



## Clinical trial results:

### Maintenance therapy with trabectedin versus observation after first line treatment with doxorubicin of patients with advanced or metastatic soft tissue sarcoma

#### Summary

EudraCT number	2016-003535-38
Trial protocol	DE GB NL PL ES FR CY IT
Global end of trial date	05 June 2020

#### Results information

Result version number	v1 (current)
This version publication date	28 January 2021
First version publication date	28 January 2021

#### Trial information

##### Trial identification

Sponsor protocol code	1447-STBSG
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02929394
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue E. Mounier 83, Bruxelles, Belgium, 1200
Public contact	Clinical Operations Department, European Organisation for the Research and treatment of Cancer, 0032 27741013, regulatory@eortc.be
Scientific contact	Clinical Operations Department, European Organisation for the Research and treatment of Cancer, 0032 27741013, regulatory@eortc.be

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2020
Global end of trial reached?	Yes
Global end of trial date	05 June 2020
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate whether maintenance trabectedin given after 6 cycles of doxorubicin first-line therapy for advanced or metastatic STS prolongs progression-free survival (PFS) as compared to an observational approach.

Protection of trial subjects:

The responsible investigator ensures that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002874.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf)).

The protocol was approved by the competent ethics committee(s) as required by the applicable national

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	France: 10
Worldwide total number of subjects	13
EEA total number of subjects	13

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	5
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 13 patients were registered by 6 institutions between 17/Nov/2017 and 29/Aug/2018.

### Pre-assignment

Screening details:

Age 18 yo WHO PS  $\leq 1$  adequate bone marrow, liver and renal function. No prior exposure to trabectedin. Histologically proven locally advanced or metastatic high grade STS (excluding histologies insensitive to chemotherapy). Non-progressive disease after 6 cycles of first-line chemotherapy with doxorubicin.

### Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	13

### Period 1

Period 1 title	Overall period - Full patient population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Arm A - Trabectedin maintenance

Arm description:

Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg.

Arm type	Experimental
Investigational medicinal product name	TRABECTEDIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours.

<b>Arm title</b>	Arm B - Observational
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Arm description:

Observation through clinical and radiological follow-up until disease progression (RECIST 1.1). Patients could receive commercial trabectedin after progression in Arm B as second line treatment as per investigator's decision.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Arm A - Trabectedin maintenance	Arm B - Observational
Started	7	6
Completed	0	1
Not completed	7	5
Toxicity	5	-
Symptomatic deterioration	1	1
Patient's decision (not related to toxicity)	-	1
Progression of disease/death due to PD	1	3

## Baseline characteristics

### Reporting groups

Reporting group title	Arm A - Trabectedin maintenance
Reporting group description: Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m <sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg.	
Reporting group title	Arm B - Observational
Reporting group description: Observation through clinical and radiological follow-up until disease progression (RECIST 1.1). Patients could receive commercial trabectedin after progression in Arm B as second line treatment as per investigator's decision.	

Reporting group values	Arm A - Trabectedin maintenance	Arm B - Observational	Total
Number of subjects	7	6	13
Age categorical Units: Subjects			
Adults (18-64 years)	5	3	8
From 65-84 years	2	3	5
Age continuous Units: years			
median	61	64	
full range (min-max)	34 to 70	45 to 74	-
Gender categorical Units: Subjects			
Female	5	2	7
Male	2	4	6
WHO performance status (PS) Units: Subjects			
WHO PS = 0	2	2	4
WHO PS = 1	5	4	9
A first line chemotherapy with Doxorubicin (6 cycles) Units: Subjects			
Yes	7	6	13
Previous treatment - Dose of Doxorubicin (mg/m <sup>2</sup> ) Units: (mg/m <sup>2</sup> )			
median	75.0	75.0	
full range (min-max)	50.0 to 75.0	60.0 to 75.0	-

### Subject analysis sets

Subject analysis set title	Overall - full patient population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Considers all 13 patients randomised.	

