Clinical trial results:
TRUSTS: A phase IIb/III multicenter study comparing the efficacy of TRabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in patients with advanced or metastatic Untreated Soft Tissue Sarcoma

Summary

EudraCT number	2009-014889-26
Trial protocol	GB DE BE HU DK AT NL SK ES PL
Global end of trial date	16 April 2016

Results information

Result version number	v1 (current)
This version publication date	04 May 2017
First version publication date	04 May 2017

Trial information

Trial identification

Sponsor protocol code	EORTC 62091

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01189253
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, 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	22 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective of the trial is to evaluate whether trabectedin given as 1st line chemotherapy for advanced / metastatic soft tissue sarcoma prolongs progression free survival, as compared to doxorubicin.

Protection of trial subjects:

The responsible investigator will ensure that this study is 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 will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

All patients received dexamethasone or an equivalent 30 minutes before administration of trabectedin.

Evidence for comparator:

Doxorubicin is the most active drug for the systemic treatment of STS. Randomized studies have shown that combination chemotherapy can sometimes provide higher response rates than single agent doxorubicin. However, even if present, this higher objective response rate did not translate into improved overall survival.The EORTC STBSG has already evaluated several new drugs given as second line chemotherapy, but the vast majority of these were found to be inactive, with the exception of agents such as trabectedin or imatinib with activity in defined subtypes of STS.

Actual start date of recruitment	06 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 66
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	133
EEA total number of subjects	112

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	79
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 133 (112 by EORTC STBSG and 21 by SARC) patients were registered by 28 institutions (9 countries) between June 2011 and August 2012.

Pre-assignment

Screening details:

The registration/randomization is one step process.

Period 1

Period 1 title	baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Trab_3hrs

Arm description:

Trabectedin 3 hrs IV

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	GFI-17027907-AAA-PB-003
Other name	YONDELIS
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.3 mg/m2 body surface area, administered as an intravenous infusion over 3 hours.

Arm title	Trab_24hrs

Arm description:

Trabectedin 24 hrs IV

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	GFI-17027907-AAA-PB-003
Other name	YONDELIS
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.5 mg/m2 body surface area, administered as an intravenous infusion over 24 hours.

Arm title	Doxo

Arm description:

Doxorubicin

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Doxorubicin will be administered on day 1 every 3 weeks at the dose of 75 mg/m² by IV according to institution guidelines. Doxorubicin will be administered for a maximum of 6 cycles (1 cycle=3weeks).

Number of subjects in period 1	Trab_3hrs	Trab_24hrs	Doxo
Started	47	43	43
Completed	47	43	43

Period 2

Period 2 title	On-study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Trab_3hrs

Arm description:

Trabectedin 3 hrs IV

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	GFI-17027907-AAA-PB-003
Other name	YONDELIS
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.3 mg/m2 body surface area, administered as an intravenous infusion over 3 hours.

Arm title	Trab_24hrs

Arm description:

Trabectedin 24 hrs IV

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	GFI-17027907-AAA-PB-003
Other name	YONDELIS
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin will be administered on day 1 every 3 weeks at the dose of 1.5 mg/m2 body surface area, administered as an intravenous infusion over 24 hours.

Arm title	Doxo

Arm description:

Doxorubicin

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Doxorubicin will be administered on day 1 every 3 weeks at the dose of 75 mg/m² by IV according to institution guidelines. Doxorubicin will be administered for a maximum of 6 cycles (1 cycle=3weeks).

Number of subjects in period 2	Trab_3hrs	Trab_24hrs	Doxo
Started	47	43	43
Completed	0	0	21
Not completed	47	43	22
Physician decision	1	2	1
Consent withdrawn by subject	1	2	1
Adverse event, non-fatal	7	8	1
Unknown	1	-	1
Patient still on treatment	-	1	-
Death not due to toxicity	2	1	1
Protocol deviation	1	2	3
Lack of efficacy	34	27	14

Baseline characteristics

Reporting groups	
Reporting group title	Trab_3hrs
Reporting group description: Trabectedin 3 hrs IV	
Reporting group title	Trab_24hrs
Reporting group description: Trabectedin 24 hrs IV	
Reporting group title	Doxo
Reporting group description: Doxorubicin	

Reporting group values	Trab_3hrs	Trab_24hrs	Doxo
Number of subjects	47	43	43
Age categorical			
Age at randomization (years)			
Units: Subjects			
60 years and over	24	22	23
From 18-59 years	23	21	20
Age continuous			
Age at randomization			
Units: years			
median	60	60	60
full range (min-max)	34 to 84	23 to 78	24 to 77
Gender categorical			
Units: Subjects			
Female	29	23	25
Male	18	20	18
WHO Performance status			
WHO Performance status			
Units: Subjects			
0=Fully active	25	21	26
1= Able to carry out work of a light nat	22	22	17
Other medical conditions			
Other medical conditions at trial entry			
Units: Subjects			
Yes	37	36	29
No	10	7	14
Site of primary tumor			
Units: Subjects			
Head and Neck	1	0	0
Trunk	1	5	0
Thoracic	7	3	4
Retro-intra abdominal	7	10	12
Lower extremity	10	14	9
Upper extremity	5	3	1
Visceral GU	2	1	2

Visceral GI	1	2	3
Visceral Gynecological	8	4	8
Visceral Breast	0	0	1
Visceral Other	2	0	0
Other	2	1	3
Unknown	1	0	0
Tumor size (cm) Units: Subjects			
≥ 2	6	4	1
2-5	8	9	5
> 5	19	21	29
Unknown	14	9	8
Growth rate Units: Subjects			
Rapid	16	12	18
Slow	5	6	4
Unknown	26	25	21
Necrosis Units: Subjects			
No	19	15	16
Yes	19	15	20
Unknown	9	13	7
Type of disease at the time of sampling Units: Subjects			
Primary	28	32	32
Recurrent	3	2	3
Metastatic	11	9	7
Recurrent and metastatic	4	0	1
Unknown	1	0	0
Tumor type (Local pathology)			
(Local pathology)			
Units: Subjects			
Adipocytic (liposarcoma)	6	11	13
Fibroblastic	5	3	1
So-called fibrohistiocytic tumours	3	3	1
Smooth muscle tumours	18	8	14
Pericytic (perivascular) tumours	0	1	0
Vascular tumours	1	2	0
Chondro-osseous tumours	0	1	1
Tumors of uncertain differentiation	7	7	8
Undifferentiated sarcoma	4	6	5
Other	3	1	0
Tumor type (Review pathology)			
(Review pathology)			
Units: Subjects			
Adipocytic (liposarcoma)	5	7	12
Fibroblastic	3	4	0
So-called fibrohistiocytic tumours	4	6	4
Smooth muscle tumours	11	4	9
Vascular tumours	1	1	0
Chondro-osseous tumours	0	1	0

Tumors of uncertain differentiation	6	5	6
GIST	1	0	0
Undifferentiated sarcoma NOS	3	3	1
Other	5	1	4
Missing	8	11	7
Tumor grade			
(review)			
Units: Subjects			
Low	2	2	2
Intermediate	18	9	18
High	13	12	11
Unknown	14	20	12
BMI			
Body Mass Index			
Units: kg/m²			
median	28.8	25.3	25.8
full range (min-max)	16.9 to 48.1	19.7 to 40	18.8 to 46.2
Tumor size			
Units: cm			
median	6	7.1	9
full range (min-max)	1 to 22	1 to 22.6	1.4 to 34

Reporting group values	Total		
Number of subjects	133		
Age categorical			
Age at randomization (years)			
Units: Subjects			
60 years and over	69		
From 18-59 years	64		
Age continuous			
Age at randomization			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	77		
Male	56		
WHO Performance status			
WHO Performance status			
Units: Subjects			
0=Fully active	72		
1= Able to carry out work of a light nat	61		
Other medical conditions			
Other medical conditions at trial entry			
Units: Subjects			
Yes	102		
No	31		
Site of primary tumor			
Units: Subjects			

Head and Neck	1		
Trunk	6		
Thoracic	14		
Retro-intra abdominal	29		
Lower extremity	33		
Upper extremity	9		
Visceral GU	5		
Visceral GI	6		
Visceral Gynecological	20		
Visceral Breast	1		
Visceral Other	2		
Other	6		
Unknown	1		
Tumor size (cm) Units: Subjects			
≥ 2	11		
2-5	22		
> 5	69		
Unknown	31		
Growth rate Units: Subjects			
Rapid	46		
Slow	15		
Unknown	72		
Necrosis Units: Subjects			
No	50		
Yes	54		
Unknown	29		
Type of disease at the time of sampling Units: Subjects			
Primary	92		
Recurrent	8		
Metastatic	27		
Recurrent and metastatic	5		
Unknown	1		
Tumor type (Local pathology)			
(Local pathology)			
Units: Subjects			
Adipocytic (liposarcoma)	30		
Fibroblastic	9		
So-called fibrohistiocytic tumours	7		
Smooth muscle tumours	40		
Pericytic (perivascular) tumours	1		
Vascular tumours	3		
Chondro-osseous tumours	2		
Tumors of uncertain differentiation	22		
Undifferentiated sarcoma	15		
Other	4		
Tumor type (Review pathology)			
(Review pathology)			

