mg/m² or 60 mg/m² + Ifosfamide 6-9 g/m²**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL[b]					
ET743-STS-201	N=130	N=130	--	--	--
	2 (1.5%)	4 (3.1%)	--	--	0.49 (0.09-2.74)
ET743-SAR-3007	N=378	--	N=172	--	--
	20 (5.3%)	--	4 (2.3%)	--	2.35 (0.79-6.97)
ET-C-002-07	N=61	--	--	N=57	--
	2 (3.3%)	--	--	4 (7%)	0.45 (0.08-2.55)
ALL RANDOMISED TRIALS WITHOUT CONTROL[c]					
ISS-25 for STS	N=1,040	--	--	--	--
	34 (3.3%)	--	--	--	--
EAP ET743-SAR-3002	N=1,803	--	--	--	--
	33 (1.8%)	--	--	--	--

INDICATION: RELAPSED PLATINUM-SENSITIVE OVARIAN CANCER			
	Any Treatment-Emergent Event, n (%)		
Trial	**Trabectedin Q3wk 3-h (1.1 mg/m²) + Doxorubicin: Q3wk 90-min (30 mg/m²)**	**Doxorubicin: q4wk 90-min (50 mg/m²)**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL			
OVA-301	N=333	N=330	--
	8 (2.4%)	3 (0.9%)	2.68 (0.71-10.2)
OVC-3006	N=286	N=282	--
	25 (8.7%)	12 (4.3%)	2.16 (1.06-4.38)
OVA-301 + OVC-3006	N=619	N=612	--
	33 (5.3%)	15 (2.5%)	2.24 (1.2-4.17)
ALL RANDOMISED TRIALS WITHOUT CONTROL[d]			
ISS-25 for ovarian	N=295	--	--
	5 (1.7%)	--	--

Key: CI = confidence interval

[a] Odds ratio (95% CI) were based on Fisher's exact test.

[b] The 3 randomised trials (Phase 2 ET473-STS-201, Phase 3 ET743-SAR 3007 and Phase 3 ET-C-002-07) have not been integrated into one database due to differences in design. Therefore, the individual studies are presented separately.

[c] Integrated safety summary (ISS-25 trials) for sarcoma includes randomised trials ET473-STS-201 and the trabectedin arm of ET473-SAR-3007 but not the trabectedin arm of ETC-002-07 or the non-randomised EAP ET473-SAR-3002, therefore the latter is also presented separately

[d] Integrated Safety Summary (3 trials: ET-B-009-99, ET743-INT-11 and ET-B-026-03) for ovarian excludes randomised Trial ET743-OVA-301 and ET743-OVC-3006. Trial ET743-OVA-301 and ET743-OVC-3006 could not be integrated due to differences in design.

Outcome: outcome of the majority of the AEs was persisting or resolved; overall, the incidence of the fatal AEs was less ≤ 0.7% and the vast majority of AEs resolved or were ongoing.

Risk factors and risk groups:

Cardiac dysfunction can be inherited or can be caused by viral infections, autoimmune diseases or exposure to toxins and certain medicines. Elderly patients are particularly at risk with more than 80% of deaths and prevalent cardiac failure cases occurring in patients≥ 65 years of age in US and Europe. Men also have a greater risk of cardiac failure than women.

Patient-related risk factors for cancer therapy-related cardiac dysfunction include: those with pre-existing cardiac risk factors such as hypertension, diabetes mellitus, smoking, previous left ventricular dysfunction, heart failure, coronary disease, increasing age, female gender, and postmenopausal status (66).

Additional risk factors for developing heart damage include hypertension, obesity, radiation therapy involving the heart region, exposure to or previous exposure to cyclophosphamide, ifosfamide or amsacrine and existing heart disease. Chemotherapy induced cardiotoxicity often presents as dose-dependent cardiomyopathy that can lead to chronic heart failure. Anthracyclines are recognised to increase the risk of cardiac dysfunction with more than 1 half of patients exposed to anthracyclines developing some degree of cardiac dysfunction 10 to 20 years after chemotherapy, with 5% developing overt chronic heart failure (67-73).

In Trial ET743-SAR-3007, higher coronary artery disease, advancing age, abnormal baseline LVEF, and cardiac medical history were identified through a Multi-variate Analysis (logistic regression) as independent risk factors of LVEF decline.

