Clinical trial results:
Efficacy of regorafenib as maintenance therapy in non-adipocytic soft tissue sarcoma having received first-line doxorubicin-based chemotherapy

Summary

EudraCT number	2018-001574-22
Trial protocol	FR
Global end of trial date	26 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	EREMISS-1801

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03793361
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Oscar Lambret
Sponsor organisation address	3 rue Frédéric Combemale – BP307, Lille, France, 59020
Public contact	Sponsor unit, Centre Oscar lambret, +33 03 20 29 59 18, promotion@o-lambret.fr
Scientific contact	Sponsor unit, Centre Oscar lambret, +33 03 20 29 59 18, 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	26 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2024
Global end of trial reached?	Yes
Global end of trial date	26 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective of the trial is to assess the efficacy, in terms of PFS, of regorafenib compared to placebo as maintenance therapy in metastatic soft-tissue, non-adipocytic sarcomas experiencing stable disease or partial tumor response after 6 cycles of doxorubicin-based chemotherapy as 1st line chemotherapy

Protection of trial subjects:

First IDMC (23/03/2021)
=> No major safety concerns. Expected AEs with regorafenib, to be further investigated during next IDMC (limited number of patients, 15). IDMC members advice to avoid waivers on inclusion criteria especially related to expected AEs.

Second IDMC (02/04/2024)
=> The IDMC has considered the present data and agrees with the conclusions of the study team that available data are sufficient to conclude without the need to restart recruitment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2019
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	France: 127
Worldwide total number of subjects	127
EEA total number of subjects	127

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)	82
From 65 to 84 years	43
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Overall, 127 patients from 17 centres were included between 16/05/2019 and 28/11/2022: Placebo, N=62; Regorafenib, N=65.
In the regorafenib group, 1 patient was excluded from all analyses, because the pathological review corrected the diagnosis to melanoma, leading to an early study withdrawal. => Study population: Placebo N=62 Regorafenib N=64

Pre-assignment

Screening details:

134 patients screened but only 127 patients included in the study.

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 of the independent review committee 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 confirmed by central review and need to know the treatment received to continue medical care, or for any reason justified by the investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo arm

Arm description:

Placebo (3 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	Regorafenib arm

Arm description:

Regorafenib (120 mg, 3 tablets) once daily, 3 weeks on / 1 week off plus Best Supportive Care (BSC)

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 (120 mg, 3 tablets) once daily, 3 weeks on / 1 week off plus Best Supportive Care (BSC)

Number of subjects in period 1[1]	Placebo arm	Regorafenib arm
Started	62	64
Completed	62	64

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In the regorafenib group, one patient was excluded because the pathological review corrected the diagnosis to melanoma, leading to an early study withdrawal. This patient has been excluded from all analyses, leading to a study population of 126 patients

Baseline characteristics

Reporting groups	
Reporting group title	Placebo arm
Reporting group description:	
Placebo (3 tablets) once daily, 3 weeks on / 1 week off plus Best Supportive Care	
Reporting group title	Regorafenib arm
Reporting group description:	
Regorafenib (120 mg, 3 tablets) once daily, 3 weeks on / 1 week off plus Best Supportive Care (BSC)	

Reporting group values	Placebo arm	Regorafenib arm	Total
Number of subjects	62	64	126
Age categorical			
Age (Years)			
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)	36	46	82
From 65-84 years	25	18	43
85 years and over	1	0	1
Age continuous			
Units: years			
median	61.5	55.5	
full range (min-max)	22 to 85	17 to 77	-
Gender categorical			
Units: Subjects			
Female	33	36	69
Male	29	28	57
Histological subtype			
Histological subtype			
Units: Subjects			
Leiomyosarcoma	37	37	74
Synovial-sarcoma	2	4	6
Other sarcoma	23	23	46
Disease staging at study entry			
Disease staging at study entry			
Units: Subjects			
Locally advanced without metastases	8	2	10
Metastatic disease only	20	22	42
Locally advanced with metastases	34	40	74
Metastases at study entry			
Metastases at study entry			
Units: Subjects			

No	8	2	10
Yes	54	62	116

Time from end doxorubicin to inclusion			
Time from end doxorubicin to inclusion			
Units: days			
median	38	39.5	
full range (min-max)	15 to 54	20 to 56	-

End points

End points reporting groups

Reporting group title	Placebo arm
Reporting group description:	
Placebo (3 tablets) once daily, 3 weeks on / 1 week off plus Best Supportive Care	
Reporting group title	Regorafenib arm
Reporting group description:	
Regorafenib (120 mg, 3 tablets) once daily, 3 weeks on / 1 week off plus Best Supportive Care (BSC)	

Primary: Progression free survival (central review)

End point title	Progression free survival (central review)
End point description:	
Progression-free survival (PFS), defined as the time between randomisation and first disease progression, based on central radiological review using RECIST 1.1 criteria, or death from any cause. For this estimate, we have censored the observation at the date of last tumour evaluation that was reviewed before start of another anticancer treatment if any, or at the date of last reviewed evaluation if the patient was alive at last follow-up with a stable disease according to central review. In each group, the PFS curve was estimated using the Kaplan-Meier method.	
End point type	Primary
End point timeframe:	
Tumour evaluation was planned every 8 weeks during the first 6 cycles and then every 3 months. Patients were followed-up until the end of the study, planned at least 8 months after last patient recruitment. All radiological imaging were centrally reviewed	

End point values	Placebo arm	Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60[1]		
Units: Survival estimate (%)				
number (confidence interval 95%)				
PFS at 6 months (IC95%)	14.6 (7.0 to 24.9)	49.5 (36.0 to 61.7)		
PFS at 12 months (IC95%)	7.3 (2.4 to 16.0)	14.7 (6.7 to 25.6)		
PFS at 24 months (IC95%)	2.7 (0.3 to 11.0)	2.8 (0.3 to 11.8)		

Notes:

[1] - In the Rego arm, exclusion of 4 patients for whom imaging was not available for central radio review

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 treatment effect (regorafenib versus placebo) after testing the proportional hazards assumption, using the scaled Schoenfeld residuals method	
Comparison groups	Regorafenib arm v Placebo arm

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.78

Notes:

[2] - Effect of treatment (Regorafenib versus placebo)
Cox model: adjusted HR (IC95%)
HR adjusted on minimisation factors: histological subtypes (leiomyosarcoma versus synovial sarcoma versus other histological subtype), response to doxorubicin-based chemotherapy (partial response versus stable disease) and centres (after pooling centres with less than 8 patients). The p-value of the test for proportional hazards assumption (based on Schoenfeld residuals) is not significant p=0.09.

Statistical analysis title	Progression free survival - not adjusted HR

Statistical analysis description:

Effect of treatment (Regorafenib versus placebo)

Comparison groups	Placebo arm v Regorafenib arm
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [3]
Method	Regression, Cox
Parameter estimate	Not applicable

Notes:

[3] - The HR was not estimated in the Cox model because the assumption of proportional hazards was violated (Schoenfeld residuals test, p-value=0.01)
P-value of the logrank test, p-value = 0.002

Statistical analysis title	Progression free survival - RMSTD

Statistical analysis description:

Effect of treatment (Regorafenib versus placebo)

Comparison groups	Placebo arm v Regorafenib arm
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.006 [5]
Method	restricted mean survival time difference
Parameter estimate	Mean difference (net)
Point estimate	2.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	4.82

Notes:

[4] - The mean absolute gain in survival times (PFS and OS, respectively) was estimated and tested using the rmstd method (restricted mean survival time difference, as published by Royston and Parmar in 2011) which remains valid if the proportional hazard assumption appears violated or questionable.

[5] - The curve has been truncated at the maximum time observed, i.e. 26 months.

Secondary: Overall survival

End point title	Overall survival

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.

End point values	Placebo arm	Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: Survival estimate (%)				
number (confidence interval 95%)				
OS at 6 months (IC95%)	87.1 (75.9 to 93.3)	87.5 (76.6 to 93.5)		
OS at 12 months (IC95%)	69.4 (56.3 to 79.2)	70.3 (57.5 to 79.9)		
OS at 24 months (IC95%)	41.4 (28.3 to 53.9)	53.1 (39.3 to 65.0)		

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	Regorafenib arm v Placebo arm
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.28
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.22

Notes:

[6] - Effect of treatment (Regorafenib versus placebo)
Cox model: adjusted HR (IC95%)
HR adjusted on minimisation factors: histological subtypes (leiomyosarcoma versus synovial sarcoma versus other histological subtype), response to doxorubicin-based chemotherapy (partial response versus stable disease) and centres (after pooling centres with less than 8 patients). The p-value of the test for proportional hazards assumption (based on Schoenfeld residuals) is not significant p=0.09.

Statistical analysis title	Overall survival - not adjusted HR

Statistical analysis description:

Effect of treatment (Regorafenib versus placebo)

Comparison groups	Regorafenib arm v Placebo arm
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.3
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.23

Notes:

[7] - The p-value of the test for proportional hazards assumption (based on Schoenfeld residuals) is not significant p=0.97.

Statistical analysis title	Overall survival - RMSTD

Statistical analysis description:

Effect of treatment (Regorafenib versus placebo)

Comparison groups	Regorafenib arm v Placebo arm
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.32 [9]
Method	restricted mean survival time difference
Parameter estimate	Mean difference (net)
Point estimate	2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	7.36

Notes:

[8] - The mean absolute gain in survival times (PFS and OS, respectively) was estimated and tested using the rmstd method (restricted mean survival time difference, as published by Royston and Parmar in 2011) which remains valid if the proportional hazard assumption appears violated or questionable
[9] - The curve has been truncated at the maximum time observed, i.e. 41 months

Secondary: Cumulative incidence of next systemic treatment.

End point title	Cumulative incidence of next systemic treatment.

End point description:

The cumulative incidence of next systemic treatment (NST) has been estimated from the time to start a subsequent line of systemic anticancer therapy, considering death as a competing event.

In each group, the cumulative incidence curve has been estimated using the Kalbfleish and Prentice method to consider competing event.
Fine and Gray models were used to estimate the subdistribution HR (sub-HR) associated with treatment effect.

End point type	Secondary

End point timeframe:

Cumulative incidence of next systemic treatment

End point values	Placebo arm	Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: Cumulative incidence (%)				
number (confidence interval 95%)				
Cumulative incidence at 6 months (95%CI)	54.8 (41.7 to 66.2)	29.7 (19.1 to 41.1)		
Cumulative incidence at 12 months (95%CI)	80.7 (68.4 to 88.5)	59.4 (46.4 to 70.2)		
Cumulative incidence at 24 months (95%CI)	87.1 (75.9 to 93.3)	79.0 (66.5 to 87.3)		

Statistical analyses

Statistical analysis title	Adjusted subdistribution hazard ratio (sub-HR)
Comparison groups	Regorafenib arm v Placebo arm
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.003 [11]
Method	Fine & Gray model
Parameter estimate	Sub-HR
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.82

Notes:

[10] - Sub-HR adjusted on minimisation factors: histological subtypes (leiomyosarcoma versus synovial sarcoma versus other histological subtype), response to doxorubicin-based chemotherapy (partial response versus stable disease) and centres (after pooling centres with less than 8 patients).
[11] - Adjusted on minimisation factors: histological subtypes (leiomyosarcoma versus synovial sarcoma versus other histological subtype), response to doxorubicin-based chemotherapy (partial response versus stable disease) and centres

Statistical analysis title	Not adjusted subdistribution hazard ratio (sub-HR)
Comparison groups	Regorafenib arm v Placebo arm

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.008
Method	Fine & Gray model
Parameter estimate	Sub-HR
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.87

Notes:

[12] - Sub-HR: Subdistribution Hazard Ratio, estimated in a Fine and Gray model considering deaths without start of another systemic treatment as competing events

Post-hoc: Progression free survival (according to the local investigator)

End point title	Progression free survival (according to the local investigator)

End point description:

Progression-free survival (PFS), defined as the time between randomisation and first disease progression, assessed by the local investigator using RECIST 1.1 criteria, or death from any cause. In each group, the PFS curve was estimated using the Kaplan-Meier method

End point type	Post-hoc

End point timeframe:

Tumour evaluation was planned every 8 weeks during the first six cycles and then every 3 months. Patients were followed-up until the end of the study, planned at least 8 months after last patient recruitment.