Reporting group values	Overall - full patient population		
Number of subjects	13		
Age categorical			
Units: Subjects			
Adults (18-64 years)	8		
From 65-84 years	5		
Age continuous			
Units: years			
median	62		
full range (min-max)	34 to 74		
Gender categorical			
Units: Subjects			
Female	7		
Male	6		
WHO performance status (PS)			
Units: Subjects			
WHO PS = 0	4		
WHO PS = 1	9		
A first line chemotherapy with Doxorubicin (6 cycles)			
Units: Subjects			
Yes	13		
Previous treatment - Dose of Doxorubicin (mg/m <sup>2</sup> )			
Units: (mg/m <sup>2</sup> )			
median	75.0		
full range (min-max)	50.0 to 75.0		

## End points

### End points reporting groups

Reporting group title	Arm A - Trabectedin maintenance
Reporting group description: Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m <sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg.	
Reporting group title	Arm B - Observational
Reporting group description: Observation through clinical and radiological follow-up until disease progression (RECIST 1.1). Patients could receive commercial trabectedin after progression in Arm B as second line treatment as per investigator's decision.	
Subject analysis set title	Overall - full patient population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Considers all 13 patients randomised.	

### Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description: PFS was estimated by the Kaplan-Meier method. Median PFS was provided with it's 95% confidence interval.  Patients who were alive without evidence of progression and who did not start a new antitumoral treatment in the absence of progression were censored at the date of their last radiological assessment.	
End point type	Primary
End point timeframe: Progression-free survival was measured from the date of randomization until the date of the first documented disease progression, start of new antitumoral treatment in the absence of documented disease progression, or death, whichever occurs first.	

End point values	Arm A - Trabectedin maintenance	Arm B - Observational		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Months				
median (confidence interval 95%)	11.3 (6.5 to 19.0)	5.4 (1.4 to 14.7)		

Attachments (see zip file)	PFS - Since randomization/1447_PFS_from_Randomization.jpg
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### Statistical analyses



<b>Statistical analysis title</b>	Kaplan-Meier
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Statistical analysis description:

There were only 13 patients available in the study (the study was closed for recruitment for poor accrual) so it is not justifiable to make statistical analysis. For the "Parameter estimate" Section, median PFS (and 95% CI) for Trabectedin Arm were described in order to avoid an error in the system.

Comparison groups	Arm A - Trabectedin maintenance v Arm B - Observational
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	Median PFS estimate
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	19

Notes:

[1] - Progression-free survival was estimated by the Kaplan-Meier method. The median survival time and its associated 95% CI was provided. For the "Parameter estimate" Section, median PFS (and 95% CI) for Trabectedin Arm were described in order to avoid an error in the system.

### Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

Overall survival was estimated by the Kaplan-Meier method. The median survival time and its associated 95% CI was provided.

End point type	Secondary
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End point timeframe:

Overall survival was measured from the date of randomization to the date of death, whatever the cause of death. Patients who were alive were censored at the date of their last follow-up.

End point values	Arm A - Trabectedin maintenance	Arm B - Observational		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Months				
median (confidence interval 95%)	9999 (15.3 to 9999)	9999 (5.3 to 9999)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS) - Since Doxorubicin

End point title	Progression-free survival (PFS) - Since Doxorubicin
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End point description:

PFS was estimated by the Kaplan-Meier method. Median PFS was provided with it's 95% confidence interval.

End point type	Secondary
End point timeframe:	
PFS was measured from the date of starting first-line Doxorubicin treatment.	

End point values	Arm A - Trabectedin maintenance	Arm B - Observational		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Months				
median (confidence interval 95%)	16.6 (11.0 to 24.2)	10.0 (6.6 to 19.5)		

<b>Attachments (see zip file)</b>	PFS - Since Doxorubicin/1447_PFS_from_Doxorubicin_start.jpg
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival - since Doxorubicin start

End point title	Overall survival - since Doxorubicin start
End point description:	
Overall survival was estimated by the Kaplan-Meier method. The median survival time and its associated 95% CI was provided.	
End point type	Secondary
End point timeframe:	
OS was measured from the date of starting first-line Doxorubicin treatment.	

