Clinical trial results:
Activity and safety of regorafenib in patients with metastatic. Soft tissue sarcoma previously treated with anthracyclin-based chemotherapy: a multinational, randomized, phase II, placebo-controlled trial

Summary

EudraCT number	2012-005743-24
Trial protocol	AT
Global end of trial date	11 March 2020

Results information

Result version number	v1 (current)
This version publication date	07 November 2025
First version publication date	07 November 2025

Trial information

Trial identification

Sponsor protocol code	REGO-SARC-1214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01900743
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Oscar Lambret
Sponsor organisation address	3 rue Frédéric Combemale, Lille, France, 59000
Public contact	Project manager, Centre Oscar Lambret, 33 320295918, promotion@o-lambret.fr
Scientific contact	Project manager, Centre Oscar Lambret, 33 320295918, promotion@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	11 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2020
Global end of trial reached?	Yes
Global end of trial date	11 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective: to investigate whether treatment with regorafenib improves the outcome of patients with metastatic soft tissue sarcoma, when compared with placebo.
The primary endpoint was progression-free survival in the intention-to-treat population, according to RECIST (version 1.1) based on central radiological review.

Protection of trial subjects:

The study was approved by an ethical and regulatory committee (French Ethical Committee [Comité de Protection des Patients Nord-Ouest IV; date of approval
March 21, 2013], Austrian Ethical Committee [Ethik Kommission Medizinische Universität Wien; number 1376/2013], and the French and Austrian Drug Agencies
[Agence Nationale de Sécurité du Médicament; date of approval March 8, 2013]).

IDMC (23/05/2014)
=> In view of the acceptable tolerability data, consistent with that already known for regorafenib, and the encouraging preliminary activity data, the IDMC members recommend continuing the study. However, due to the number of deaths, the IDMC recommends particular vigilance with regard to toxicities and wishes to meet again at the end of the year to reassess tolerability

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 June 2013
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	Austria: 15
Country: Number of subjects enrolled	France: 203
Worldwide total number of subjects	218
EEA total number of subjects	218

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)	143
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 218 pts included between 12/06/2013 and 19/10/2017,
- placebo: n=111
- regorafenib: n=107
stratified in 5 cohorts
-Cohort A: Liposarcoma
-Cohort B: leiomyosarcoma
-Cohort C: synovial sarcoma
-Cohort D: other sarcoma
-Cohort E: non-adipocytic patients previously treated with both chemotherapy and pazopanib

Pre-assignment

Screening details:

One patient was included twice, his duplicate was deleted from the analysis.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Patients, investigators and radiologists were all blinded to treatment allocation. At the treating sites, only pharmacists were aware of the allocated treatment. Unblinding could be done by the sponsor on request of the investigator in case of emergency (safety issue), progression and need to know the treatment received to continue medical care, or for any reason justified by the investigator. A cross-over was authorized after confirmed progression.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A - Placebo arm

Arm description:

Patients with liposarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Cohort A - Regorafenib arm

Arm description:

Patients with liposarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)

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

Dosage and administration details:

Regorafenib: 4 tablets, once daily, 3 weeks on / 1 week off + Best Supportive Care

Arm title	Cohort B -Placebo arm

Arm description:

Patients with Leiomyosarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Cohort B - Regorafenib arm
Arm description:	
Patients with Leiomyosarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Regorafenib: 4 tablets, once daily, 3 weeks on / 1 week off + Best Supportive Care	
Arm title	Cohort C - Placebo arm
Arm description:	
Patients with synovial sarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Cohort C - Regorafenib arm
Arm description:	
Patients with synovial sarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Regorafenib: 4 tablets, once daily, 3 weeks on / 1 week off + Best Supportive Care	
Arm title	Cohort D -Placebo arm
Arm description:	
Patients with other sarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Cohort D -Regorafenib arm
Arm description:	
Patients with other sarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Regorafenib: 4 tablets, once daily, 3 weeks on / 1 week off + Best Supportive Care	
Arm title	Cohort E -Placebo arm

Arm description:

Patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib and treated by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Cohort E - Regorafenib arm

Arm description:

Patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib and treated by Regorafenib(160mg, 4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)

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

Dosage and administration details:

Regorafenib: 4 tablets, once daily, 3 weeks on / 1 week off + Best Supportive Care

Number of subjects in period 1	Cohort A - Placebo arm	Cohort A - Regorafenib arm	Cohort B -Placebo arm
Started	23	20	28
Completed	23	20	28

Number of subjects in period 1	Cohort B - Regorafenib arm	Cohort C - Placebo arm	Cohort C - Regorafenib arm
Started	28	14	13
Completed	28	14	13

Number of subjects in period 1	Cohort D -Placebo arm	Cohort D - Regorafenib arm	Cohort E -Placebo arm
Started	27	28	19
Completed	27	28	19

Number of subjects in period 1	Cohort E - Regorafenib arm
Started	18
Completed	18

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A - Placebo arm
Reporting group description:	
Patients with liposarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort A - Regorafenib arm
Reporting group description:	
Patients with liposarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort B -Placebo arm
Reporting group description:	
Patients with Leiomyosarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort B - Regorafenib arm
Reporting group description:	
Patients with Leiomyosarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort C - Placebo arm
Reporting group description:	
Patients with synovial sarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort C - Regorafenib arm
Reporting group description:	
Patients with synovial sarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort D -Placebo arm
Reporting group description:	
Patients with other sarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort D -Regorafenib arm
Reporting group description:	
Patients with other sarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort E -Placebo arm
Reporting group description:	
Patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib and treated by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort E - Regorafenib arm
Reporting group description:	
Patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib and treated by Regorafenib(160mg, 4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	

Reporting group values	Cohort A - Placebo arm	Cohort A - Regorafenib arm	Cohort B -Placebo arm
Number of subjects	23	20	28
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)	11	15	18
From 65-84 years	12	5	10
85 years and over	0	0	0
Age continuous			
Units: years			
median	65	57.5	60
full range (min-max)	22 to 80	24 to 76	30 to 76
Gender categorical			
Units: Subjects			
Female	9	8	21
Male	14	12	7
ECOG performance status			
ECOG performance status			
Units: Subjects			
ECOG=0	10	10	13
ECOG=1	12	10	15
ECOG=2	1	0	0
Missing	0	0	0
Metastasis			
Metastasis at inclusion			
Units: Subjects			
No	4	1	0
Yes	19	19	28
Histological subtype (definitive)			
Histological subtype (definitive)			
Units: Subjects			
Liposarcoma	23	20	0
Leiomysarcoma	0	0	28
Synovial sarcoma	0	0	0
Other sarcoma	0	0	0
Histopronostic grade			
Histopronostic grade			
Units: Subjects			
Grade 1	2	6	2
Grade 2	13	7	17
Grade 3	5	4	7
Missing	3	3	2
Not applicable	0	0	0