Units: Subjects			
Adipocytic (liposarcoma)	24		
Fibroblastic	7		
So-called fibrohistiocytic tumours	14		
Smooth muscle tumours	24		
Vascular tumours	2		
Chondro-osseous tumours	1		
Tumors of uncertain differentiation	17		
GIST	1		
Undifferentiated sarcoma NOS	7		
Other	10		
Missing	26		
Tumor grade			
(review)			
Units: Subjects			
Low	6		
Intermediate	45		
High	36		
Unknown	46		
BMI			
Body Mass Index			
Units: kg/m²			
median			
full range (min-max)	-		
Tumor size			
Units: cm			
median			
full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Trab_3hrs
Reporting group description: Trabectedin 3 hrs IV	
Reporting group title	Trab_24hrs
Reporting group description: Trabectedin 24 hrs IV	
Reporting group title	Doxo
Reporting group description: Doxorubicin	
Reporting group title	Trab_3hrs
Reporting group description: Trabectedin 3 hrs IV	
Reporting group title	Trab_24hrs
Reporting group description: Trabectedin 24 hrs IV	
Reporting group title	Doxo
Reporting group description: Doxorubicin	

Primary: PFS

End point title	PFS

End point description:

Progression free survival will be censored on the date of the last tumor assessment documenting absence of progression for patients:
1. who are alive and progression free at the time of the analysis
2. who have withdrawn their consent to continue in the study
3. who are lost to follow up
4. in whom documentation of disease progression or death occurs after 2 or more consecutive missed tumor assessments
Note that patients will not be censored if, prior to observing progression, they
1. stop protocol treatment, for example due to toxicity or personal preference
2. change therapy and receive a non protocol anti-cancer treatment
These patients will continue to be followed for progression.

End point type	Primary

End point timeframe:

Progression free survival will be measured from the date of randomization until the date of objective PD, symptomatic deterioration or death from any cause, whichever happen first.
Results are presented for PFS at 30 months.

End point values	Trab_3hrs	Trab_24hrs	Doxo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	43	43	
Units: Patient				
No progression	1	3	4	
Progression	46	40	39	

Statistical analyses

Statistical analysis title	Hazard Ratio Trab_24hrs versus Doxorubicin
Comparison groups	Trab_24hrs v Doxo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.317 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.4

Notes:

[1] - Cox-model for PFS

[2] - 1-sided p-value

Statistical analysis title	Hazard Ratio Trab_3hrs versus Doxorubicin
Comparison groups	Doxo v Trab_3hrs
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.71

Notes:

[3] - 1-sided p-value

Statistical analysis title	Hazard Ratio Trab_3hrs versus Trab_24hrs
Comparison groups	Trab_24hrs v Trab_3hrs

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.88

Secondary: OS

End point title	OS

End point description:

OS at 42 months

End point type	Secondary

End point timeframe:

Overall survival will be measured from the date of randomization to the date of death; alive patients will be censored at the date of last follow-up.

End point values	Trab_3hrs	Trab_24hrs	Doxo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	43	43	
Units: patients				
Dead	35	33	26	
Alive	12	10	17	

Statistical analyses

Statistical analysis title	Hazard Ratio Trab_24hrs versus Doxorubicin
Comparison groups	Doxo v Trab_24hrs
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.892 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	2.32

Notes:
[4] - 1-sided p-value

Statistical analysis title	Hazard Ratio Trab_3hrs versus Doxorubicin
Comparison groups	Trab_3hrs v Doxo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.921 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.4

Notes:
[5] - 1-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AE will be recorded after each cycle (worst grade per cycle). Hematological and biochemistry AE will be assessed on the basis of at least every 3 weeks blood counts (weekly during the two first cycles for serum chemistry/hematological tests)

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (AEs reported as "other" are not reported as not available from the list of SOC). AEs are evaluated using CTC grading, SAEs using MedDRA. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Trab_3hrs
Reporting group description:	
Trabectidin 3 hrs IV	
Reporting group title	Doxo
Reporting group description:	
Doxorubicin	
Reporting group title	Trab_24hrs
Reporting group description:	
Trabectidin 24 hrs IV	