End point values	Arm A - Trabectedin maintenance	Arm B - Observational		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Months				
median (confidence interval 95%)	9999 (20.6 to 9999)	9999 (9.9 to 9999)		

<b>Attachments (see zip file)</b>	OS - since Doxorubicin/1447_OS_from_Doxorubicin_start.jpg
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Start from randomization up to 30 days after administration of the last dose.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items. (2 AEs are reported as "other" and are not reported as not available from the list of SOC). Both AEs and SAEs are evaluated using CTC grading.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	Arm A
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Reporting group description:

Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength

Serious adverse events	Arm A		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
ARTERIAL STENOSIS			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIAC FAILURE			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders ABDOMINAL PAIN UPPER alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	    1 / 7 (14.29%) 0 / 1 0 / 0		
Respiratory, thoracic and mediastinal disorders PLEURAL EFFUSION alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	    1 / 7 (14.29%) 0 / 1 0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	   1 / 7 (14.29%) 1		
ASPARTATE AMINOTRANSFERASE INCREASED alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	   1 / 7 (14.29%) 3		
CPK INCREASED alternative dictionary used: CTCAE 4 alternative assessment type:			

Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	7		
CREATININE INCREASED			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
EJECTION FRACTION DECREASED			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	8		
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEVROMA			
alternative dictionary used: CTCAE 4			
alternative assessment type: Systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p>		
<p>Cardiac disorders</p> <p>CARDIAC DISORDERS - OTHER, ARTERIAL STENOSIS</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HEART FAILURE</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p> <p>2 / 7 (28.57%)</p> <p>2</p>		
<p>Nervous system disorders</p> <p>DYSGEUSIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 7 (14.29%)</p> <p>1</p>		
<p>Blood and lymphatic system disorders</p> <p>ANEMIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 7 (28.57%)</p> <p>4</p>		
<p>General disorders and administration site conditions</p> <p>EDEMA LIMBS</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>FATIGUE</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p>	<p>2 / 7 (28.57%)</p> <p>2</p>		

<p>subjects affected / exposed</p> <p>3 / 7 (42.86%)</p> <p>occurrences (all)</p> <p>4</p> <p>FEVER</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 7 (14.29%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Gastrointestinal disorders</p> <p>ABDOMINAL PAIN</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>2 / 7 (28.57%)</p> <p>occurrences (all)</p> <p>3</p> <p>DIARRHEA</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 7 (14.29%)</p> <p>occurrences (all)</p> <p>1</p> <p>DRY MOUTH</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 7 (14.29%)</p> <p>occurrences (all)</p> <p>1</p> <p>MUCOSITIS ORAL</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>2 / 7 (28.57%)</p> <p>occurrences (all)</p> <p>2</p> <p>NAUSEA</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>3 / 7 (42.86%)</p> <p>occurrences (all)</p> <p>3</p> <p>VOMITING</p>			

alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Respiratory, thoracic and mediastinal disorders COUGH alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Musculoskeletal and connective tissue disorders BONE PAIN alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)  INFLAMMATORY LEGS alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)  PAIN IN EXTREMITY alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1  1 / 7 (14.29%) 1  1 / 7 (14.29%) 1		
Metabolism and nutrition disorders ANOREXIA alternative dictionary used: CTCAE 4 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2017	<p>The protocol and patient information sheet have been updated according to the VHP comments:</p> <ul style="list-style-type: none"><li>- Contraceptive methods considered to be highly effective, listed in the protocol, are now in line with Clinical Trial Facilitation group (CTFG) guidance.</li><li>- A definition of women of childbearing potential has been included.</li><li>- According to the Trabectedin SmPC, a note for advice on the possibility of ovules/sperm conservation has been added in the inclusion criteria.</li><li>- It has been clarified that protocol waivers are not acceptable. A new section 16.4 regarding protocol and GCP compliance has been added as well.</li><li>- Complete blood counts must be performed weekly for the first two cycles.</li></ul> <p>This amendment has been discussed and agreed by the study team and study coordinator.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Despite many efforts from all the parties involved, only few patients (13 patients in total) were recruited. The study was closed for recruitment on 10/08/2018 for poor accrual but two patients were included after that because they consented earlier.

Notes: