



Clinical trial results:

A stratified, multicenter, phase II study evaluating the efficacy and toxicity of Sorafenib in locally advanced or metastatic angiosarcoma not amenable to curative surgery

Summary

EudraCT number	2007-004651-10
Trial protocol	FR
Global end of trial date	01 January 2015

Results information

Result version number	v1 (current)
This version publication date	21 August 2025
First version publication date	21 August 2025

Trial information

Trial identification

Sponsor protocol code	Angio-Next-0710
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00874874
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Oscar Lambret
Sponsor organisation address	3 rue Frédéric Combemale – BP307, LILLE, France, 59020
Public contact	Emilie DECOUPIGNY, Centre Oscar Lambret, 33 320295568, e-decoupigny@o-lambret.fr
Scientific contact	Nicolas PENEL, Centre Oscar Lambret, 33 320295920, n-penel@o-lambret.fr

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	01 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2015
Global end of trial reached?	Yes
Global end of trial date	01 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

9-month progression-free rate

Protection of trial subjects:

In accordance with the regulations in force, the clinical study protocol and the various amendments are submitted by the study sponsor to a CPP in the region where it operates.

An independent trial monitoring committee will be set up to guarantee patient protection, ensure that the trial is conducted ethically, assess the benefit/risk ratio of the trial and review the scientific results during and at the end of the trial. The monitoring committee will meet every 6 months and will be composed of 3 members (- A radiologist - An oncologist - A methodologist).

This Biomedical Research is conducted in accordance with: the Public Health Law n° 2004-806 of August 9, 2004 and the application decree n° 2006-477 of April 2006, the law n° 2004-800 of August 6, 2004 relating to bioethics, the use of your blood samples and your tumor tissues is subject to your prior written agreement. The law n° 2004-801 of August 6, 2004 relating to the protection of individuals with regard to the processing of personal data and modifying the law n° 78-17 of January 6, 1978 relating to data processing, files and freedoms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

Notes:

Subjects enrolled per age group

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

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

88 pts were included from 06/2008 to 01/2014, from 21 French centers, in 4 strata (histological subtype), described hereinafter as Arms.

- Stratum A: 26 pts (06/2008 - 06/2009)
- Stratum B: 15 pts (06/2008 - 06/2009)
- Stratum C: 20 pts (06/2009 - 02/2011)
- Stratum D: 27 pts (05/2011 - 01/2014)

Treatment was similar in all strata.

Pre-assignment

Screening details:

Not available

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Stratum A

Arm description:

This arm is actually a subgroup. Stratum A included all forms of superficial angiosarcoma (skin, scalp, soft tissue and breast angiosarcoma).

Arm type	Subgroup
Investigational medicinal product name	NEXAVAR
Investigational medicinal product code	
Other name	SORAFENIB
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 X 400 mg / day with 12 hours interval per os for 270 days

Arm title	Stratum B
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Arm description:

This arm is actually a subgroup. Stratum B included all forms of of bone or visceral angiosarcoma.

Arm type	Subgroup
Investigational medicinal product name	NEXAVAR
Investigational medicinal product code	
Other name	SORAFENIB
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 X 400 mg / day with 12 hours interval per os for 270 days

Arm title	Stratum C
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Arm description:

This arm is actually a subgroup. Stratum C included epithelioid hemangioendothelioma, hemangiopericitomas and solitary fibrous tumors.

Arm type	Subgroup
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Investigational medicinal product name	NEXAVAR
Investigational medicinal product code	
Other name	SORAFENIB
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
2 X 400 mg / day with 12 hours interval per os for 270 days	
Arm title	Stratum D

Arm description:

This arm is actually a subgroup. Stratum D included chordomas.