Reporting group values	Cohort B - Regorafenib arm	Cohort C - Placebo arm	Cohort C - Regorafenib arm
Number of subjects	28	14	13
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)	17	13	12
From 65-84 years	11	1	1
85 years and over	0	0	0
Age continuous			
Units: years			
median	60.5	35.5	46
full range (min-max)	32 to 74	20 to 68	21 to 73
Gender categorical			
Units: Subjects			
Female	19	5	5
Male	9	9	8
ECOG performance status			
ECOG performance status			
Units: Subjects			
ECOG=0	12	9	7
ECOG=1	16	5	6
ECOG=2	0	0	0
Missing	0	0	0
Metastasis			
Metastasis at inclusion			
Units: Subjects			
No	0	1	0
Yes	28	13	13
Histological subtype (definitive)			
Histological subtype (definitive)			
Units: Subjects			
Liposarcoma	0	0	0
Leiomysarcoma	28	0	0
Synovial sarcoma	0	14	13
Other sarcoma	0	0	0
Histopronostic grade			
Histopronostic grade			
Units: Subjects			
Grade 1	1	0	0
Grade 2	10	8	3
Grade 3	14	5	9
Missing	3	1	1
Not applicable	0	0	0

Reporting group values	Cohort D -Placebo arm	Cohort D - Regorafenib arm	Cohort E -Placebo arm
Number of subjects	27	28	19
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)	16	14	16
From 65-84 years	11	14	3
85 years and over	0	0	0
Age continuous			
Units: years			
median	55	62.5	60
full range (min-max)	20 to 78	26 to 81	36 to 76
Gender categorical			
Units: Subjects			
Female	8	15	14
Male	19	13	5
ECOG performance status			
ECOG performance status			
Units: Subjects			
ECOG=0	13	11	8
ECOG=1	14	17	11
ECOG=2	0	0	0
Missing	0	0	0
Metastasis			
Metastasis at inclusion			
Units: Subjects			
No	0	2	2
Yes	27	26	17
Histological subtype (definitive)			
Histological subtype (definitive)			
Units: Subjects			
Liposarcoma	0	1	0
Leiomysarcoma	0	1	11
Synovial sarcoma	0	0	1
Other sarcoma	27	26	7
Histopronostic grade			
Histopronostic grade			
Units: Subjects			
Grade 1	1	1	0
Grade 2	7	6	3
Grade 3	13	13	10
Missing	0	0	6
Not applicable	6	8	0

Reporting group values	Cohort E - Regorafenib arm	Total	
Number of subjects	18	218	
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)	11	143	
From 65-84 years	7	75	
85 years and over	0	0	
Age continuous			
Units: years			
median	61		
full range (min-max)	41 to 71	-	
Gender categorical			
Units: Subjects			
Female	14	118	
Male	4	100	
ECOG performance status			
ECOG performance status			
Units: Subjects			
ECOG=0	9	102	
ECOG=1	8	114	
ECOG=2	0	1	
Missing	1	1	
Metastasis			
Metastasis at inclusion			
Units: Subjects			
No	0	10	
Yes	18	208	
Histological subtype (definitive)			
Histological subtype (definitive)			
Units: Subjects			
Liposarcoma	0	44	
Leiomysarcoma	13	81	
Synovial sarcoma	0	28	
Other sarcoma	5	65	
Histopronostic grade			
Histopronostic grade			
Units: Subjects			
Grade 1	2	15	
Grade 2	7	81	
Grade 3	5	85	
Missing	4	23	
Not applicable	0	14	

End points

End points reporting groups

Reporting group title	Cohort A - Placebo arm
Reporting group description:	
Patients with liposarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort A - Regorafenib arm
Reporting group description:	
Patients with liposarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort B -Placebo arm
Reporting group description:	
Patients with Leiomyosarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort B - Regorafenib arm
Reporting group description:	
Patients with Leiomyosarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort C - Placebo arm
Reporting group description:	
Patients with synovial sarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort C - Regorafenib arm
Reporting group description:	
Patients with synovial sarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort D -Placebo arm
Reporting group description:	
Patients with other sarcoma and treatment by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort D -Regorafenib arm
Reporting group description:	
Patients with other sarcoma and treatment by Regorafenib (160 mg, 4 tablets, once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort E -Placebo arm
Reporting group description:	
Patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib and treated by placebo (4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	
Reporting group title	Cohort E - Regorafenib arm
Reporting group description:	
Patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib and treated by Regorafenib(160mg, 4 tablets once daily, 3 weeks on / 1 week off plus Best Supportive Care)	

Primary: Progression-free survival - cohort A

End point title	Progression-free survival - cohort A[1]
End point description:	
Progression-Free Survival measured from the date of randomization until the date of radiological progression or death whatever the cause (if death occurs before progression). Patients without tumor progression or death at the time of analysis censored at their last date of radiological tumor assessment. The date of disease of progression was the date of first observation of progression (primary analysis on	

intent-to-treat analysis, according to RECIST 1.1 guidelines).

End point type	Primary

End point timeframe:

Tumor evaluation was planned every 1 month during the first 4 months, at 6 months and then every 3 months.

Notes:

[1] - 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 results provided are results by cohort and treatment group.

End point values	Cohort A - Placebo arm	Cohort A - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	26 (10 to 44)	25 (9 to 45)		
At 6 months	8 (1 to 24)	20 (6 to 39)		
At 9 months	8 (1 to 24)	5 (0 to 20)		

Statistical analyses

Statistical analysis title	Progression free survival

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort A - Regorafenib arm v Cohort A - Placebo arm
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.7
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.64

Notes:

[2] - Effect of treatment (Regorafenib versus placebo)
Cox model

Primary: Progression-free survival - cohort B

End point title	Progression-free survival - cohort B[3]

End point description:

Progression-Free Survival measured from the date of randomization until the date of radiological progression or death whatever the cause (if death occurs before progression). Patients without tumor progression or death at the time of analysis censored at their last date of radiological tumor assessment. The date of disease of progression was the date of first observation of progression (primary analysis on intent-to-treat analysis, according to RECIST 1.1 guidelines and central radiological review).

End point type	Primary

End point timeframe:

Tumor evaluation was planned every 1 month during the first 4 months, at 6 months and then every 3 months
Based on data from a complete review carried out in 2021

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: The results provided are results by cohort and treatment group.