End point values	Placebo arm	Regorafenib arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: Survival estimate (%)				
number (confidence interval 95%)				
PFS at 6 months (IC95%)	27.4 (17.0 to 38.8)	51.6 (38.8 to 63.0)		
PFS at 12 months (IC95%)	9.7 (3.9 to 18.5)	17.2 (9.2 to 27.3)		
PFS at 24 months (IC95%)	6.5 (2.1 to 14.4)	2.4 (0.7 to 10.8)		

Statistical analyses

Statistical analysis title	PFS according to the site - adjusted HR

Statistical analysis description:

Effect of treatment (Regorafenib versus placebo)

Comparison groups	Regorafenib arm v Placebo arm

Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	other[13]
P-value	= 0.005
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.85

Notes:

[13] - Cox model: adjusted HR (IC95%)
HR adjusted on minimisation factors: histological subtypes (leiomyosarcoma versus synovial sarcoma versus other histological subtype), response to doxorubicin-based chemotherapy (partial response versus stable disease) and centres (after pooling centres with less than 8 patients). The p-value of the test for proportional hazards assumption (based on Schoenfeld residuals) is not significant p=0.32.

Statistical analysis title	PFS according to the site - not adjusted HR
Statistical analysis description:	
Effect of treatment (Regorafenib versus placebo)	
Comparison groups	Regorafenib arm v Placebo arm
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.03 [14]
Method	Regression, Cox
Parameter estimate	Not applicable

Notes:

[14] - The HR was not estimated in the Cox model because the assumption of proportional hazards was violated (Schoenfeld residuals test, p-value=0.03)
P-value of the logrank test, p-value = 0.03

Statistical analysis title	PFS according to the site - RMSTD
Statistical analysis description:	
Effect of treatment (Regorafenib versus placebo)	
Comparison groups	Regorafenib arm v Placebo arm
Number of subjects included in analysis	126
Analysis specification	Post-hoc
Analysis type	other[15]
P-value	= 0.051 [16]
Method	restricted mean survival time difference
Parameter estimate	Mean difference (net)
Point estimate	2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	4.58

Notes:

[15] - The mean absolute gain in survival times (PFS and OS, respectively) was estimated and tested using the rmstd method (restricted mean survival time difference, as published by Royston and Parmar in 2011) which remains valid if the proportional hazard assumption appears violated or questionable.

[16] - The curve has been truncated at the maximum time observed, i.e. 32 months

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. We did not collect adverse events (AEs) unequivocally related to sarcoma progression.

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo arm
Reporting group description: -	
Reporting group title	Regorafenib arm

Reporting group description: -

Serious adverse events	Placebo arm	Regorafenib arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)	15 / 64 (23.44%)	
number of deaths (all causes)	41	39	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage	Additional description: Haemorrhage		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 62 (1.61%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome	Additional description: Acute coronary syndrome		

subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure	Additional description: Heart failure		
subjects affected / exposed	1 / 62 (1.61%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased	Additional description: Ejection fraction decreased		
subjects affected / exposed	0 / 62 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever	Additional description: Fever		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash		
subjects affected / exposed	0 / 62 (0.00%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular	Additional description: Rash maculo-papular		

subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: Infection		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo arm	Regorafenib arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 62 (77.42%)	61 / 64 (95.31%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain	Additional description: Tumour pain		
subjects affected / exposed	2 / 62 (3.23%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Vascular disorders			
Haemorrhage	Additional description: Haemorrhage		
subjects affected / exposed	2 / 62 (3.23%)	4 / 64 (6.25%)	
occurrences (all)	2	5	
Hot flashes	Additional description: Hot flashes		
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 62 (1.61%)	13 / 64 (20.31%)	
occurrences (all)	3	20	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	2 / 62 (3.23%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Anorexia	Additional description: Anorexia		
subjects affected / exposed	3 / 62 (4.84%)	15 / 64 (23.44%)	
occurrences (all)	3	21	
Face oedema	Additional description: Face oedema		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	21 / 62 (33.87%)	40 / 64 (62.50%)	
occurrences (all)	30	68	
Fever	Additional description: Fever		
subjects affected / exposed	2 / 62 (3.23%)	6 / 64 (9.38%)	
occurrences (all)	2	7	
General disorders and administration site conditions - other	Additional description: General disorders and administration site conditions - other		
subjects affected / exposed	1 / 62 (1.61%)	6 / 64 (9.38%)	
occurrences (all)	1	6	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Oedema	Additional description: Oedema		
subjects affected / exposed	2 / 62 (3.23%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Pain	Additional description: Pain		
subjects affected / exposed	13 / 62 (20.97%)	19 / 64 (29.69%)	
occurrences (all)	18	25	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	3 / 62 (4.84%)	13 / 64 (20.31%)	
occurrences (all)	4	15	
Reproductive system and breast disorders			
Vaginal discharge	Additional description: Vaginal discharge		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	2 / 62 (3.23%)	4 / 64 (6.25%)	
occurrences (all)	2	4	

Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 62 (3.23%)	5 / 64 (7.81%)	
occurrences (all)	6	6	
Hiccups	Additional description: Hiccups		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Voice alteration	Additional description: Voice alteration		
subjects affected / exposed	2 / 62 (3.23%)	12 / 64 (18.75%)	
occurrences (all)	2	17	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	2 / 62 (3.23%)	2 / 64 (3.13%)	
occurrences (all)	2	3	
Depression	Additional description: Depression		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	3 / 62 (4.84%)	2 / 64 (3.13%)	
occurrences (all)	3	2	
Psychiatric disorders - other	Additional description: Psychiatric disorders - other		
subjects affected / exposed	2 / 62 (3.23%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Investigations			
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	2 / 62 (3.23%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	2 / 62 (3.23%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Hematuria	Additional description: Hematuria		

subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	0 / 62 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridemia	Additional description: Hypertriglyceridemia		
subjects affected / exposed	0 / 62 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hypoalbuminemia	Additional description: Hypoalbuminemia		
subjects affected / exposed	2 / 62 (3.23%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Hypocalcemia	Additional description: Hypocalcemia		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia	Additional description: Hypoglycaemia		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 62 (1.61%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	0 / 62 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Investigations - other	Additional description: Investigations - other		

subjects affected / exposed	4 / 62 (6.45%)	4 / 64 (6.25%)	
occurrences (all)	6	5	
Lipase increased	Additional description: Lipase increased		
subjects affected / exposed	0 / 62 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	2 / 62 (3.23%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Reduced creatinine clearance	Additional description: Reduced creatinine clearance		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	3 / 62 (4.84%)	15 / 64 (23.44%)	
occurrences (all)	7	33	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications - other	Additional description: Injury, poisoning and procedural complications - other		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Wound	Additional description: Wound		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cardiac disorders			
Conduction disorder	Additional description: Conduction disorder		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cardiac disorders - other	Additional description: Cardiac disorders - other		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	0 / 62 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Ejection fraction decreased	Additional description: Ejection fraction decreased		

subjects affected / exposed	0 / 62 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Heart failure	Additional description: Heart failure		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pericarditis	Additional description: Pericarditis		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Cognitive disturbance	Additional description: Cognitive disturbance		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	2 / 62 (3.23%)	6 / 64 (9.38%)	
occurrences (all)	2	6	
Headache	Additional description: Headache		
subjects affected / exposed	2 / 62 (3.23%)	8 / 64 (12.50%)	
occurrences (all)	9	8	
Peripheral neuropathy	Additional description: Peripheral neuropathy		
subjects affected / exposed	1 / 62 (1.61%)	3 / 64 (4.69%)	
occurrences (all)	3	5	
Somnolence	Additional description: Somnolence		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	3 / 62 (4.84%)	2 / 64 (3.13%)	
occurrences (all)	3	2	
Blood disorder - other	Additional description: Blood disorder - other		

subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	0 / 62 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	5	
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	0 / 62 (0.00%)	7 / 64 (10.94%)	
occurrences (all)	0	9	
Ear and labyrinth disorders			
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	0 / 62 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	5	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Dry eye	Additional description: Dry eye		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Eye disorders - other	Additional description: Eye disorders - other		
subjects affected / exposed	0 / 62 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	3 / 62 (4.84%)	6 / 64 (9.38%)	
occurrences (all)	8	9	
Anal fissure	Additional description: Anal fissure		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Constipation	Additional description: Constipation		
subjects affected / exposed	5 / 62 (8.06%)	13 / 64 (20.31%)	
occurrences (all)	7	19	
Diarrhoea	Additional description: Diarrhoea		