Preventability:

Cardiac dysfunction is a known risk of certain chemotherapies that can only be prevented through avoiding their use. The SmPCs of the chemotherapies known to be cardiotoxic contain warnings about the risk of cardiac toxicity and in some cases (e.g., doxorubicin) frequent ECG monitoring is advised. Patients with cardiac dysfunction can be treated with various medications including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, ß-blockers, diuretics, nitrates and hydralazine. However, these may not halt the progression of disease. A Cochrane review of randomised controlled trials found that none of the cardioprotective medicines evaluated (N-acetylcysteine, phenethylamines, coenzyme Q10, a combination of vitamins E and C and N-acetylcysteine, L-carnitine, carvedilol, amifostine and dexrazoxane) showed a cardioprotective effect in preventing heart damage in cancer patients treated with anthracyclines up to November 2010.

Impact on the risk-benefit balance of the product:

Cardiac dysfunction can have a considerable negative impact on the patient as it can be life-threatening. Initial symptoms may include dyspnoea, dizziness, light-headedness, fainting during physical activity, chest pain especially after physical exertion or heavy meals, and cardiac murmurs. As cardiomyopathy

progresses, the heart becomes weaker, and this can lead to cardiac failure or arrhythmias. Despite general improvements in recognition, treatment, and management of cardiac failure there is a high risk of mortality with 1-year and 8-year mortality estimated at 11% and 41% respectively in a study of prevalent cases in Europe.

Study ET743SAR3007, a Phase 3, randomised, open-label, active-controlled, parallel group, multicentre trial comparing trabectedin with dacarbazine in the treatment of patients with unresectable, locally advanced or metastatic L-sarcoma, showed a higher incidence of high grade (Grade 3 and 4) cardiac dysfunction events in patients in the trabectedin arm compared to the dacarbazine arm. However, all patients in the study were at risk of cardiomyopathy as prior anthracycline chemotherapy was required for enrollment. Analysis of previous anticancer therapy of all enrolled subjects also demonstrated that despite randomisation, median cumulative anthracycline exposure was greater in the trabectedin group as compared with the dacarbazine group, suggesting an increased baseline risk for cardiac events within the trabectedin treatment group.

The majority of cases reported confounding factors including relevant cardiac history, cardiovascular risk factors, previous or concomitant use of anthracycline, or other anti-neoplastic agents.

Public health impact:

Although cardiac dysfunction is a major public health issue, the potential public health impact and trabectedin use is expected to be low as the causal association has yet to be confirmed.

Important Potential Risk – Pancreatitis, Lipase and/or Amylase Increased: (*MedDRA Standardised MedDRA Query [SMQ]: Acute pancreatitis*).

Potential mechanisms:

The mechanism is unknown.

Evidence sources and strength of evidence:

- PSUR 19 (cutoff date 17 September 2022)
- Investigator's Brochure v.15
- Yondelis SmPC

Characterisation of the risk:

Table 38: SVII.3.1 Any Pancreatitis, Lipase and/or Amylase Increased Treatment-Emergent Event

INDICATION: SOFT TISSUE SARCOMA					
	Any Treatment-Emergent Event, n (%)				
Trial	**Trabectedin Q3wk 24-h (1.5 mg/m²)**	**Trabectedin Qwk 3 h (0.58 mg/m²)**	**Dacarbazine Q3wk 20-min (1.0 g/m²)**	**Doxorubicin Q3wk-75 mg/m² or 60 mg/m² + Ifosfamide 6-9 g/m²**	**Odds Ratio[a] (95% CI)**
ALL RANDOMISED TRIALS WITH CONTROL*					
ET743-STS-201	N=130	N=130	--	--	--
	11 (8.5%)	5 (3.8%)	--	--	2.31 (0.78-6.85)
ET743-SAR-3007	N=378	--	N=172	--	--
	20 (5.3%)	--	3 (1.7%)	--	3.15 (0.92-10.74)
ET-C-002-07	N=61	--	--	N=57	--
	4 (6.6%)	--	--	2 (3.5%)	1.93 (0.34-10.97)
ALL RANDOMISED TRIALS WITHOUT CONTROL**					
ISS-25 for STS	N=1,040	--	--	--	--
	39 (3.8%)	--	--	--	--