End point values	Cohort B - Placebo arm	Cohort B - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	11.6 (3.0 to 26.8)	21.4 (8.7 to 37.8)		
At 6 months	7.7 (1.4 to 21.8)	7.1 (1.3 to 20.4)		
At 12 months	3.9 (0.3 to 16.5)	3.6 (0.3 to 15.4)		

Statistical analyses

Statistical analysis title	Progression free survival - adjusted HR

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort B - Regorafenib arm v Cohort B -Placebo arm
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.21
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.21

Notes:

[4] - Effect of treatment (Regorafenib versus placebo)
Cox model: Adjusted HR (IC95%)
HR adjusted on stratification factors (Country: France versus Austria; prior exposure to pazopanib: Yes vs no)

Statistical analysis title	Progression free survival - not adjusted HR

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards

assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort B - Regorafenib arm v Cohort B -Placebo arm
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.21
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.22

Notes:

[5] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Primary: Progression-free survival - cohort C

End point title	Progression-free survival - cohort C[6]

End point description:

Progression-Free Survival measured from the date of randomization until the date of radiological progression or death whatever the cause (if death occurs before progression). Patients without tumor progression or death at the time of analysis censored at their last date of radiological tumor assessment. The date of disease of progression was the date of first observation of progression (primary analysis on intent-to-treat analysis, according to RECIST 1.1 guidelines and central radiological review).

End point type	Primary

End point timeframe:

Tumor evaluation was planned every 1 month during the first 4 months, at 6 months and then every 3 months
Based on data from a complete review carried out in 2021

Notes:

[6] - 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 results provided are results by cohort and treatment group.

End point values	Cohort C - Placebo arm	Cohort C - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	0 (0 to 0)	42.3 (15.6 to 67.1)		
At 6 months	0 (0 to 0)	21.2 (3.6 to 48.4)		
At 12 months	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Progression free survival - adjusted HR

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method.

Comparison groups	Cohort C - Regorafenib arm v Cohort C - Placebo arm
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.46

Notes:

[7] - Effect of treatment (Regorafenib versus placebo)
Cox model: Adjusted HR (IC95%)
HR adjusted on stratification factors (Country: France versus Austria; prior exposure to pazopanib: Yes vs no)

Statistical analysis title	Progression free survival - not adjusted H

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method.

Comparison groups	Cohort C - Regorafenib arm v Cohort C - Placebo arm
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.45

Notes:

[8] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Primary: Progression-free survival - cohort D

End point title	Progression-free survival - cohort D[9]

End point description:

Progression-Free Survival measured from the date of randomization until the date of radiological progression or death whatever the cause (if death occurs before progression). Patients without tumor progression or death at the time of analysis censored at their last date of radiological tumor assessment. The date of disease of progression was the date of first observation of progression (primary analysis on intent-to-treat analysis, according to RECIST 1.1 guidelines and central radiological review).

End point type	Primary

End point timeframe:

Tumor evaluation was planned every 1 month during the first 4 months, at 6 months and then every 3 months
Based on data from a complete review carried out in 2021

Notes:

[9] - 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 results provided are results by cohort and treatment group.

End point values	Cohort D - Placebo arm	Cohort D - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	10.0 (2.0 to 25.3)	46.4 (27.6 to 63.3)		
At 6 months	4.9 (0.4 to 19.5)	16.9 (5.4 to 33.7)		
At 12 months	4.9 (0.4 to 19.5)	4.2 (0.3 to 17.7)		

Statistical analyses

Statistical analysis title	Progression free survival - adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort D -Regorafenib arm v Cohort D -Placebo arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.03
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.95

Notes:

[10] - Effect of treatment (Regorafenib versus placebo)
Cox model: Adjusted HR (IC95%)
HR adjusted on stratification factors (Country: France versus Austria; prior exposure to pazopanib: Yes vs no)

Statistical analysis title	Progression free survival - not adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort D -Regorafenib arm v Cohort D -Placebo arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.03
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.94

Notes:

[11] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Primary: Progression-free survival - cohort E

End point title	Progression-free survival - cohort E[12]

End point description:

Progression-Free Survival measured from the date of randomization until the date of radiological progression or death whatever the cause (if death occurs before progression). Patients without tumor progression or death at the time of analysis censored at their last date of radiological tumor assessment. The date of disease of progression was the date of first observation of progression (primary analysis on intent-to-treat analysis, according to RECIST 1.1 guidelines and central radiological review).

End point type	Primary

End point timeframe:

Tumor evaluation was planned every 1 month during the first 4 months, at 6 months and then every 3 months.
Based on data from a complete review carried out in 2021

Notes:

[12] - 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 results provided are results by cohort and treatment group.

End point values	Cohort E - Placebo arm	Cohort E - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	5 (0 to 21)	33 (14 to 54)		
At 6 months	0 (0 to 0)	22 (7 to 43)		
At 12 months	0 (0 to 0)	6 (0 to 22)		

Statistical analyses

Statistical analysis title	Progression free survival - adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI)

associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort E - Regorafenib arm v Cohort E -Placebo arm
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.007
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.74

Notes:

[13] - Analysis: model adjusted for histology (leiomyosarcoma vs. other sarcoma, one patient with synovial sarcoma was considered as other sarcoma for this analysis), number of prior lines of systemic treatment (<4 vs. 4+).

Statistical analysis title	Progression free survival - not adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort E - Regorafenib arm v Cohort E -Placebo arm
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.0023
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.67

Notes:

[14] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Statistical analysis title	Progression free survival - Post-hoc adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatmeant effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort E - Regorafenib arm v Cohort E -Placebo arm

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.12
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.28

Notes:

[15] - Post-hoc analysis: model adjusted for histology (Leiomyosarcoma vs. other sarcoma, one patient with synovial sarcoma was considered as other sarcoma for this analysis), number of prior lines of systemic treatment (<4 vs. 4+) and histological grade (I and II vs III). Ten cases are excluded in this analysis because of missing data for the grade: six in placebo arm and four in regorafenib arm.

Secondary: Overall Survival - cohort A

End point title	Overall Survival - cohort A[16]

End point description:

OS, defined as the time interval from the date of randomisation to the date of death from any cause. In each group, the OS curve was estimated using the Kaplan-Meier method

End point type	Secondary

End point timeframe:

Until the end of the study

Notes:

[16] - 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 results provided are results by cohort and treatment group.

End point values	Cohort A - Placebo arm	Cohort A - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	91.3 (69.5 to 97.6)	73.9 (48.2 to 88.2)		
At 6 months	77.6 (54.3 to 90.0)	42.2 (20.5 to 62.6)		

Statistical analyses

Statistical analysis title	Overall survival - not adjusted HR

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort A - Regorafenib arm v Cohort A - Placebo arm

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.21
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	3.21

Notes:

[17] - Effect of treatment (Regorafenib versus placebo)
Cox model: not ajusted HR (IC95%)

Secondary: Overall Survival - cohort B

End point title	Overall Survival - cohort B[18]

End point description:

OS, defined as the time interval from the date of randomisation to the date of death from any cause. In each group, the OS curve was estimated using the Kaplan-Meier method

End point type	Secondary

End point timeframe:

Until the end of the study

Notes:

[18] - 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 results provided are results by cohort and treatment group.

End point values	Cohort B - Placebo arm	Cohort B - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	92.9 (74.4 to 98.2)	92.9 (74.4 to 98.2)		
At 6 months	78.6 (58.4 to 89.8)	78.6 (58.4 to 89.8)		
At 12 months	46.4 (27.6 to 63.3)	60.7 (40.4 to 76.0)		

Statistical analyses

Statistical analysis title	Overall survival - adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort B - Regorafenib arm v Cohort B -Placebo arm

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.15
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.15

Notes:

[19] - Effect of treatment (Regorafenib versus placebo)
Cox model: adjusted HR (IC95%)
HR - Adjusted on stratification factors (Country: France versus Austria; prior exposure to pazopanib: Yes vs no)

Statistical analysis title	Overall survival - not adjusted HR

Statistical analysis description:

Cox model were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort B - Regorafenib arm v Cohort B -Placebo arm
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.17
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.18

Notes:

[20] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Secondary: Best tumor response, according to full central review -Cohort B

End point title	Best tumor response, according to full central review -Cohort

End point description:

End point type	Secondary

End point timeframe:

Best tumor response, according to full central review (and clinical information if applicable) – by treatment arm (cohort B)

Notes:

[21] - 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 results provided are results by cohort and treatment group.

End point values	Cohort B - Placebo arm	Cohort B - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Best response				
number (not applicable)				
Complete response	0	0		
Partial response	0	0		
Stable disease	12	17		
Progressive disease	16	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - cohort C

End point title	Overall Survival - cohort C[22]

End point description:

OS, defined as the time interval from the date of randomisation to the date of death from any cause. In each group, the OS curve was estimated using the Kaplan-Meier method

End point type	Secondary

End point timeframe:

Until the end of the study

Notes:

[22] - 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 results provided are results by cohort and treatment group.

End point values	Cohort C - Placebo arm	Cohort C - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	85.7 (53.9 to 96.2)	92.3 (56.6 to 98.9)		
At 6 months	64.3 (34.3 to 83.3)	76.9 (44.2 to 91.9)		
At 12 months	35.7 (13.0 to 59.4)	61.5 (30.8 to 81.8)		

Statistical analyses

Statistical analysis title	Overall survival - adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards

assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort C - Regorafenib arm v Cohort C - Placebo arm
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.78
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	2.01

Notes:

[23] - Effect of treatment (Regorafenib versus placebo)
Cox model: adjusted HR (IC95%)
HR - Adjusted on stratification factors (Country: France versus Austria; prior exposure to pazopanib: Yes vs no)

Statistical analysis title	Overall survival - not adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort C - Regorafenib arm v Cohort C - Placebo arm
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.94
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	2.13

Notes:

[24] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Secondary: Best tumor response, according to full central review -Cohort C

End point title	Best tumor response, according to full central review -Cohort

End point description:

End point type	Secondary

End point timeframe:

Best tumor response, according to full central review (and clinical information if applicable) – by treatment arm (cohort C)

Notes:

[25] - 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 results provided are results by cohort and treatment group.

End point values	Cohort C - Placebo arm	Cohort C - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12[26]		
Units: Best response				
number (not applicable)				
Complete response	0	0		
Partial response	0	0		
Stable disease	3	8		
Progressive disease	11	4		

Notes:

[26] - One patient had no central review due to issue in quality control

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - cohort D

End point title	Overall Survival - cohort D[27]

End point description:

OS, defined as the time interval from the date of randomisation to the date of death from any cause. In each group, the OS curve was estimated using the Kaplan-Meier method

End point type	Secondary

End point timeframe:

Until the end of the study

Notes:

[27] - 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 results provided are results by cohort and treatment group.

End point values	Cohort D - Placebo arm	Cohort D - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	77.8 (57.1 to 89.3)	82.1 (62.3 to 92.2)		
At 6 months	66.7 (45.7 to 81.1)	75.0 (54.6 to 87.2)		
At 12 months	37.0 (19.6 to 54.6)	53.6 (33.8 to 69.8)		

Statistical analyses

Statistical analysis title	Overall survival - adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort D -Regorafenib arm v Cohort D -Placebo arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.91
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.7

Notes:

[28] - Effect of treatment (Regorafenib versus placebo)
Cox model: adjusted HR (IC95%)
HR - Adjusted on stratification factors (Country: France versus Austria; prior exposure to pazopanib: Yes vs no)

Statistical analysis title	Overall survival - not adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort D -Regorafenib arm v Cohort D -Placebo arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.82
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.63

Notes:

[29] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Secondary: Best tumor response, according to full central review -Cohort D

End point title	Best tumor response, according to full central review -Cohort

End point description:

End point type	Secondary

End point timeframe:

Best tumor response, according to full central review (and clinical information if applicable) – by treatment arm (cohort D)

Notes:

[30] - 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 results provided are results by cohort and treatment group.

End point values	Cohort D - Placebo arm	Cohort D - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26[31]		
Units: Best response				
number (not applicable)				
Complete response	0	0		
Partial response	0	1		
Stable disease	9	12		
Progressive disease	18	13		

Notes:

[31] - 2 patients had no central review due to issue in quality control

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - cohort E

End point title	Overall Survival - cohort E[32]

End point description:

OS, defined as the time interval from the date of randomisation to the date of death from any cause. In each group, the OS curve was estimated using the Kaplan-Meier method

End point type	Secondary

End point timeframe:

Until the end of the study

Notes:

[32] - 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 results provided are results by cohort and treatment group.

End point values	Cohort E - Placebo arm	Cohort E - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: Survival estimate (%)				
number (confidence interval 95%)				
At 3 months	89 (64 to 97)	88 (61 to 97)		
At 6 months	79 (53 to 91)	83 (55 to 94)		
At 12 months	37 (16 to 57)	65 (38 to 82)		

Statistical analyses

Statistical analysis title	Overall survival - adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort E - Regorafenib arm v Cohort E -Placebo arm
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.07
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	1.06

Notes:

[33] - Analysis: model adjusted for histology (leiomyosarcoma vs. other sarcoma, one patient with synovial sarcoma was considered as other sarcoma for this analysis), number of prior lines of systemic treatment (<4 vs. 4+).

Statistical analysis title	Overall survival - not adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort E - Regorafenib arm v Cohort E -Placebo arm
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.058
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	1.03

Notes:

[34] - Effect of treatment (Regorafenib versus placebo)
Cox model: not adjusted HR (IC95%)

Statistical analysis title	Overall survival - Post-hoc adjusted HR

Statistical analysis description:

Cox models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) associated with the treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method

Comparison groups	Cohort E - Regorafenib arm v Cohort E -Placebo arm

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.09
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	1.17

Notes:

[35] - Post-hoc analysis: model adjusted for histology (Leiomyosarcoma vs. other sarcoma, one patient with synovial sarcoma was considered as other sarcoma for this analysis), number of prior lines of systemic treatment (<4 vs. 4+) and histological grade (I and II vs III). Ten cases are excluded in this analysis because of missing data for the grade: six in placebo arm and four in regorafenib arm.

Secondary: Best tumor response, according to full central review -Cohort E

End point title	Best tumor response, according to full central review -Cohort

End point description:

End point type	Secondary

End point timeframe:

Best tumor response, according to full central review (and clinical information if applicable) – by treatment arm (cohort E)

Notes:

[36] - 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 results provided are results by cohort and treatment group.

End point values	Cohort E - Placebo arm	Cohort E - Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: Best response				
number (not applicable)				
Complete response	0	0		
Partial response	0	0		
Stable disease	8	13		
Progressive disease	11	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety was evaluated during the whole treatment duration up to the visit performed 30 (+/- 7) days after permanent treatment discontinuation.

Adverse event reporting additional description:

AE additional description
AEs are detailed by treatment group: regorafenib versus placebo across all cohorts combined.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Regorafenib arm

Reporting group description: -

Reporting group title	Placebo arm

Reporting group description: -

Serious adverse events	Regorafenib arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 107 (48.60%)	21 / 111 (18.92%)	
number of deaths (all causes)	102	109	
number of deaths resulting from adverse events	6	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	Additional description: Malignant neoplasm progression		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor pain	Additional description: Tumor pain		
subjects affected / exposed	5 / 107 (4.67%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial hypertension	Additional description: Arterial hypertension		
subjects affected / exposed	3 / 107 (2.80%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Hypotension		

subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor hemorrhage	Additional description: Tumor hemorrhage		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Neurosurgery	Additional description: Neurosurgery		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery	Additional description: Surgery		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia	Additional description: Asthenia		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever	Additional description: Fever		
subjects affected / exposed	5 / 107 (4.67%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	6 / 107 (5.61%)	4 / 111 (3.60%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pain	Additional description: Pain		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	Additional description: Acute respiratory distress syndrome		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration	Additional description: Aspiration		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	3 / 107 (2.80%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemothorax	Additional description: Hemothorax		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: Pneumothorax		

subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure	Additional description: Respiratory failure		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress	Additional description: Respiratory distress		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Hypercalcemia	Additional description: Hypercalcemia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia	Additional description: Hyperglycemia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemia	Additional description: Hypoglycemia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture	Additional description: Acetabulum fracture		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Postoperative wound complication	Additional description: Postoperative wound complication		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest	Additional description: Cardiac arrest		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia	Additional description: Myocardial ischaemia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Motor dysfunction	Additional description: Motor dysfunction		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (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			
Anemia	Additional description: Anemia		
subjects affected / exposed	2 / 107 (1.87%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	4 / 107 (3.74%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ascites	Additional description: Ascites		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation	Additional description: Gastric perforation		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula	Additional description: Gastrointestinal fistula		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal perforation	Additional description: Gastrointestinal perforation		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration	Additional description: Hernial eventration		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation	Additional description: Intestinal perforation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus	Additional description: Subileus		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	3 / 107 (2.80%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury	Additional description: Hepatocellular injury		

subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Jaundice	Additional description: Jaundice		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity	Additional description: Skin toxicity		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin exfoliation	Additional description: Skin exfoliation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash	Additional description: Rash		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 107 (0.93%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain	Additional description: Flank pain		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis	Additional description: Pyelonephritis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis	Additional description: Peritonitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Staphylococcal infection	Additional description: Staphylococcal infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Regorafenib arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 107 (100.00%)	105 / 111 (94.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma	Additional description: Skin papilloma		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Tumor pain	Additional description: Tumor pain		
subjects affected / exposed	5 / 107 (4.67%)	3 / 111 (2.70%)	
occurrences (all)	5	3	
Vascular disorders			
Anal hemorrhage	Additional description: Anal hemorrhage		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Arterial hypertension	Additional description: Arterial hypertension		
subjects affected / exposed	32 / 107 (29.91%)	5 / 111 (4.50%)	
occurrences (all)	46	6	
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	11 / 107 (10.28%)	3 / 111 (2.70%)	
occurrences (all)	20	3	
Flushing	Additional description: Flushing		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Haematoma	Additional description: Haematoma		

subjects affected / exposed	1 / 107 (0.93%)	2 / 111 (1.80%)	
occurrences (all)	1	2	
Hematuria	Additional description: Hematuria		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Hemoptysis	Additional description: Hemoptysis		
subjects affected / exposed	6 / 107 (5.61%)	2 / 111 (1.80%)	
occurrences (all)	11	3	
Hemorrhage	Additional description: Hemorrhage		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	4 / 107 (3.74%)	3 / 111 (2.70%)	
occurrences (all)	4	3	
Metrorrhagia	Additional description: Metrorrhagia		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Mouth hemorrhage	Additional description: Mouth hemorrhage		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	2	
Thrombosis	Additional description: Thrombosis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	0 / 107 (0.00%)	2 / 111 (1.80%)	
occurrences (all)	0	2	
Superior vena cava syndrome	Additional description: Superior vena cava syndrome		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Rectal hemorrhage	Additional description: Rectal hemorrhage		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Surgical and medical procedures			