subjects affected / exposed	13 / 62 (20.97%)	24 / 64 (37.50%)	
occurrences (all)	17	33	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	4 / 62 (6.45%)	10 / 64 (15.63%)	
occurrences (all)	4	11	
Cheilitis	Additional description: Cheilitis		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders - other	Additional description: Gastrointestinal disorders - other		
subjects affected / exposed	2 / 62 (3.23%)	1 / 64 (1.56%)	
occurrences (all)	3	2	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 62 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	3	
Mucositis oral	Additional description: Mucositis oral		
subjects affected / exposed	5 / 62 (8.06%)	26 / 64 (40.63%)	
occurrences (all)	5	38	
Nausea	Additional description: Nausea		
subjects affected / exposed	10 / 62 (16.13%)	8 / 64 (12.50%)	
occurrences (all)	12	11	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	4 / 62 (6.45%)	4 / 64 (6.25%)	
occurrences (all)	4	5	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	6 / 62 (9.68%)	4 / 64 (6.25%)	
occurrences (all)	7	4	
Eczema	Additional description: Eczema		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hyperkeratosis	Additional description: Hyperkeratosis		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	

Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	4 / 62 (6.45%)	1 / 64 (1.56%)	
occurrences (all)	5	1	
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	7 / 62 (11.29%)	30 / 64 (46.88%)	
occurrences (all)	9	48	
Rash	Additional description: Rash		
subjects affected / exposed	1 / 62 (1.61%)	12 / 64 (18.75%)	
occurrences (all)	1	19	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Urinary frequency	Additional description: Urinary frequency		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	0 / 62 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	4	
Thyroid disorder	Additional description: Thyroid disorder		
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders - other	Additional description: Musculoskeletal and connective tissue disorders - other		

subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	4 / 62 (6.45%)	18 / 64 (28.13%)	
occurrences (all)	4	24	
Osteonecrosis of jaw	Additional description: Osteonecrosis of jaw		
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Infections and infestations			
Infection	Additional description: Infection		
subjects affected / exposed	2 / 62 (3.23%)	8 / 64 (12.50%)	
occurrences (all)	2	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2018	Compliance with Regulation (EU) No. 2016/79 (RGPD) and the CNIL reference methodology, MR001 of May 3, 2018, and clarification of the statistical methodology, data studied, and bibliography. Addition of a clarification for the declaration of SAEs.
31 December 2018	The patient diary (monthly and quarterly): containing useful information on taking the treatment, the study schedule, and a table for recording daily doses of the treatment. The BP monitoring sheet: A sheet for recording hypertension measurements taken at home by the patient, a nurse, or their treating physician. Update of the list of investigators
04 February 2019	Update on the BI of regorafenib and impact on the protocol
16 October 2019	Update of selection criteria , TTT blinding procedures, update of schedule and update of CP list + update of BI
24 March 2020	MSI - recruitment suspended due to the health situation
14 April 2020	MUS for the possibility of sending TTT to the patient's home, remote consultations,
25 May 2020	MSI - resumption of recruitment
09 October 2020	Modification of sample size determination with extension of the recruitment period, update of the study schedule, list of CP and BI
22 February 2021	Protocol modification: clarification of an inclusion criterion, treatment administration procedures, procedures for lifting the blind, addition of the COVID-19 vaccine to the list of authorized treatments + synopsis + update of the list of CP + BI + NICE (clarification on treatment administration and duration of contraception after stopping treatment)
03 February 2022	Extension of the recruitment period by 6 months following a 2-month suspension of recruitment due to a problem with the supply of TTT and update of the CP list.
28 September 2022	Extension of the recruitment period by 5 months + Update of the CP list + Modification of NICE following BI update + RGPD info
17 April 2023	Protocol modification: addition of exploratory objective, clarification of centralized review procedures List of CP: update
04 September 2023	Update of the CP list => modification of the CP list Update of the Regorafenib IB => modification of the protocol: Rare AE

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/40210087