Clinical trial results:
A Phase II multicenter study comparing the efficacy of the oral angionenesis inhibitor nintedanib with the intravenous cytotoxis compound ifosfamide for treatment of patients with advanced metastatic soft tissue sarcoma after failure of systemic non-oxazaphosporine-based first line chemotherapy for inoperable disease "ANITA"

Summary

EudraCT number	2016-002093-12
Trial protocol	BE GB PL NL ES LT
Global end of trial date	13 May 2021
Results information	
Result version number	v1 (current)
This version publication date	19 May 2022
First version publication date	19 May 2022

Trial information

Trial identification	
Sponsor protocol code	1506-STBSG
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02808247
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	EORTC
Sponsor organisation address	Avenue E Mounier 83/11, Brussels, Belgium, 1200
Public contact	Clinical Operations Department, European Organisation for the Research and, 0032 27741345, regulatory@eortc.org
Scientific contact	Clinical Operations Department, European Organisation for the Research and, 0032 27741345, regulatory@eortc.org

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	18 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2020
Global end of trial reached?	Yes
Global end of trial date	13 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate whether nintedanib given as second-line therapy for advanced, inoperable and/or metastatic STS prolongs progression-free survival when compared with ifosfamide.

Protection of trial subjects:

The responsible investigator ensure 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 had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-goodclinicalpractice_en.pdf). The protocol was approved by the competent ethics committee(s) as required

Background therapy:

Ifosfamide 3 g/m2 intravenously on days 1, 2 and 3 every 21 days for up to a maximum of 6 cycles.

Evidence for comparator:

Investigational arm: Nintedanib 200 mg twice daily orally.

Actual start date of recruitment	26 July 2017
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: 10
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	80
EEA total number of subjects	67

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)	53
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 80 patients were randomized (40 pts per arm) between July 26, 2017 and November 21, 2019 by 18 institutions in 8 countries.

Pre-assignment

Screening details:

- Histologically proven advanced, inoperable (medical or surgical) and/or metastatic malignant STS of intermediate or high grade,
- One line of previous systemic chemotherapy for advanced, inoperable and/or metastatic malignant STS.
- No active brain metastases

Period 1

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

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	Ifosfamide

Arm description:

Ifosfamide 3 g/m2 intravenously on days 1, 2 and 3 every 21 days for up to a maximum of 6 cycles.

Arm type	Active comparator
Investigational medicinal product name	ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion, Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ifosfamide 3 g/m2 intravenously on days 1, 2 and 3 every 21 days for up to a maximum of 6 cycles.

Arm title	Nintedanib

Arm description:

Nintedanib 200 mg twice daily orally.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Nintedanib 200 mg twice daily orally.

Number of subjects in period 1	Ifosfamide	Nintedanib
Started	40	40
Completed	38	39
Not completed	2	1
Consent withdrawn by subject	2	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ifosfamide
Reporting group description:	
Ifosfamide 3 g/m2 intravenously on days 1, 2 and 3 every 21 days for up to a maximum of 6 cycles.	
Reporting group title	Nintedanib
Reporting group description:	
Nintedanib 200 mg twice daily orally.	

Reporting group values	Ifosfamide	Nintedanib	Total
Number of subjects	40	40	80
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	26	53
From 65-84 years	13	14	27
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	23	20	43
Male	17	20	37
Performance status			
WHO performance status			
Units: Subjects			
Cat 0	22	20	42
Cat 1	14	19	33
Cat 2	3	1	4
Missing	1	0	1
Tumor Type Units: Subjects			
Liposarcoma	11	11	22
Fibroblastic sarcoma	4	5	9
Leiomyosarcoma	17	14	31
Vascular Tumours	2	1	3
Tumors of uncertain differentiation	1	2	3
MPNST	2	3	5
Undifferentiated / unclassified sarcoma	3	3	6
Other	0	1	1
Tumor grade Units: Subjects			
Low	1	0	1

Intermediate	13	19	32
High	23	20	43
Not assessable	3	1	4
Tumor size			
Units: mm			
median	72.5	94	
inter-quartile range (Q1-Q3)	45 to 137.5	65 to 142.5	-

End points

End points reporting groups

Reporting group title	Ifosfamide
Reporting group description:	
Ifosfamide 3 g/m2 intravenously on days 1, 2 and 3 every 21 days for up to a maximum of 6 cycles.	
Reporting group title	Nintedanib
Reporting group description:	
Nintedanib 200 mg twice daily orally.	

Primary: Progression free survival

End point title	Progression free survival
End point description:	
Progression-free survival will be measured from the date of randomization until the date of first documented progression or death, whichever occurs first. Patients who are alive without evidence of progression at their last radiological assessment will be censored at that date. As per the clinical evaluation schedule, radiological follow-up was to be discontinued after starting a new treatment in the absence of progression. When this occurs, follow-up was censored at the date of starting new treatment. Note that death after starting new treatment is still considered an event for this endpoint.	
End point type	Primary
End point timeframe:	
Progression-free survival will be measured from the date of randomization until the date of first documented progression or death, whichever occurs first.	

End point values	Ifosfamide	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: months				
median (confidence interval 95%)	4.4 (2.9 to 6.7)	2.5 (1.5 to 3.4)		

Attachments (see zip file)	Progression free survival/1506_PFS.pdf

Statistical analyses

Statistical analysis title	Primary analysis of progression free survival
Comparison groups	Nintedanib v Ifosfamide
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07 [1]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.56

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.14
upper limit	2.13

Notes:

[1] - From a Cox proportional hazards adjusted for stratification factors tumor grade and histology

Secondary: Progression free rate at 12 weeks

End point title	Progression free rate at 12 weeks

End point description:

Patients achieving RECIST 1.1 CR, PR or SD at the 12 week disease assessment will be considered a success for this endpoint. All other conditions, e.g. no available imaging, RECIST 1.1 progression prior to or at week 12, non-evaluable assessments, switching to new anti-tumor treatment in the absence of documented progression, or early death will be counted as a failure.
Note that when an assessment was performed later than the foreseen time window of 12 weeks, but before and after was documented as a stable disease (or response), then the 12 week assessment was not considered a failure for this analysis.

End point type	Secondary

End point timeframe:

Patients achieving RECIST 1.1 CR, PR or SD at the 12 week disease assessment will be considered a success for this endpoint.

End point values	Ifosfamide	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: subjects				
No	22	26		
Yes	18	14		

Statistical analyses

Statistical analysis title	Interim analysis

Statistical analysis description:

Decision rule: If less than 19 out of these 36 patients on nintedanib are progression-free at the 12 week assessment, the trial will stop early. Otherwise, the trial will continue as planned.
Note that if more than 17 failures are observed in the nintedanib arm, the trial should be stopped.

Comparison groups	Nintedanib v Ifosfamide
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	> 0.1 [3]
Method	Decision rule based on A'Hern design
Parameter estimate	Binomial estimate and exact 80% CI
Point estimate	0.35

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.249
upper limit	0.463

Notes:

[2] - This interim look originates from a single arm, single stage A'Hern design with type I and II error fixed at alpha = 0.1 and beta = 0.15, testing the null hypothesis H0: P ≤ 40% versus HA: P > 40%. The decision rule is computed under the alternative hypothesis that P = 60%. The analysis is done in the Nintedanib arm only.
[3] - Decision rule: If less than 19 out of the first 36 patients on nintedanib are progression-free at the 12 week assessment, the trial will stop early. Otherwise, the trial will continue as planned.
Therefore this trial was closed for futility

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Overall survival (OS) was computed from the date of start of treatment to the date of death (due to any cause). Patients alive at the time of analysis will be censored at the date of last follow-up.

End point values	Ifosfamide	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Months				
median (confidence interval 95%)	24.1 (10.9 to 100)	13.7 (9.4 to 23.4)		

Attachments (see zip file)	1506_OS.pdf

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Ifosfamide v Nintedanib
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111 [4]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	3.06

Notes:

[4] - Cox Proportional hazards model adjusted for stratification factors tumor grade and histology

Secondary: Best response

End point title	Best response

End point description:

End point type	Secondary

End point timeframe:

Best response observed on treatment

End point values	Ifosfamide	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: subjects				
Partial response	2	2		
Stable disease	23	18		
Progressive disease	10	19		
Early death	2	0		
Not evaluable	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time on nintedanib treatment

End point title	Time on nintedanib treatment[5]

End point description:

computed from the date of start of treatment to the date of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Patients alive and still on protocol treatment at the time of the analysis will be censored at the date of last known treatment administration.

End point type	Secondary

End point timeframe:

computed from the date of start of treatment to the date of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is only valid in one arm, i.e. in the arm of patients who received nintedanib treatment

End point values	Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Months				
median (confidence interval 95%)	2.5 (1.4 to 3.4)			

Attachments (see zip file)	1506_ntrt.jpeg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, laboratory and physical abnormalities were collected till 90 days after the end of treatment. For SAEs: all SAEs till 30 days after end of treatment; afterwards, only related SA

Adverse event reporting additional description:

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	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Ifosfamide

Reporting group description:

Ifosfamide

Reporting group title	Nintedanib

Reporting group description:

Nintedanib

Serious adverse events	Ifosfamide	Nintedanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 38 (42.11%)	8 / 39 (20.51%)	
number of deaths (all causes)	18	24	
number of deaths resulting from adverse events	0	0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ENCEPHALOPATHY			
alternative dictionary used:			

MedDRA 24.1			
subjects affected / exposed	4 / 38 (10.53%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 38 (10.53%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHEST PAIN			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILE DUCT STENOSIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 38 (7.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ANAL ABSCESS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED INFECTION			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ifosfamide	Nintedanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 38 (86.84%)	35 / 39 (89.74%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOR PAIN			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Vascular disorders			
HYPERTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 38 (18.42%)	15 / 39 (38.46%)	
occurrences (all)	12	35	
HYPOTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
LYMPHEDEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PHLEBITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 38 (10.53%)	2 / 39 (5.13%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
FATIGUE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	22 / 38 (57.89%)	18 / 39 (46.15%)	
occurrences (all)	41	30	
FEVER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 38 (10.53%)	3 / 39 (7.69%)	
occurrences (all)	4	3	
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MALAISE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 38 (10.53%)	4 / 39 (10.26%)	
occurrences (all)	5	5	
PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
SUDDEN DEATH NOS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
BRONCHIAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
COUGH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 38 (5.26%)	2 / 39 (5.13%)	
occurrences (all)	2	4	
DYSPNEA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	4 / 38 (10.53%)	4 / 39 (10.26%)	
occurrences (all)	5	6	
HICCUPS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HOARSENESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
RESPIRATORY, THORACIC-OTHER-HAEMOPTYSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VOICE ALTERATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
DEPRESSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
INSOMNIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PSYCHIATRIC DISORDERS - OTHER: PSYCHOLOGIC DISTRES			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Investigations			
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
WEIGHT LOSS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 38 (15.79%)	6 / 39 (15.38%)	
occurrences (all)	7	8	
Cardiac disorders			
ATRIAL FIBRILLATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MYOCARDIAL INFARCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PALPITATIONS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nervous system disorders			
DEPRESSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
DIZZINESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
DYSGEUSIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 38 (2.63%)	6 / 39 (15.38%)	
occurrences (all)	1	6	
ENCEPHALOPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 38 (23.68%)	0 / 39 (0.00%)	
occurrences (all)	15	0	
HEADACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HICCUPS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PARESTHESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
SYNCOPE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	8 / 38 (21.05%)	1 / 39 (2.56%)	
occurrences (all)	19	3	
BLOOD&LYMPHATIC SYSTEM DISORDERS:MEDULLAR TOXICITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 38 (13.16%)	0 / 39 (0.00%)	
occurrences (all)	7	0	
INFECTIONS AND INFESTATIONS-OTHER: BLOOD INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PANCYTOPENIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
BLURRED VISION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 38 (10.53%)	4 / 39 (10.26%)	
occurrences (all)	7	6	
ANAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
BLOATING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
CONSTIPATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	11 / 38 (28.95%)	4 / 39 (10.26%)	
occurrences (all)	18	7	
DIARRHEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 38 (15.79%)	14 / 39 (35.90%)	
occurrences (all)	9	31	
DRY MOUTH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ESOPHAGEAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 38 (10.53%)	1 / 39 (2.56%)	
occurrences (all)	4	1	
FLATULENCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 38 (5.26%)	3 / 39 (7.69%)	
occurrences (all)	2	3	

NAUSEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	17 / 38 (44.74%)	10 / 39 (25.64%)	
occurrences (all)	38	13	
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
SMALL INTESTINAL PERFORATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
VOMITING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	11 / 38 (28.95%)	7 / 39 (17.95%)	
occurrences (all)	19	12	
Hepatobiliary disorders			
BILE DUCT STENOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HEPATIC INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
PORTAL HYPERTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 38 (13.16%)	0 / 39 (0.00%)	
occurrences (all)	6	0	
DRY SKIN			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
PRURITUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 38 (13.16%)	0 / 39 (0.00%)	
occurrences (all)	6	0	
RENAL&URINARY DISORDERS-OTHER: RENAL TUBULOPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
URINARY FREQUENCY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
URINARY TRACT PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
BACK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	3	
BONE PAIN			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
BUTTOCK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
CHEST WALL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
MUSCULOSKELETAL &CONNECTIVE TIS.DIS.RCALF SWELLING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL&CONNECTIVE TISSUE DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL&CONNECTIVE TISSUE DISORDER-GROIN P			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MYALGIA			
alternative dictionary used: CTCAE			

4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 38 (10.53%)	6 / 39 (15.38%)	
occurrences (all)	4	7	
Infections and infestations			
BILIARY TRACT INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
BRONCHIAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
INFECTIONS AND INFESTATIONS - PLASTRON RIGHT FOSSA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
INFECTIONS AND INFESTATIONS-OTHER: SIGMOIDITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
INFECTIONS AND INFESTATIONS-OTHER:HERPES LABIALIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LIP INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
LUNG INFECTION			
alternative dictionary used: CTCAE			

4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MUCOSAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PERITONITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SEPSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
WOUND INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
ACIDOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ANOREXIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	14 / 38 (36.84%)	7 / 39 (17.95%)	
occurrences (all)	19	11	
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
HYPOGLYCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
HYPOKALEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

As the study was closed for futility, there is limited follow-up data for QoL, HE and long term endpoints such as overall survival

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34062484