Cataract operation	Additional description: Cataract operation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	44 / 107 (41.12%)	23 / 111 (20.72%)	
occurrences (all)	49	25	
Appetite disorder	Additional description: Appetite disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Asthenia	Additional description: Asthenia		
subjects affected / exposed	72 / 107 (67.29%)	46 / 111 (41.44%)	
occurrences (all)	107	55	
Cachexia	Additional description: Cachexia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Chills	Additional description: Chills		
subjects affected / exposed	4 / 107 (3.74%)	1 / 111 (0.90%)	
occurrences (all)	4	1	
Discomfort	Additional description: Discomfort		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Edema peripheral	Additional description: Edema peripheral		
subjects affected / exposed	7 / 107 (6.54%)	7 / 111 (6.31%)	
occurrences (all)	9	7	
Effusion	Additional description: Effusion		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Face edema	Additional description: Face edema		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Fever	Additional description: Fever		
subjects affected / exposed	18 / 107 (16.82%)	6 / 111 (5.41%)	
occurrences (all)	37	6	
General physical health deterioration	Additional description: General physical health deterioration		

subjects affected / exposed	3 / 107 (2.80%)	2 / 111 (1.80%)	
occurrences (all)	3	2	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	4 / 107 (3.74%)	3 / 111 (2.70%)	
occurrences (all)	4	3	
Local swelling	Additional description: Local swelling		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Malaise	Additional description: Malaise		
subjects affected / exposed	3 / 107 (2.80%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Mucosal dryness	Additional description: Mucosal dryness		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Pain	Additional description: Pain		
subjects affected / exposed	3 / 107 (2.80%)	3 / 111 (2.70%)	
occurrences (all)	3	3	
Weight loss	Additional description: Weight loss		
subjects affected / exposed	26 / 107 (24.30%)	10 / 111 (9.01%)	
occurrences (all)	26	10	
Immune system disorders			
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Amenorrhoea	Additional description: Amenorrhoea		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Breast pain	Additional description: Breast pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gynaecomastia	Additional description: Gynaecomastia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Pelvic pain	Additional description: Pelvic pain		

subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Phimosis	Additional description: Phimosis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Vaginal inflammation	Additional description: Vaginal inflammation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal burning sensation	Additional description: Vulvovaginal burning sensation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis	Additional description: Atelectasis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Cough	Additional description: Cough		
subjects affected / exposed	13 / 107 (12.15%)	10 / 111 (9.01%)	
occurrences (all)	14	10	
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	26 / 107 (24.30%)	2 / 111 (1.80%)	
occurrences (all)	27	2	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	22 / 107 (20.56%)	15 / 111 (13.51%)	
occurrences (all)	23	17	
Lower respiratory tract congestion	Additional description: Lower respiratory tract congestion		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Lung disorder	Additional description: Lung disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Nasal discomfort	Additional description: Nasal discomfort		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		

subjects affected / exposed	5 / 107 (4.67%)	1 / 111 (0.90%)	
occurrences (all)	7	1	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	4 / 107 (3.74%)	2 / 111 (1.80%)	
occurrences (all)	4	2	
Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	11 / 107 (10.28%)	3 / 111 (2.70%)	
occurrences (all)	11	3	
Confusional state	Additional description: Confusional state		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Depressive symptom	Additional description: Depressive symptom		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	4 / 107 (3.74%)	5 / 111 (4.50%)	
occurrences (all)	4	5	
Libido decreased	Additional description: Libido decreased		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Mental disorder	Additional description: Mental disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

Investigations			
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	51 / 107 (47.66%)	45 / 111 (40.54%)	
occurrences (all)	117	79	
Blood chloride decreased	Additional description: Blood chloride decreased		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	0 / 107 (0.00%)	3 / 111 (2.70%)	
occurrences (all)	0	3	
Blood uric acid increased	Additional description: Blood uric acid increased		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	5 / 107 (4.67%)	8 / 111 (7.21%)	
occurrences (all)	8	8	
Hypoglycemia	Additional description: Hypoglycemia		
subjects affected / exposed	13 / 107 (12.15%)	5 / 111 (4.50%)	
occurrences (all)	23	8	
Hyperamylasemia	Additional description: Hyperamylasemia		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Hypercalcemia	Additional description: Hypercalcemia		
subjects affected / exposed	8 / 107 (7.48%)	11 / 111 (9.91%)	
occurrences (all)	9	15	
Hypercreatininemia	Additional description: Hypercreatininemia		
subjects affected / exposed	24 / 107 (22.43%)	37 / 111 (33.33%)	
occurrences (all)	86	98	
Hyperglycemia	Additional description: Hyperglycemia		
subjects affected / exposed	48 / 107 (44.86%)	37 / 111 (33.33%)	
occurrences (all)	101	64	
Hyperkalemia	Additional description: Hyperkalemia		
subjects affected / exposed	11 / 107 (10.28%)	8 / 111 (7.21%)	
occurrences (all)	23	14	
Hyperlipasemia	Additional description: Hyperlipasemia		

subjects affected / exposed	12 / 107 (11.21%)	1 / 111 (0.90%)	
occurrences (all)	12	1	
Hypernatraemia	Additional description: Hypernatraemia		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Hypertriglyceridemia	Additional description: Hypertriglyceridemia		
subjects affected / exposed	3 / 107 (2.80%)	1 / 111 (0.90%)	
occurrences (all)	4	1	
Hypoalbuminemia	Additional description: Hypoalbuminemia		
subjects affected / exposed	48 / 107 (44.86%)	34 / 111 (30.63%)	
occurrences (all)	152	69	
Hypocalcemia	Additional description: Hypocalcemia		
subjects affected / exposed	39 / 107 (36.45%)	8 / 111 (7.21%)	
occurrences (all)	70	15	
Hypokalemia	Additional description: Hypokalemia		
subjects affected / exposed	26 / 107 (24.30%)	9 / 111 (8.11%)	
occurrences (all)	63	10	
Hypophosphatemia	Additional description: Hypophosphatemia		
subjects affected / exposed	34 / 107 (31.78%)	6 / 111 (5.41%)	
occurrences (all)	51	8	
Hypovolaemia	Additional description: Hypovolaemia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Iron deficiency	Additional description: Iron deficiency		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hyponatremia	Additional description: Hyponatremia		
subjects affected / exposed	36 / 107 (33.64%)	32 / 111 (28.83%)	
occurrences (all)	85	39	
Injury, poisoning and procedural complications			
Contusion	Additional description: Contusion		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Eschar	Additional description: Eschar		

subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Fall	Additional description: Fall		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Hand fracture	Additional description: Hand fracture		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	10 / 107 (9.35%)	4 / 111 (3.60%)	
occurrences (all)	10	4	
Ejection fraction decreased	Additional description: Ejection fraction decreased		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	3 / 107 (2.80%)	2 / 111 (1.80%)	
occurrences (all)	3	2	
Ventricular hypokinesia	Additional description: Ventricular hypokinesia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dysaesthesia	Additional description: Dysaesthesia		

subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Dysarthria	Additional description: Dysarthria		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Headache	Additional description: Headache		
subjects affected / exposed	24 / 107 (22.43%)	11 / 111 (9.91%)	
occurrences (all)	36	12	
Hyperaesthesia	Additional description: Hyperaesthesia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Motor dysfunction	Additional description: Motor dysfunction		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	7 / 107 (6.54%)	3 / 111 (2.70%)	
occurrences (all)	9	5	
Paraplegia	Additional description: Paraplegia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	1 / 107 (0.93%)	2 / 111 (1.80%)	
occurrences (all)	1	2	
Somnolence	Additional description: Somnolence		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	4 / 107 (3.74%)	1 / 111 (0.90%)	
occurrences (all)	4	1	
Vertigo	Additional description: Vertigo		

subjects affected / exposed	6 / 107 (5.61%)	0 / 111 (0.00%)	
occurrences (all)	6	0	
Tremor	Additional description: Tremor		
subjects affected / exposed	4 / 107 (3.74%)	0 / 111 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anemia	Additional description: Anemia		
subjects affected / exposed	104 / 107 (97.20%)	103 / 111 (92.79%)	
occurrences (all)	597	289	
Leukocytosis	Additional description: Leukocytosis		
subjects affected / exposed	0 / 107 (0.00%)	2 / 111 (1.80%)	
occurrences (all)	0	2	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	104 / 107 (97.20%)	103 / 111 (92.79%)	
occurrences (all)	584	276	
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	87 / 107 (81.31%)	85 / 111 (76.58%)	
occurrences (all)	437	204	
Platelet count increased	Additional description: Platelet count increased		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	9 / 107 (8.41%)	3 / 111 (2.70%)	
occurrences (all)	20	5	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	33 / 107 (30.84%)	8 / 111 (7.21%)	
occurrences (all)	124	12	
White blood cell count increased	Additional description: White blood cell count increased		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Auditory disorder	Additional description: Auditory disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Deafness	Additional description: Deafness		

subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Ear discomfort	Additional description: Ear discomfort		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hearing impaired	Additional description: Hearing impaired		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Dry eye	Additional description: Dry eye		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed	5 / 107 (4.67%)	2 / 111 (1.80%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	3 / 107 (2.80%)	0 / 111 (0.00%)	
occurrences (all)	6	0	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	25 / 107 (23.36%)	16 / 111 (14.41%)	
occurrences (all)	40	16	
Anal inflammation	Additional description: Anal inflammation		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	3 / 107 (2.80%)	3 / 111 (2.70%)	
occurrences (all)	3	3	
Ascites	Additional description: Ascites		

subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Breath odour	Additional description: Breath odour		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Cheilitis	Additional description: Cheilitis		
subjects affected / exposed	3 / 107 (2.80%)	0 / 111 (0.00%)	
occurrences (all)	6	0	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	7 / 107 (6.54%)	0 / 111 (0.00%)	
occurrences (all)	7	0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	52 / 107 (48.60%)	10 / 111 (9.01%)	
occurrences (all)	130	13	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	10 / 107 (9.35%)	2 / 111 (1.80%)	
occurrences (all)	11	2	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	6 / 107 (5.61%)	0 / 111 (0.00%)	
occurrences (all)	6	0	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	4 / 107 (3.74%)	1 / 111 (0.90%)	
occurrences (all)	5	1	
Constipation	Additional description: Constipation		
subjects affected / exposed	29 / 107 (27.10%)	11 / 111 (9.91%)	
occurrences (all)	45	11	
Gingival pain	Additional description: Gingival pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Faeces discoloured	Additional description: Faeces discoloured		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Gastritis	Additional description: Gastritis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		

subjects affected / exposed	5 / 107 (4.67%)	1 / 111 (0.90%)	
occurrences (all)	5	1	
Gastrointestinal motility disorder	Additional description: Gastrointestinal motility disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 107 (0.00%)	3 / 111 (2.70%)	
occurrences (all)	0	3	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Haematochezia	Additional description: Haematochezia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	7 / 107 (6.54%)	1 / 111 (0.90%)	
occurrences (all)	9	1	
Intestinal transit time abnormal	Additional description: Intestinal transit time abnormal		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Mouth ulceration	Additional description: Mouth ulceration		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	6 / 107 (5.61%)	1 / 111 (0.90%)	
occurrences (all)	11	2	
Nausea	Additional description: Nausea		
subjects affected / exposed	23 / 107 (21.50%)	14 / 111 (12.61%)	
occurrences (all)	28	15	
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Subileus	Additional description: Subileus		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Stomatitis	Additional description: Stomatitis		

subjects affected / exposed	38 / 107 (35.51%)	3 / 111 (2.70%)	
occurrences (all)	51	3	
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	26 / 107 (24.30%)	12 / 111 (10.81%)	
occurrences (all)	33	12	
Hepatobiliary disorders			
Hyperbilirubinemia	Additional description: Hyperbilirubinemia		
subjects affected / exposed	40 / 107 (37.38%)	10 / 111 (9.01%)	
occurrences (all)	97	18	
Hypertransaminasemia	Additional description: Hypertransaminasemia		
subjects affected / exposed	63 / 107 (58.88%)	35 / 111 (31.53%)	
occurrences (all)	246	82	
Jaundice	Additional description: Jaundice		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Jaundice cholestatic	Additional description: Jaundice cholestatic		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne	Additional description: Acne		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Alopecia	Additional description: Alopecia		
subjects affected / exposed	14 / 107 (13.08%)	1 / 111 (0.90%)	
occurrences (all)	15	1	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	5 / 107 (4.67%)	2 / 111 (1.80%)	
occurrences (all)	6	2	
Eczema	Additional description: Eczema		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Erythema	Additional description: Erythema		

subjects affected / exposed	4 / 107 (3.74%)	0 / 111 (0.00%)	
occurrences (all)	4	0	
Hair disorder	Additional description: Hair disorder		
subjects affected / exposed	4 / 107 (3.74%)	0 / 111 (0.00%)	
occurrences (all)	4	0	
Hand foot skin reaction	Additional description: Hand foot skin reaction		
subjects affected / exposed	47 / 107 (43.93%)	3 / 111 (2.70%)	
occurrences (all)	86	3	
Hyperkeratosis	Additional description: Hyperkeratosis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Pain of skin	Additional description: Pain of skin		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Night sweats	Additional description: Night sweats		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Skin toxicity	Additional description: Skin toxicity		
subjects affected / exposed	4 / 107 (3.74%)	1 / 111 (0.90%)	
occurrences (all)	7	1	
Skin exfoliation	Additional description: Skin exfoliation		
subjects affected / exposed	12 / 107 (11.21%)	0 / 111 (0.00%)	
occurrences (all)	13	0	
Skin disorder	Additional description: Skin disorder		
subjects affected / exposed	1 / 107 (0.93%)	2 / 111 (1.80%)	
occurrences (all)	1	2	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 107 (0.93%)	3 / 111 (2.70%)	
occurrences (all)	1	3	
Radiation skin injury	Additional description: Radiation skin injury		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Rash	Additional description: Rash		