Serious adverse events	Trab_3hrs	Doxo	Trab_24hrs
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 46 (47.83%)	11 / 40 (27.50%)	17 / 41 (41.46%)
number of deaths (all causes)	11	15	9
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLADDER CANCER			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR PAIN			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HYPOTENSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHLEBITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CATHETER SITE INFLAMMATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
FATIGUE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARYNGEAL INFLAMMATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 46 (4.35%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
ANXIETY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	3 / 46 (6.52%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD CREATINE PHOSPHOKINASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CREATININE RENAL CLEARANCE DECREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC ENZYME INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIPASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
HIP FRACTURE			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSFUSION REACTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
PERICARDIAL EFFUSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBRAL ISCHAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMNOLENCE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 46 (4.35%)	1 / 40 (2.50%)	3 / 41 (7.32%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	1 / 40 (2.50%)	3 / 41 (7.32%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	3 / 46 (6.52%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	3 / 46 (6.52%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
MACULAR OEDEMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL VEIN THROMBOSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPEPSIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC ULCER HAEMORRHAGE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 46 (8.70%)	0 / 40 (0.00%)	5 / 41 (12.20%)
occurrences causally related to treatment / all	3 / 4	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 46 (8.70%)	1 / 40 (2.50%)	4 / 41 (9.76%)
occurrences causally related to treatment / all	3 / 4	1 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATOCELLULAR INJURY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	2 / 40 (5.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
HAEMATURIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETERIC OBSTRUCTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT OBSTRUCTION			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL PAIN			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BACTERAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERIAL INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BURKHOLDERIA CEPACIA COMPLEX INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

STAPHYLOCOCCAL INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SKIN INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 46 (0.00%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERKALAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Trab_3hrs	Doxo	Trab_24hrs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 46 (97.83%)	38 / 40 (95.00%)	41 / 41 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOR PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	9 / 46 (19.57%)	9 / 40 (22.50%)	14 / 41 (34.15%)
occurrences (all)	15	18	30
OTHER NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Vascular disorders			
FLUSHING			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	3	0	2
HYPERTENSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 46 (10.87%)	1 / 40 (2.50%)	3 / 41 (7.32%)
occurrences (all)	8	1	9
HYPOTENSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	1	1	2
PHLEBITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	5 / 41 (12.20%)
occurrences (all)	0	0	11
OTHER VASCULAR DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	1	1	2
THROMBOEMBOLIC EVENT			

alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	3 / 40 (7.50%)	4 / 41 (9.76%)
occurrences (all)	4	5	5
Surgical and medical procedures			
SURGICAL AND MEDICAL PROCEDURES			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	3 / 40 (7.50%)	0 / 41 (0.00%)
occurrences (all)	3	6	0
EDEMA FACE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
EDEMA TRUNK			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
EDEMA LIMBS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	11 / 46 (23.91%)	2 / 40 (5.00%)	11 / 41 (26.83%)
occurrences (all)	21	2	22
FATIGUE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	33 / 46 (71.74%)	27 / 40 (67.50%)	30 / 41 (73.17%)
occurrences (all)	131	85	136
FLU LIKE SYMPTOMS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	1 / 40 (2.50%)	2 / 41 (4.88%)
occurrences (all)	3	1	2
FEVER			