Arm type	Subgroup
Investigational medicinal product name	NEXAVAR
Investigational medicinal product code	
Other name	SORAFENIB
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 X 400 mg / day with 12 hours interval per os for 270 days

Number of subjects in period 1	Stratum A	Stratum B	Stratum C
Started	26	15	20
Completed	23	13	18
Not completed	3	2	2
No treatment received (gastrointestinal bleeding)	1	-	-
Physician decision	-	1	-
Consent withdrawn by subject	-	-	1
Drop out of study at day 7 (pulmonary embolism)	1	-	-
Severe toxicity after 15 days of treatment	-	-	-
Drop out of study at day 11 (Grade 4 anemia)	-	1	-
Disease progression at day 21	-	-	1
No treatment received (Grade 3 thrombocytopenia)	1	-	-

Number of subjects in period 1	Stratum D
Started	27
Completed	26
Not completed	1
No treatment received (gastrointestinal bleeding)	-
Physician decision	-
Consent withdrawn by subject	-
Drop out of study at day 7 (pulmonary embolism)	-

Severe toxicity after 15 days of treatment	1
Drop out of study at day 11 (Grade 4 anemia)	-
Disease progression at day 21	-
No treatment received (Grade 3 thrombocytopenia)	-

Baseline characteristics

Reporting groups

Reporting group title	Stratum A
Reporting group description: This arm is actually a subgroup. Stratum A included all forms of superficial angiosarcoma (skin, scalp, soft tissue and breast angiosarcoma).	
Reporting group title	Stratum B
Reporting group description: This arm is actually a subgroup. Stratum B included all forms of of bone or visceral angiosarcoma.	
Reporting group title	Stratum C
Reporting group description: This arm is actually a subgroup. Stratum C included epithelioid hemangioendothelioma, hemangiopericitomas and solitary fibrous tumors.	
Reporting group title	Stratum D
Reporting group description: This arm is actually a subgroup. Stratum D included chordomas.	

Reporting group values	Stratum A	Stratum B	Stratum C
Number of subjects	26	15	20
Age categorical			
Units: Subjects			
Adults (18-64 years)	13	13	14
From 65-84 years	13	2	6
85 years and over	0	0	0
Age continuous			
Units: years			
median	65	55	57
full range (min-max)	31 to 82	19 to 80	31 to 76
Gender categorical			
Units: Subjects			
Female	18	6	8
Male	8	9	12
Tumor arising in irradiated field			
Analysis were performed in ITT only			
Units: Subjects			
yes	13	1	1
no	13	14	19
Associated lymphedema			
Units: Subjects			
Yes	6	1	0
No	20	14	20
Histological subtype			
Units: Subjects			
Epithelioid angiosarcoma	9	4	0
Non-epithelioid angiosarcoma	17	11	0
Epithelioid hemangioendothelioma	0	0	15
Solitary fibrous tumor / Hemangiopericytoma	0	0	5
Chordoma	0	0	0

Presence of metastasis			
Units: Subjects			
Yes	19	14	16
No	7	1	4
Performans status			
Units: Subjects			
Score 0	9	5	10
Score 1	11	7	7
Score 2	6	3	3
Unknown	0	0	0
Tissular location			
Units: Subjects			
Skin / scalp	9	0	1
Soft tissues	7	0	6
Breast	10	0	0
Viscera	0	15	13
Bones	0	0	0
Anatomical location			
Units: Subjects			
Pelvis	0	0	0
Head and neck	3	0	3
Trunck	2	1	4
Sacrum	0	0	0
Rachis	0	0	0
Lumbar rachis	0	0	0
Lumbosacral	0	0	0
Upper limb and shoulder	5	1	1
Lower limb and hip	4	0	2
Breast	10	0	0
Peritoneum	1	0	0
Thoracic wall	1	0	0
Cardiac	0	4	0
Spleen	0	2	0
Pulmonary artery	0	2	0
Bladder	0	1	0
Bone	0	1	0
Duodenum	0	1	0
Liver	0	1	4
Colon	0	1	0
Cervical	0	0	1
Intracanal L1 L2	0	0	1
Parietal, diaphragmatic and visceral pleura	0	0	1
Retroperitoneum	0	0	1
Trunk and lung	0	0	1
Unknown	0	0	1
Reporting group values	Stratum D	Total	
Number of subjects	27	88	