EAP ET743-SAR-3002	N=1,803	--	--	--	--
	36 (2.0%)	--	--	--	--
INDICATION: RELAPSED PLATINUM-SENSITIVE OVARIAN CANCER					
	Any Treatment-Emergent Event, n (%)				
Trial	**Trabectedin Q3wk 3-h (1.1 mg/m²) + Doxorubicin: Q3wk 90-min (30 mg/m²)**	**Doxorubicin: q4wk 90-min (50 mg/m²)**	**Odds Ratio[a] (95% CI)**		
ALL RANDOMISED TRIALS WITH CONTROL					
OVA-301	N=333	N=330	--		
	36 (10.8%)	13 (3.9%)	2.96 (1.54-5.68)		
OVC-3006	N=286	N=282	--		
	16 (5.6%)	1 (0.4%)	16.65 (2.19-126.43)		
OVA-301 + OVC-3006	N=619	N=612	--		
	52 (8.4%)	14 (2.3%)	3.92 (2.15-7.15)		
ALL RANDOMISED TRIALS WITHOUT CONTROL***					
ISS-25 for ovarian	N=295	--	--		
	7 (2.4%)	--	--		

Key: CI = confidence interval

[a] Odds ratio (95% CI) were based on Fisher's exact test.

* The 3 randomised trials (Phase 2 ET473-STS-201, Phase 3 ET743-SAR 3007 and Phase 3 ET-C-002-07) have not been integrated into 1 database due to differences in design. Therefore, the individual studies are presented separately.

** Integrated Safety Summary (ISS-25 trials) for sarcoma includes randomised trials ET473-STS-201 and the Trabectedin arm of ET473-SAR-3007 but not the Trabectedin arm of ETC-002-07 or the non-randomised EAP ET473-SAR-3002, therefore the latter is also presented separately.

*** Integrated Safety Summary (3 trials: ET-B-009-99, ET743-INT-11 and ET-B-026-03) for ovarian excludes randomised Trial ET743-OVA-301 and ET743-OVC-3006. Trial ET743-OVA-301 and ET743-OVC-3006 could not be integrated due to differences in design.

Overall, the outcome was favourable for the majority of the AEs and the vast majority reported grade 2 or 3 AEs in severity.

Risk factors and risk groups:

Concomitant use of drugs described to produce pancreatitis, including ranitidine, paroxetine, celecoxib, and/ or capecitabine, any previous or concomitant biliary tract disease, or gallstones, prior history of cholecystectomy or other biliary or pancreatic surgery, hypercholesterolemia, history of use of ethanol (alcoholism), recent abdominal trauma, pancreatic malignancy, or a family history of pancreatitis. Risk factors for developing severe acute pancreatitis (with increased mortality) are older age (>55), obesity (body mass index >30), organ failure and pleural effusion and/or infiltrates at admission. Several populations at higher risk have been identified during research in drug-induced pancreatitis. Predisposing demographic characteristics are female gender and younger age. Three types of diseases were recognised as the most frequent predisposing health factors in drug-induced pancreatitis: inflammatory bowel diseases, human immunodeficiency virus (HIV) infection and cancer treated by combined chemotherapy.

Preventability:

Patients at risk of pancreatitis should be monitored for signs and symptoms.

Impact on the risk-benefit balance of the product:

Potentially life threatening.

Public health impact:

The public health impact of these events is expected to be low.

SVII.3.2 Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table 39: Summary of safety concerns

Important identified risks	Injection site reactions
Important potential risks	AML/MDS Cardiac Dysfunction Pancreatitis, lipase and/or amylase increased
Missing information	None

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

There are no post-authorisation efficacy studies imposed by the competent authority or which are a specific obligation and/or condition of the marketing authorisation.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Table 40: Part V.1 Description of routine risk minimization measures by safety concern.

