Clinical trial results:
Efficacy of Gemcitabine With Pazopanib as Second Line Treatment in Patient With Metastatic or Relapsed Uterine (LMS03)

Summary

EudraCT number	2011-001308-36
Trial protocol	FR
Global end of trial date	30 March 2018

Results information

Result version number	v1 (current)
This version publication date	23 April 2021
First version publication date	23 April 2021

Trial information

Trial identification

Sponsor protocol code	SARCOME 11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01442662
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 RUE DE TOLBIAC, PARIS, France, 75013
Public contact	N. AIT RAHMOUNE, UNICANCER, 33 (0) 1 71 93 674 04, n.ait-rahmoune@unicancer.fr
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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	31 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2018
Global end of trial reached?	Yes
Global end of trial date	30 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the combination of gemcitabine and pazopanib for treating patients with leiomyosarcoma (uterine or soft tissue) either metastatic and/or inoperable at relapse after first-line anthracycline-based therapy, according to the 9-month PFS rate.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was performed in compliance with the principles laid down in the declaration of Helsinki, good Clinical Practice and European regulation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 106
Worldwide total number of subjects	106
EEA total number of subjects	106

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)	72
From 65 to 84 years	34

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date: 20-Oct-2011
Last patient included: 12-May-2016

Pre-assignment

Screening details:

Patients with histologically confirmed leiomyosarcoma (uterine or soft tissue) either metastatic and/or inoperable at relapse after first-line anthracycline-based therapy.
Patients having received adjuvant therapy less than one year before relapse are considered as having received first-line therapy. Furthermore, if the maximum anthracycline do

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment arm

Arm description:

Patients recreived:
- Gemcitabine (1000 mg/m2/day) was to be administered intravenously on D1 and D8 of a 21-day cycle. The gemcitabine solution was perfused at a rate of 10 mg/m2/min. Gemcitabine treatment was planned for a maximum of 8 cycles.
- Oral pazopanib was taken daily at a dose of 800 mg/day (4 x 200-mg tablets). If after 6-8 weeks of being treated with pazopanib plus gemcitabine, the tumour response was stable disease (SD), partial (PR) or complete response (CR). The patients could have been treated with pazopanib monotherapy until disease progression, limiting toxicity, or patient’s refusal to continue treatment.

Arm type	Experimental
Investigational medicinal product name	GEMCITABIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1000 mg/m2/day) was to be administered intravenously on D1 and D8 of a 21-day cycle. The gemcitabine solution was perfused at a rate of 10 mg/m2/min. Gemcitabine treatment was planned for a maximum of 8 cycles.

Investigational medicinal product name	PAZOPANIB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral pazopanib was taken daily at a dose of 800 mg/day (4 x 200-mg tablets). If after 6-8 weeks of being treated with pazopanib plus gemcitabine, the tumour response was stable disease (SD), partial (PR) or complete response (CR). The patients could have been treated with pazopanib monotherapy until disease progression, limiting toxicity, or patient’s refusal to continue treatment.

Number of subjects in period 1[1]	Treatment arm
Started	105
Completed	105

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 105 patients were included and treated in this study

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	71	71	
From 65-84 years	34	34	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	90	90	
Male	15	15	

End points

End points reporting groups

Reporting group title	Treatment arm

Reporting group description:

Patients recreived:
- Gemcitabine (1000 mg/m2/day) was to be administered intravenously on D1 and D8 of a 21-day cycle. The gemcitabine solution was perfused at a rate of 10 mg/m2/min. Gemcitabine treatment was planned for a maximum of 8 cycles.
- Oral pazopanib was taken daily at a dose of 800 mg/day (4 x 200-mg tablets). If after 6-8 weeks of being treated with pazopanib plus gemcitabine, the tumour response was stable disease (SD), partial (PR) or complete response (CR). The patients could have been treated with pazopanib monotherapy until disease progression, limiting toxicity, or patient's refusal to continue treatment.

Primary: Primary endpoint (9month PFS)

End point title	Primary endpoint (9month PFS)[1]

End point description:

To assess the efficacy of the combination of gemcitabine and pazopanib for treating patients with leiomyosarcoma (uterine or soft tissue) either metastatic and/or inoperable at relapse after firstline anthracycline-based therapy, according to the 9-month PFS rate.