Age categorical Units: Subjects			
Adults (18-64 years)	15	55	
From 65-84 years	11	32	
85 years and over	1	1	
Age continuous Units: years			
median	64		
full range (min-max)	30 to 86	-	
Gender categorical Units: Subjects			
Female	10	42	
Male	17	46	
Tumor arising in irradiated field			
Analysis were performed in ITT only			
Units: Subjects			
yes	0	15	
no	27	73	
Associated lymphedema Units: Subjects			
Yes	0	7	
No	27	81	
Histological subtype Units: Subjects			
Epithelioid angiosarcoma	0	13	
Non-epithelioid angiosarcoma	0	28	
Epithelioid hemangioendothelioma	0	15	
Solitary fibrous tumor / Hemangiopericytoma	0	5	
Chordoma	27	27	
Presence of metastasis Units: Subjects			
Yes	14	63	
No	13	25	
Performans status Units: Subjects			
Score 0	11	35	
Score 1	13	38	
Score 2	2	14	
Unknown	1	1	
Tissular location Units: Subjects			
Skin / scalp	0	10	
Soft tissues	3	16	
Breast	0	10	
Viscera	0	28	
Bones	24	24	
Anatomical location Units: Subjects			
Pelvis	19	19	
Head and neck	3	9	

Trunk	1	8	
Sacrum	1	1	
Rachis	1	1	
Lumbar rachis	1	1	
Lumbosacral	1	1	
Upper limb and shoulder	0	7	
Lower limb and hip	0	6	
Breast	0	10	
Peritoneum	0	1	
Thoracic wall	0	1	
Cardiac	0	4	
Spleen	0	2	
Pulmonary artery	0	2	
Bladder	0	1	
Bone	0	1	
Duodenum	0	1	
Liver	0	5	
Colon	0	1	
Cervical	0	1	
Intracanal L1 L2	0	1	
Parietal, diaphragmatic and visceral pleura	0	1	
Retroperitoneum	0	1	
Trunk and lung	0	1	
Unknown	0	1	

End points

End points reporting groups

Reporting group title	Stratum A
Reporting group description: This arm is actually a subgroup. Stratum A included all forms of superficial angiosarcoma (skin, scalp, soft tissue and breast angiosarcoma).	
Reporting group title	Stratum B
Reporting group description: This arm is actually a subgroup. Stratum B included all forms of of bone or visceral angiosarcoma.	
Reporting group title	Stratum C
Reporting group description: This arm is actually a subgroup. Stratum C included epithelioid hemangioendothelioma, hemangiopericitomas and solitary fibrous tumors.	
Reporting group title	Stratum D
Reporting group description: This arm is actually a subgroup. Stratum D included chordomas.	

Primary: Primary endpoint : 9-month progression free rate

End point title	Primary endpoint : 9-month progression free rate ^[1]
End point description: Disease was assessed according to the RECIST, version 1.1. An independent third-party radiologist reviewed selected imaging studies to verify all imaging performed during the treatment period with the trial drug to ensure consistent, unbiased application of the RECIST. Stratum A, B, C : 9-month progression free rate was defined as the rate of patients without progression at 9 month (stable disease, complete or partial response) in the intent-to-treat population. Stratum D : 9-month progression-free rate was estimated as progression-free survival rate at 9 month. Progression-free survival times were calculated using Kaplan-Meier method from the date of inclusion until progression (imaging according to RECIST criteria and panel review) or death; patients who did not progress and did not die were censored at the time of last news.	
End point type	Primary
End point timeframe: Progression free-rate at 9 months from inclusion.	
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: This is a single arm study so no statistical analysis was planned.	

End point values	Stratum A	Stratum B	Stratum C	Stratum D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	20	27
Units: percent				
number (confidence interval 95%)	3.8 (0.1 to 19.6)	0 (0 to 0)	30.0 (11.9 to 54.3)	73.0 (46.1 to 88.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

End point title	Overall response rate
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End point description:

Disease was assessed according to the RECIST, version 1.1. An independent third-party radiologist reviewed selected imaging studies to verify all imaging performed during the treatment period with the trial drug to ensure consistent, unbiased application of the RECIST.