Safety concern	Routine risk minimisation activities
Injection site reactions	**Routine Risk Communication:** *SmPC Section 4.4 and 4.8* *Patient leaflet (PL) section 2, 3 and 4.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation to administer through a central venous line in SmPC sections 4.2, 4.4 and 6.6 and PL section 3. Advice for patient to inform nurse or doctor immediately if they notice redness, swelling, itchiness and discomfort at injection site in PL section 4. **Other routine risk minimisation measures beyond the product information**: Section 4.2 of the SmPC clearly states that 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.
AML/MDS	**Routine Risk Communication:** *SmPC Section 5.3* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Insufficient evidence of risk to warrant SmPC and PL information at present. **Other routine risk minimisation measures beyond the product information**: Section 4.2 of the SmPC clearly states that 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.
Cardiac Dysfunction	**Routine Risk Communication**: *SmPC Section 4.4 and 4.8* *PL section 2 and 4* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for cardiac assessments including left ventricular ejection fraction (LVEF) monitoring before and during treatment with trabectedin in SmPC section 4.4. Advice for patient to inform doctor of any cardiac problems prior to starting treatment in PL section 2. **Other routine risk minimisation measures beyond the product information**: Section 4.2 of the SmPC clearly states that 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.
Pancreatitis, lipase and/or amylase increased	**Routine risk communication:** Insufficient evidence of risk to warrant SmPC and PL information at present. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Insufficient evidence of risk to warrant SmPC and PL information at present. **Other routine risk minimisation measures beyond the product information:** Section 4.2 of the SmPC clearly states that 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.

V.2 Additional risk minimisation measures

Not applicable.

V.3 Summary table of risk minimisation measures

Table 41: Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Injection site reactions	**Routine risk minimisation measures:** *SmPC Sections 4.4 and 4.8.* *SmPC Sections 4.2, 4.4 and 6.6 where it is recommended to administer trabectedin through a central venous line.* *PL Section 2, 3 and 4.* **Additional risk minimisation measures:** *None*	None proposed
AML/MDS	**Routine risk minimisation measures:** *SmPC Section 5.3* **Additional risk minimisation measures**: None.	None proposed
Cardiac Dysfunction	**Routine risk minimisation measures**: *SmPC Sections 4.4 and 4.8.* *PL Section 2 and 4.* **Additional risk minimisation measures**: *None.*	None proposed
Pancreatitis, lipase and/or amylase increased	**Routine risk minimisation measures:** No risk minimisation measures. **Additional risk minimisation measures:** *None.*	None proposed

Part VI: Summary of the risk management plan

Summary of risk management plan for Yondelis® (TRABECTEDIN)

This is a summary of the Risk Management Plan (RMP) for Yondelis®. The RMP details important risks of Yondelis®, how these risks can be minimised, and how more information will be obtained about Yondelis®'s risks and uncertainties (missing information).

Yondelis®'s Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Yondelis® should be used.

This summary of the RMP for Yondelis® should be read in the context of all information including the assessment report of the evaluation and its plain-language summary, which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Yondelis®'s RMP.

I. The medicine and what it is used for

Yondelis® is authorised for the treatment of adult patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients (see SmPCs for the full indication).

Yondelis® in combination with pegylated liposomal doxorubicin (PLD) is authorised for the treatment of patients with platinum sensitive relapsed ovarian cancer (ROC) (see SmPC for the full indication).

It contains trabectedin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Yondelis® benefits can be found in Yondelis® EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/yondelis#overview-section.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Yondelis®, together with measures to minimise such risks and the proposed studies for learning more about Yondelis®'s risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation measures***.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

II.A List of important risks and missing information

Important risks of Yondelis® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yondelis®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs

further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risks	Injection site reactions
Important Potential Risks	Acute Myeloid Leukaemia/ Myelodysplasia (AML/MDS) Cardiac Dysfunction Pancreatitis, lipase and/or amylase increased
Missing Information	None