alternative dictionary used: CTC 4.0			
subjects affected / exposed	13 / 46 (28.26%)	3 / 40 (7.50%)	7 / 41 (17.07%)
occurrences (all)	14	3	9
INJECTION SITE REACTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
OTHER GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 46 (8.70%)	4 / 40 (10.00%)	2 / 41 (4.88%)
occurrences (all)	6	5	2
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences (all)	5	2	0
PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	10 / 46 (21.74%)	6 / 40 (15.00%)	11 / 41 (26.83%)
occurrences (all)	23	8	27
Immune system disorders			
IMMUNE SYSTEM DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	5	1	1
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
COUGH			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	8 / 46 (17.39%)	7 / 40 (17.50%)	12 / 41 (29.27%)
occurrences (all)	23	10	17
DYSPNEA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	17 / 46 (36.96%)	7 / 40 (17.50%)	10 / 41 (24.39%)
occurrences (all)	31	14	17
OTHER RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	9 / 46 (19.57%)	7 / 40 (17.50%)	7 / 41 (17.07%)
occurrences (all)	12	14	11
EPISTAXIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
PLEURAL EFFUSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	4	0	2
PHARYNGOLARYNGEAL PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Psychiatric disorders			
ANXIETY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	2 / 40 (5.00%)	9 / 41 (21.95%)
occurrences (all)	2	2	12
DEPRESSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	2 / 40 (5.00%)	3 / 41 (7.32%)
occurrences (all)	3	6	12
INSOMNIA			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	3 / 46 (6.52%)	4 / 40 (10.00%)	6 / 41 (14.63%)
occurrences (all)	4	13	9
OTHER PSYCHIATRIC DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Investigations			
HEMOGLOBIN INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	3	0	2
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	17 / 46 (36.96%)	14 / 40 (35.00%)	15 / 41 (36.59%)
occurrences (all)	58	35	69
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	30 / 46 (65.22%)	30 / 40 (75.00%)	28 / 41 (68.29%)
occurrences (all)	132	70	130
LYMPHOCYTE COUNT INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	1	0	2
OTHER INVESTIGATIONS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	6 / 46 (13.04%)	3 / 40 (7.50%)	5 / 41 (12.20%)
occurrences (all)	16	4	6
PLATELET COUNT DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	16 / 46 (34.78%)	9 / 40 (22.50%)	18 / 41 (43.90%)
occurrences (all)	65	18	70
WEIGHT GAIN			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	2 / 46 (4.35%)	3 / 40 (7.50%)	9 / 41 (21.95%)
occurrences (all)	11	3	41
WEIGHT LOSS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 46 (15.22%)	14 / 40 (35.00%)	6 / 41 (14.63%)
occurrences (all)	37	31	36
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	20 / 46 (43.48%)	25 / 40 (62.50%)	25 / 41 (60.98%)
occurrences (all)	103	59	110
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	3 / 41 (7.32%)
occurrences (all)	2	0	11
Cardiac disorders			
LEFT VENTRICULAR SYSTOLIC DYSFUNCTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
OTHER CARDIAC DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 46 (10.87%)	2 / 40 (5.00%)	1 / 41 (2.44%)
occurrences (all)	7	2	2
PALPITATIONS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	6 / 46 (13.04%)	3 / 40 (7.50%)	3 / 41 (7.32%)
occurrences (all)	10	5	3
VENTRICULAR ARRHYTHMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

DIZZINESS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	5	0	5
HEADACHE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 46 (15.22%)	4 / 40 (10.00%)	10 / 41 (24.39%)
occurrences (all)	13	6	29
DYSGEUSIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	3 / 40 (7.50%)	4 / 41 (9.76%)
occurrences (all)	3	10	9
OTHER NERVOUS SYSTEM DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 46 (10.87%)	3 / 40 (7.50%)	2 / 41 (4.88%)
occurrences (all)	8	11	4
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	2 / 40 (5.00%)	4 / 41 (9.76%)
occurrences (all)	5	2	4
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	32 / 46 (69.57%)	26 / 40 (65.00%)	32 / 41 (78.05%)
occurrences (all)	139	70	165
FEBRILE NEUTROPENIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	6 / 46 (13.04%)	3 / 40 (7.50%)	5 / 41 (12.20%)
occurrences (all)	8	3	6
Ear and labyrinth disorders			

EAR AND LABYRINTH DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	5 / 41 (12.20%)
occurrences (all)	1	0	5
Eye disorders			
EYE DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	4 / 40 (10.00%)	5 / 41 (12.20%)
occurrences (all)	13	7	16
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	1 / 40 (2.50%)	2 / 41 (4.88%)
occurrences (all)	3	1	3
CONSTIPATION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	16 / 46 (34.78%)	13 / 40 (32.50%)	24 / 41 (58.54%)
occurrences (all)	42	19	76
DIARRHEA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	9 / 46 (19.57%)	5 / 40 (12.50%)	7 / 41 (17.07%)
occurrences (all)	12	6	10
FLATULENCE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	2	1	2
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	1 / 40 (2.50%)	3 / 41 (7.32%)
occurrences (all)	5	2	11
GASTROINTESTINAL PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	5 / 40 (12.50%)	7 / 41 (17.07%)
occurrences (all)	4	5	11
MUCOSITIS ORAL			

alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 46 (8.70%)	14 / 40 (35.00%)	5 / 41 (12.20%)
occurrences (all)	9	22	5
NAUSEA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	26 / 46 (56.52%)	18 / 40 (45.00%)	30 / 41 (73.17%)
occurrences (all)	72	45	168
OTHER GASTROINTESTINAL DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 46 (15.22%)	13 / 40 (32.50%)	11 / 41 (26.83%)
occurrences (all)	10	16	36
VOMITING			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	20 / 46 (43.48%)	8 / 40 (20.00%)	16 / 41 (39.02%)
occurrences (all)	41	11	89
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	1 / 40 (2.50%)	4 / 41 (9.76%)
occurrences (all)	6	1	8
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	21 / 40 (52.50%)	0 / 41 (0.00%)
occurrences (all)	13	85	0
DRY SKIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	3 / 40 (7.50%)	0 / 41 (0.00%)
occurrences (all)	5	5	0
OTHER SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	4 / 40 (10.00%)	1 / 41 (2.44%)
occurrences (all)	1	4	1
ERYTHEMA MULTIFORME			

alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
RASH MACULO-PAPULAR			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
PRURITUS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences (all)	2	3	0
Renal and urinary disorders			
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
HEMATURIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
OTHER RENAL AND URINARY DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	6 / 46 (13.04%)	3 / 40 (7.50%)	4 / 41 (9.76%)
occurrences (all)	7	7	5
PROTEINURIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	3	0	0
URINARY FREQUENCY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 46 (8.70%)	3 / 40 (7.50%)	0 / 41 (0.00%)
occurrences (all)	4	5	0
Endocrine disorders			

ENDOCRINE DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	4	0	15
BACK PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences (all)	4	2	0
BONE PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 46 (0.00%)	1 / 40 (2.50%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
MYALGIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 46 (15.22%)	1 / 40 (2.50%)	7 / 41 (17.07%)
occurrences (all)	11	1	23
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 46 (2.17%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	6	0	2
OTHER MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 46 (10.87%)	1 / 40 (2.50%)	4 / 41 (9.76%)
occurrences (all)	9	1	5
Infections and infestations			
INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	15 / 46 (32.61%)	9 / 40 (22.50%)	7 / 41 (17.07%)
occurrences (all)	31	17	8

Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	8 / 46 (17.39%)	8 / 40 (20.00%)	13 / 41 (31.71%)
occurrences (all)	20	13	23
HYPERCALCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 46 (4.35%)	0 / 40 (0.00%)	3 / 41 (7.32%)
occurrences (all)	2	0	4
DEHYDRATION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 46 (6.52%)	5 / 40 (12.50%)	2 / 41 (4.88%)
occurrences (all)	3	6	2
HYPERGLYCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	10 / 46 (21.74%)	8 / 40 (20.00%)	4 / 41 (9.76%)
occurrences (all)	23	17	15
HYPERKALEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	11 / 46 (23.91%)	2 / 40 (5.00%)	8 / 41 (19.51%)
occurrences (all)	14	2	14
HYPERNATREMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 46 (10.87%)	1 / 40 (2.50%)	3 / 41 (7.32%)
occurrences (all)	7	1	5
HYPOALBUMINEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	13 / 46 (28.26%)	5 / 40 (12.50%)	10 / 41 (24.39%)
occurrences (all)	46	9	26
HYPOGLYCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 46 (8.70%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	4	2	0
HYPOCALCEMIA			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	8 / 46 (17.39%)	4 / 40 (10.00%)	7 / 41 (17.07%)
occurrences (all)	18	5	20
HYPOKALEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	9 / 46 (19.57%)	5 / 40 (12.50%)	7 / 41 (17.07%)
occurrences (all)	14	12	11
HYPONATREMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	8 / 46 (17.39%)	5 / 40 (12.50%)	2 / 41 (4.88%)
occurrences (all)	15	8	3
OTHER METABOLISM AND NUTRITION DISORDERS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 46 (10.87%)	4 / 40 (10.00%)	5 / 41 (12.20%)
occurrences (all)	9	17	29

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2011	Changes in the main criteria for inclusion. Additional information on Trabectidin -Metabolism and elimination - Safety data - Treatment schedule modifications: CPK elevation - impact on other medication Precision of Clinical evaluation, laboratory tests and follow-up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 July 2013	Following an IDMC (04/07/2013), it has been decided to close this study (phase II) and not proceed to the phase III part, as none of the experimental arms provided any real benefit compared to the standard.	-

Notes:

Limitations and caveats

None reported