Overall response rate was defined as the rate of patients with complete or partial response at the time of interest, on intent to treat population.

End point type	Secondary
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End point timeframe:

Overall response rate at 4, 6 and 9 months.

End point values	Stratum A	Stratum B	Stratum C	Stratum D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	20	27
Units: percent				
number (confidence interval 95%)				
Overall response rate at 4 months	15.4 (4.4 to 34.9)	13.3 (1.7 to 40.5)	5.0 (0.1 to 24.9)	0 (0 to 0)
Overall response rate at 6 months	11.5 (2.4 to 30.2)	0 (0 to 0)	5.0 (0.1 to 24.9)	3.7 (0.1 to 19.0)
Overall response rate at 9 months	0 (0 to 0)	0 (0 to 0)	5.0 (0.1 to 24.9)	3.7 (0.1 to 19.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival ^[2]
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End point description:

Survival endpoints were estimated using Kaplan-Meier method. Overall survival times were calculated from the date of inclusion until death; patients who did not die were censored at the time of last news. Stratum D: Median OS was not reached. 12-months overall survival rate was 86.5% (95% CI : 55.8-96.5%).

End point type	Secondary
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End point timeframe:

Median overall survival (all study)

Notes:

[2] - 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: Median overall survival was not reached in stratum D.

End point values	Stratum A	Stratum B	Stratum C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	15	20	
Units: month				
number (not applicable)	12.2	8.9	19.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival ^[3]
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End point description:

Progression-free survival times were calculated using Kaplan-Meier method from the date of inclusion until progression (imaging according to RECIST criteria and panel review) or death; patients who did not progress and did not die were censored at the time of last news.

Stratum D : median PFS was not reached.

End point type	Secondary
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End point timeframe:

Median Progression-free survival (all study)

Notes:

[3] - 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: Median progression-free survival was not reached in stratum D.

End point values	Stratum A	Stratum B	Stratum C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	15	20	
Units: month				
number (confidence interval 95%)	1.8 (1.5 to 3.2)	3.8 (1.9 to 5.7)	5.8 (3.3 to 20.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were carried forward from the date of consent until 30 days after the last treatment was administered. Serious AEs were carried forward without a time delay.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Stratum A and B
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Reporting group description:

Data were given for grouped stratum A and B.

Reporting group title	Stratum C
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Reporting group description: -

Reporting group title	Stratum D
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Reporting group description: -

Serious adverse events	Stratum A and B	Stratum C	Stratum D
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 39 (58.97%)	6 / 20 (30.00%)	10 / 27 (37.04%)
number of deaths (all causes)	25	9	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	0 / 27 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	0 / 27 (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
Pulmonary embolism			

subjects affected / exposed	2 / 39 (5.13%)	0 / 20 (0.00%)	0 / 27 (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
Surgical and medical procedures			
Lesion excision			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	0 / 27 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prolapse			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
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 physical health deterioration			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 39 (2.56%)	1 / 20 (5.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anorexia and bulimia syndrome subjects affected / exposed	1 / 39 (2.56%)	1 / 20 (5.00%)	0 / 27 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 39 (7.69%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Haemorrhage			
subjects affected / exposed	7 / 39 (17.95%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	4 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 39 (2.56%)	0 / 20 (0.00%)	0 / 27 (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
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 20 (0.00%)	0 / 27 (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
Pericarditis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 20 (0.00%)	0 / 27 (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			
Epilepsy			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	0 / 27 (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
Neuromuscular pain			

subjects affected / exposed	5 / 39 (12.82%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 20 (0.00%)	0 / 27 (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
Platelet count decreased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 20 (0.00%)	0 / 27 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 39 (2.56%)	0 / 20 (0.00%)	0 / 27 (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
Musculoskeletal and connective tissue disorders			
Motor dysfunction			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myalgia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 20 (5.00%)	0 / 27 (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
Infections and infestations			
Infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 20 (0.00%)	0 / 27 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Stratum A and B	Stratum C	Stratum D
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 39 (94.87%)	20 / 20 (100.00%)	27 / 27 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 39 (7.69%)	0 / 20 (0.00%)	7 / 27 (25.93%)
occurrences (all)	3	0	9
Haemorrhage			
subjects affected / exposed	4 / 39 (10.26%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences (all)	4	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Asthenia			