II.B Summary of important risks

Important identified risk: Injection site reaction	
Evidence for linking the risk to the medicine	- Periodic Safety Update Report (PSUR) 19 (cutoff date 17 September 2022) - Investigator's Brochure v.15 - Clinical trials (Company Core Data Sheet [CCDS] v.16) • In patients with soft tissue sarcoma, in the integrated clinical trials phase 2 and 3, assigned to the recommended regimen [1.5 mg/m^2, 24-hour infusion every 3 weeks], injection site reactions incidence was of 8.5%. In patients with ovarian cancer, in the integrated phase 3 clinical trials, assigned to combination therapy with trabectedin plus pegylated liposomal doxorubicin (PLD), catheter site inflammation and catheter site pain incidence was of 1.6% and 2.4% respectively. - Clinical trial and post-marketing (CCDS v.14 and Summary of Product Characteristics [SmPC]) • During clinical studies and post-marketing surveillance, a few cases of trabectedin extravasation with subsequent tissue necrosis requiring debridement have been reported. SmPC includes these adverse drug reactions (ADRs) as uncommon ADRs.
Risk factors and risk groups	In one trial on the use of fosaprepitant, younger age (<50 years) and low body mass index (<22) were both risk factors for injections site reactions (63). The potential for tissue damage is affected by the factors such as the drug concentration, high vesicant potential of drug and the unfiltered amount, tissue exposure and extravasated zone, repeated use of drugs having the vesicant characteristic. The risk factors affecting the formation of extravasation or making this formation easier involves patient characteristics (e.g., extreme age, patients with fragile veins, sedated or confused patients, etc.), diseases where patients are exposed to repeated treatment infusion requiring indwelling catheters such as cancer patients, issues related to the venous access line (such as peripheral i.v. particularly in areas such as antecubital fossa, on hand, on foot, wrist, thickness of the i.v. catheter tip, i.v. catheter length, placement of central catheter in the region instable to motion, bending or dislocation of the catheter, injection needle on the port not fully accessed, excessive back pressure around the needle, fibrin deposition or thrombosis at the catheter) or issues with the insertion line technique (such as inexperienced staff and insufficient information on the drug management) (64, 65).
Risk minimisation measures	**Routine Risk Communication:** SmPC Section 4.4 and 4.8 Patient Leaflet (PL) section 2, 3 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Recommendation to administer through a central venous line in SmPC sections 4.2, 4.4 and 6.6 and PL section 3. Advice for patient to inform nurse or doctor immediately if they notice redness, swelling, itchiness and discomfort at injection site in PL section 4. **Other routine risk minimisation measures beyond the product information**:

	Section 4.2 of the SmPC clearly states that 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. **Additional risk minimisation measures**: None.

Important potential risk: AML/MDS	
Evidence for linking the risk to the medicine	- PSUR 19 (cutoff date 17 September 2022) - Investigator's Brochure v.15 - Secondary haematological malignancies Ad hoc report (23 September 2014) • The cumulative analysis identified 28 cases reporting haematological malignancies in patients who received trabectedin irrespective of causality. The source distribution of cases was 22 cases from clinical trials and 6 spontaneous cases. Twelve (12) cases out of the 28 reported a fatal outcome, 9 due to AML and 3 due to other causes. • Based on this cumulative review of clinical studies and spontaneous cases, the role of trabectedin in the occurrence of AML/MDS is yet to be determined. The majority of the reported cases adequately documented were heavily confounded, mainly by previous or concomitant chemotherapy or radiotherapy well known to induce secondary malignancies and specifically AML/MDS. Only one case was not considered to be confounded.
Risk factors and risk groups	Patients heavily pre-treated with chemotherapy and radiation. Among other cytotoxic drugs, PLD and alkylating agents such as ifosfamide have been associated with an increased risk for secondary AML and MDS. Other risk factors include smoking which can double or triple the risk of AML, genetics, blood disorders such as myelodysplastic syndrome, autoimmune conditions such as rheumatoid arthritis, and being overweight.
Risk minimisation measures	**Routine Risk Communication**: SmPC Section 5.3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Insufficient evidence of risk to warrant SmPC and PL information at present. **Other routine risk minimisation measures beyond the product information**: Section 4.2 of the SmPC clearly states that 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. **Additional risk minimisation measures**: None.

Important potential risk: Cardiac dysfunction	
Evidence for linking the risk to the medicine	- PSUR 19 (cutoff date 17 September 2020) - Investigator's Brochure v.15 - Yondelis® SmPC - Cardiac Safety Report (28 June 2018) • This report summarizes the cardiac safety data from clinical studies and integrated data analysis sets for subjects with solid tumours who received trabectedin as a monotherapy or in combination with Doxil®. The specific clinical studies and integrated safety analysis sets contributing to this report include: Three randomized, open-label, Phase 3 studies (SAR-3007, OVA-301, and OVC-3006). In Study SAR-3007, trabectedin was administered as a monotherapy and in the 2 other studies (OVA-301 and OVC-3006), trabectedin was