End point type	Primary

End point timeframe:

9 month

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Efficacy endpoints were reported as rates with 95% CIs. Kaplan-Meier analyses were used for the time-to-event outcomes and Kaplan-Meier plots were

End point values	Treatment arm			
Subject group type	Reporting group			
Number of subjects analysed	105			
Units: percent				
arithmetic mean (confidence interval 5%)	32.1 (23.1 to 41.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety data were collected for each cycle of the gemcitabine-pazopanib combination and every 6 weeks for pazopanib monotherapy.
Serious adverse events were collected since patient's consent until 30 days after last study treatment adlinistration

Adverse event reporting additional description:

For non serious adverse events only name of event must be take into account.
The number of subjects affected and the number of occurrence are not available and will be always noted "1"

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	All patients treated

Reporting group description: -

Serious adverse events	All patients treated		
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 105 (67.62%)		
number of deaths (all causes)	105		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Ischemic stroke			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischemic attacks			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Metastasectomy			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema lower limb			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thorax pain			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea exacerbated			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial pneumonitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 105 (7.62%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		
SGPT increased			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy secondary			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Diplopia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bicytopenia			
subjects affected / exposed	5 / 105 (4.76%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Febrile aplasia			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	33 / 105 (31.43%)			
occurrences causally related to treatment / all	44 / 44			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytosis				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombopenia				
subjects affected / exposed	15 / 105 (14.29%)			
occurrences causally related to treatment / all	15 / 15			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sigmoiditis				

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangiolitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzymes increased			
subjects affected / exposed	5 / 105 (4.76%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Hepatic insufficiency			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin eruption			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Acute renal insufficiency			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All patients treated		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 105 (32.38%)		
Vascular disorders			
Transient ischemic attack			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other vascular toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
General disorders and administration site conditions			

Anorexia subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Weight loss subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Fatigue/asthenia subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Fever subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Oedema subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Thyroid gland perturbation subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Other general toxicities subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasms subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Interstitial pneumopathy subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Other pulmonary and upper air tract toxicities subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Investigations			

Hypokalaemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hyperuricemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hyponatremia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other biological investigation toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Cardiac disorders			
Decrease in LVEF			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Cardiac ischemia/heart attack/angina			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Temporary ECG modifications			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
QTc prolongation			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Torsade de pointes			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Arrhythmia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other cardiac toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Nervous system disorders			
Anxiety/depression			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Neurosensory problems			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Neuromotor problems			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other neurological toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Haemoglobin decreased			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Neutrophil count decreased			

subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Other haematological toxicities subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Ear and labyrinth disorders			
Loss of hearing subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Other auditive toxicities subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Eye disorders			
Visual problems subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Other ocular toxicities subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Dyspepsia			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Mucositis/stomatitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other digestive toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hepatobiliary disorders			
Elevated ASAT/ALAT			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Elevated bilirubin			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Elevated phosphatase alkaline			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other hepatobiliary toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Depigmentation of the hair/skin			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Skin eruptions/rash			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Hand and foot syndrome			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other skin/hair toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Renal and urinary disorders			
Kidney failure			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Elevation of creatinine level			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other renal toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		
Other musculo-skeletal toxicities			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2011	Precision concerning one inclusion criteria, information concerning dose adptation and precision concerning exams required by the protocol
12 December 2011	New name of the sponsor
12 July 2012	Submision of the new investigator brochure
26 March 2013	Modification of protocol in order to take in account new requirement concerning liver tests
04 July 2014	Protocole updated
14 January 2015	Protocol updated
02 February 2016	Submision of the new investigator's brichure and protocole was updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 December 2013	After information of safety concerning severe liver toxicity observed in another clinical trial with the same study products, it was decided to interrupt inclusion. After evaluation of this event, the relation with the study treatment was not confirmed. It was decided to continue inclusion.	-

Notes:

Limitations and caveats

None reported