subjects affected / exposed	15 / 39 (38.46%)	13 / 20 (65.00%)	13 / 27 (48.15%)
occurrences (all)	15	21	18
Mucosal disorder			
subjects affected / exposed	6 / 39 (15.38%)	2 / 20 (10.00%)	3 / 27 (11.11%)
occurrences (all)	6	2	5
Epistaxis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 20 (10.00%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Hyperthermia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 20 (10.00%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Sweating fever			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 39 (0.00%)	2 / 20 (10.00%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Investigations			
Weight decreased			
subjects affected / exposed	2 / 39 (5.13%)	2 / 20 (10.00%)	11 / 27 (40.74%)
occurrences (all)	2	3	19
Alanine aminotransferase increased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	7 / 27 (25.93%)
occurrences (all)	0	0	7
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	9 / 27 (33.33%)
occurrences (all)	0	0	11
Metabolic disorder	Additional description: Alkaline phosphatase increased		

subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	11 / 27 (40.74%)
occurrences (all)	0	0	11
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	9 / 27 (33.33%)
occurrences (all)	0	0	9
Hyperbilirubinaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	9 / 27 (33.33%)
occurrences (all)	0	0	10
Hypercreatinaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	4
Hyperkalaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	8 / 27 (29.63%)
occurrences (all)	0	0	8
Hypokalaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	5 / 27 (18.52%)
occurrences (all)	0	0	6
Hyponatraemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	10 / 27 (37.04%)
occurrences (all)	0	0	10
Nervous system disorders			
Dysphonia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 20 (10.00%)	3 / 27 (11.11%)
occurrences (all)	0	2	3
Discomfort			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 39 (0.00%)	3 / 20 (15.00%)	0 / 27 (0.00%)
occurrences (all)	0	4	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 7	0 / 20 (0.00%) 0	13 / 27 (48.15%) 13
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	6 / 27 (22.22%) 6
Leukopenia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	6 / 27 (22.22%) 6
Lymphopenia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	21 / 27 (77.78%) 22
Neutropenia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	4 / 27 (14.81%) 4
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	3 / 27 (11.11%) 3
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	2 / 27 (7.41%) 2
Dry eye subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 20 (0.00%) 0	2 / 27 (7.41%) 3
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 6	2 / 20 (10.00%) 4	0 / 27 (0.00%) 0
Anorexia and bulimia syndrome subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 6	4 / 20 (20.00%) 4	5 / 27 (18.52%) 6
Constipation subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	3 / 20 (15.00%) 5	5 / 27 (18.52%) 6
Diarrhoea			

subjects affected / exposed	9 / 39 (23.08%)	6 / 20 (30.00%)	16 / 27 (59.26%)
occurrences (all)	9	16	27
Nausea			
subjects affected / exposed	7 / 39 (17.95%)	5 / 20 (25.00%)	11 / 27 (40.74%)
occurrences (all)	8	10	13
Dysgeusia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Dry mouth			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Colitis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 20 (10.00%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Hand-foot-and-mouth disease			
subjects affected / exposed	11 / 39 (28.21%)	9 / 20 (45.00%)	12 / 27 (44.44%)
occurrences (all)	11	15	31
Skin toxicity			
subjects affected / exposed	16 / 39 (41.03%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences (all)	24	0	0
Alopecia			
subjects affected / exposed	0 / 39 (0.00%)	5 / 20 (25.00%)	13 / 27 (48.15%)
occurrences (all)	0	5	14
Rash			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	3
Erythema			
subjects affected / exposed	0 / 39 (0.00%)	3 / 20 (15.00%)	2 / 27 (7.41%)
occurrences (all)	0	5	2
Pruritus			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Dry skin			
subjects affected / exposed	0 / 39 (0.00%)	5 / 20 (25.00%)	9 / 27 (33.33%)
occurrences (all)	0	5	13

Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	17 / 27 (62.96%)
occurrences (all)	0	0	17
Endocrine disorders			
Hot flush			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Neuromuscular pain			
subjects affected / exposed	16 / 39 (41.03%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences (all)	17	0	0
Sacral pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	4
Myalgia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 20 (10.00%)	3 / 27 (11.11%)
occurrences (all)	0	3	4
Pain	Additional description: Thigh pain		
subjects affected / exposed	0 / 39 (0.00%)	0 / 20 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Infections and infestations			
Infection			
subjects affected / exposed	7 / 39 (17.95%)	0 / 20 (0.00%)	0 / 27 (0.00%)
occurrences (all)	8	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2008	Substantial Change number 2: 1. The non-inclusion criterion "Previous treatment with Bevacizumab", appearing in the section "Prohibited concomitant treatment" has been added in the synopsis and in the non-inclusion criteria section. 2. To coincide with the maximum time frame for SAEs reporting, the time frame for the end-of-study review was changed to 30 days instead of 3 weeks. 3. In the "serious adverse events" chapter: - definition of SAEs not considered serious (e.g. hospitalization <24h); - addition of a chapter on notification to the competent authorities; - addition of a chapter on notification to BAYER SCHERING Pharma. 4. It was specified that the statistical analysis will be performed according to the stratification factors defined in the protocol. 5. To comply with the product's marketing authorization and because of its half-life, the frequency of drug intake in case of dose reduction was corrected to : 2 x 200mg 1 time/day. 6. The study schedule has been corrected. Indeed, the histological confirmation at day 15 is a typographical error.
06 April 2009	Substantial Change number 4: The major changes include: 1. Interim analysis on the primary endpoint, which is progression-free survival at 9 months. In summary, 44 and 24 patients should be included in strata A and B respectively with $p_0 = 0.13$ and $p_1 = 0.32$ (expected progression-free survival at 9 months), $\alpha = 0.10$, and a power of 95% and 81% in strata A and B strata, respectively. This design allows for an interim analysis in each stratum after inclusion of 24 and 12 patients, with a stopping decision if more than 20 progressions out of 24 patients before 9 months in stratum A and more than 10 progressions out of 12 patients before 9 months in stratum B. 2. Creation of Stratum C: Epithelioid hemangioendotheliomas, hemangiopericytomas and malignant solitary fibrous tumors. There are three arguments in favor of creating this stratum: - The favorable benefit/risk ratio of Sorafenib for angiosarcoma observed in the 1st IDMC - The absence of a therapeutic standard for other vascular sarcomas (epithelioid hemangioendotheliomas and hemangiopericytomas) - The biological rationale suggesting efficacy in these situations.

31 January 2011	Rationale for Substantial Change number 5: 1. The creation of a D stratum: chordomas The rationale behind the addition of this new stratum is based on: - The lack of a therapeutic standard, - Prolonged stabilization with the use of targeted therapies such as tyrosine kinase inhibitors (while chemotherapies remain ineffective) ineffective), - Characterization by expression of a functional target of Sorafenib, suggesting its efficacy in this indication This stratum will include 25 patients with metastatic and progressive chordoma. The clinical studies on which the rationale is based were conducted in limited on limited cohorts, which does not allow for statistical hypothesis. The benefit/risk ratio within this stratum will be reviewed on a semi-annual basis by semi-annually by the IDMC set up for this study. Therefore, changes are being made to the protocol regarding inclusion criteria, study duration and total number of patients. 2. Update of the Nexavar summary of product characteristics This document was revised on January 5, 2011, and mentions new data : - warnings and precautions for use, - fatal or life-threatening adverse events (see table below). This new version cancels and replaces the current reference document in this study. The information and consent note for patients includes these elements. 3. Change in telephone and monitor contact information 4. Updated Declaration of Helsinki
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22285963>

<http://www.ncbi.nlm.nih.gov/pubmed/23589078>

<http://www.ncbi.nlm.nih.gov/pubmed/24005614>

<http://www.ncbi.nlm.nih.gov/pubmed/26202596>