	administered in combination with Doxil®; Integrated safety data from 10 Phase 2 studies and 1 Phase 3 study (SAR-3007) in STS and other solid tumours where trabectedin was administered as a monotherapy at a dose of 1.5 mg/m^2 once every 3 weeks as a 24-h i.v. infusion (q3wk; 24-h); Integrated safety data from the 2 Phase 3 ovarian cancer studies (OVA-301 and OVC-3006) where trabectedin was administered in combination with Doxil®. • The analysis confirmed the need for caution when administering trabectedin as monotherapy to patients with risk factors for developing cardiac related treatment emergent AEs or myocardial dysfunction (i.e., those patients with a left ventricular ejection fraction (LVEF) <lower limit of normal (LLN), a history of cardiovascular disease or prior cumulative anthracycline dose of ≥300 mg/m^2). If, after careful consideration of benefit versus risk, treatment with trabectedin is initiated in patients with risk factors for developing cardiac-related AEs or myocardial dysfunction, close monitoring for symptoms and signs of myocardial dysfunction, including but not limited to regular LVEF assessments, is strongly recommended. For subjects with a Grade 3 or 4 cardiac AEs or serious cardiac events indicative of cardiomyopathy or for subjects with an LVEF that decreases below the LLN, trabectedin should be discontinued. Additionally, the data suggested that administration of trabectedin concurrently with Doxil® is associated with an increased risk for cardiotoxicity compared with Doxil® monotherapy.
Risk factors and risk groups	Cardiac dysfunction can be inherited or can be caused by viral infections, autoimmune diseases or exposure to toxins and certain medicines. Elderly patients are particularly at risk with more than 80% of deaths and prevalent cardiac failure cases occurring in patients≥ 65 years of age in US and Europe. Men also have a greater risk of cardiac failure than women. Patient-related risk factors for cancer therapy-related cardiac dysfunction include: those with pre-existing cardiac risk factors such as hypertension, diabetes mellitus, smoking, previous left ventricular dysfunction, heart failure, coronary disease, increasing age, female gender, and postmenopausal status (66). Additional risk factors for developing heart damage include hypertension, obesity, radiation therapy involving the heart region, exposure to or previous exposure to cyclophosphamide, ifosfamide or amsacrine and existing heart disease. Chemotherapy induced cardiotoxicity often presents as dose-dependent cardiomyopathy that can lead to chronic heart failure. Anthracyclines are recognised to increase the risk of cardiac dysfunction with more than 1 half of patients exposed to anthracyclines developing some degree of cardiac dysfunction 10 to 20 years after chemotherapy, with 5% developing overt chronic heart failure (67-73). In Trial ET743-SAR-3007, higher coronary artery disease, advancing age, abnormal baseline LVEF, and cardiac medical history were identified through a Multi-variate Analysis (logistic regression) as independent risk factors of LVEF decline.
Risk minimisation measures	**Routine Risk Communication**: SmPC Section 4.4 and 4.8 PL section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for cardiac assessments including LVEF monitoring before and during treatment with trabectedin in SmPC section 4.4. Advice for patient to inform doctor of any cardiac problems prior to starting treatment in PL section 2. **Other routine risk minimisation measures beyond the product information**:

	Section 4.2 of the SmPC clearly states that 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. **Additional risk minimization measures**: None.

Important potential risk: Pancreatitis, Lipase and/or Amylase increased	
Evidence for linking the risk to the medicine	- PSUR 19 (cutoff date 17 September 2022) - Investigator's Brochure v.15 - Yondelis® SmPC
Risk factors and risk groups	Concomitant use of drugs described to produce pancreatitis, including ranitidine, paroxetine, celecoxib, and/ or capecitabine, any previous or concomitant biliary tract disease, or gallstones, prior history of cholecystectomy or other biliary or pancreatic surgery, hypercholesterolemia, history of use of ethanol (alcoholism), recent abdominal trauma, pancreatic malignancy, or a family history of pancreatitis. Risk factors for developing severe acute pancreatitis (with increased mortality) are older age (>55), obesity (body mass index >30), organ failure and pleural effusion and/or infiltrates at admission. Several populations at higher risk have been identified during research in drug-induced pancreatitis. Predisposing demographic characteristics are female gender and younger age. Three types of diseases were recognised as the most frequent predisposing health factors in drug-induced pancreatitis: inflammatory bowel diseases, human immunodeficiency virus (HIV) infection and cancer treated by combined chemotherapy.
Risk minimisation measures	**Routine risk minimization measures:** No risk minimisation measures. **Additional risk minimisation measures:** None proposed.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Yondelis®.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Yondelis®.

Part VII: Annexes

Table of Contents

Annex 3: Specific adverse reaction follow-up forms

Not applicable.

Annex 5: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 6: Other supporting data (including referenced material)

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