subjects affected / exposed	22 / 107 (20.56%)	1 / 111 (0.90%)	
occurrences (all)	26	1	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Chromaturia	Additional description: Chromaturia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Dysuria	Additional description: Dysuria		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Nocturia	Additional description: Nocturia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	11 / 107 (10.28%)	9 / 111 (8.11%)	
occurrences (all)	14	9	
Pyelocaliectasis	Additional description: Pyelocaliectasis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Blood thyroid stimulating hormone decreased	Additional description: Blood thyroid stimulating hormone decreased		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Blood thyroid stimulating hormone increased	Additional description: Blood thyroid stimulating hormone increased		
subjects affected / exposed	3 / 107 (2.80%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Cushingoid	Additional description: Cushingoid		

subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Hyperparathyroidism	Additional description: Hyperparathyroidism		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	7 / 107 (6.54%)	1 / 111 (0.90%)	
occurrences (all)	9	1	
Thyroid disorder	Additional description: Thyroid disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Tri-iodothyronine decreased	Additional description: Tri-iodothyronine decreased		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	15 / 107 (14.02%)	8 / 111 (7.21%)	
occurrences (all)	21	10	
Back pain	Additional description: Back pain		
subjects affected / exposed	11 / 107 (10.28%)	10 / 111 (9.01%)	
occurrences (all)	12	11	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Chondrocalcinosis	Additional description: Chondrocalcinosis		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Fistula	Additional description: Fistula		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Flank pain	Additional description: Flank pain		

subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	7 / 107 (6.54%)	4 / 111 (3.60%)	
occurrences (all)	8	4	
Joint effusion	Additional description: Joint effusion		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	17 / 107 (15.89%)	4 / 111 (3.60%)	
occurrences (all)	20	4	
Pain in jaw	Additional description: Pain in jaw		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal disorder	Additional description: Musculoskeletal disorder		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	15 / 107 (14.02%)	4 / 111 (3.60%)	
occurrences (all)	17	4	
Neck pain	Additional description: Neck pain		
subjects affected / exposed	3 / 107 (2.80%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Tendon disorder	Additional description: Tendon disorder		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Scoliosis	Additional description: Scoliosis		

subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Torticollis	Additional description: Torticollis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	4 / 107 (3.74%)	1 / 111 (0.90%)	
occurrences (all)	4	1	
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Ear infection	Additional description: Ear infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Fungal sepsis	Additional description: Fungal sepsis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Infection	Additional description: Infection		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	2 / 107 (1.87%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	1 / 107 (0.93%)	3 / 111 (2.70%)	
occurrences (all)	1	3	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	2 / 107 (1.87%)	0 / 111 (0.00%)	
occurrences (all)	2	0	

Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 107 (0.93%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	0 / 107 (0.00%)	4 / 111 (3.60%)	
occurrences (all)	0	4	
Vaginal infection	Additional description: Vaginal infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	3 / 107 (2.80%)	1 / 111 (0.90%)	
occurrences (all)	5	1	
Tracheitis	Additional description: Tracheitis		
subjects affected / exposed	0 / 107 (0.00%)	2 / 111 (1.80%)	
occurrences (all)	0	2	
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Tonsillitis	Additional description: Tonsillitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection	Additional description: Vulvovaginal mycotic infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection	Additional description: Viral upper respiratory tract infection		
subjects affected / exposed	0 / 107 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Viral infection	Additional description: Viral infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2013	Removal of exclusion criterion No. 25, clarification/modification of eligibility criteria, change of service provider for drug management, addition of procedures for reporting serious adverse events related to pregnancy, addition of investigation centers. Addition of German coordinator, update of study schedule, correction of typographical errors, modification of contact details
22 November 2013	New participating centers / Change of IP Appendix C of the protocol: clarification of histology
18 June 2014	MS1 (Austria) Participation of Germany, Change in eligibility criteria Details on the declaration of SAEs for pregnancies
16 September 2015	Change in the person responsible for secondary packaging, labeling, and distribution of the product
08 October 2015	Addition of cohort E (change in the number of patients to be included, change in selection criteria, extension of the study duration), modification of liver monitoring procedures and treatment adjustments to be adopted in the event of liver toxicity, update of the study schedule, modifications to paragraph 8.8 "Dose reductions and treatment delay" following the update of the SPCs, update of the section on interactions with other medicinal products Update of the contact details of the persons involved in the study at the sponsor's site
23 May 2016	Update of the list of participating centers
04 October 2016	- Modification of a non-inclusion criterion: "More than 3 to 4 lines of systemic treatment for metastatic sarcoma." - Addition of a stratification criterion in cohort E: "Number of lines of systemic treatment for metastatic sarcoma: 0 to 3 lines versus 4 lines." - 24-month extension and update of protocol signatories
16 December 2016	MS2 (Austria) Addition of cohort E (change in the number of patients to be included, change in selection criteria, extension of the study duration), modification of liver monitoring procedures and treatment djustments to be adopted in the event of liver toxicity, update of the study schedule, modifications to paragraph 8.8 "Dose reductions and treatment delay" following the update of the SPCs, update of the section on interactions with other medicinal products. Change in protocol signatories, change in the sponsor team, update to the study schedule
28 April 2017	- Temporary halt to recruitment (problem with supply of treatment in the study) - Update of the list of participating centers
19 September 2017	- Recruitment resumes as of 09/19/17 - Update of the list of participating centers

20 October 2017	- BI update (version 12) + update with BI v 9-10-11 + BI update (version 13) following the ANSM NR Following the BI update (versions 12 and 13): changes to expected adverse events and actions to be taken in the event of infection - Update of the list of participating centers - modification of NICE
12 March 2019	RGPD compliance
04 November 2019	- BI update (versions 14 and 15) - Update of the list of participating centers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 April 2017	Temporary halt to recruitment (problem with supply of treatment in the study)	19 September 2017

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27751846

http://www.ncbi.nlm.nih.gov/pubmed/29902612

http://www.ncbi.nlm.nih.gov/pubmed/31918233

http://www.ncbi.nlm.nih.gov/pubmed/28295221

http://www.ncbi.nlm.nih.gov/pubmed/29722789

http://www.ncbi.nlm.nih.gov/pubmed/33322802