Clinical trial results:
Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock. A Randomized, Double-blind, Placebo Controlled Dose Selection Study; The Astonish study

Summary

EudraCT number	2018-004827-36
Trial protocol	BE FR ES DK FI IE
Global end of trial date	09 May 2022

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information

Trial identification

Sponsor protocol code	MOT-C-203

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	INOTREM S.A.
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2022
Global end of trial reached?	Yes
Global end of trial date	09 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of two doses of nangibotide on organ dysfunction (Sequential Organ Failure Assessment (SOFA score) in patients with septic shock in relation to their soluble TREM-1 (sTREM-1) plasma levels (patients with high sTREM-1 levels at baseline and all patients)

Protection of trial subjects:

This study included vulnerable patient populations. Patients with septic shock were unconscious or lack capacity to provide informed consent at the time of inclusion into the clinical trial. An emergency informed consent procedure would be applied according to applicable regulations and according to the approval of the respective ethics committee (EC) or institutional review board (IRB).
The incidence of septic shock increased with age, therefore elderly patients aged 65 years and above (as defined in ICH E7) represented a significant portion of patients with septic shock. Therefore, patients up to age of 85 years would be enrolled into the study.

Background therapy:

In addition to study drug, patients were received standard of care, which included fluid therapy, vasopressor treatment, IMV and sedation.

Evidence for comparator:

Matching placebo

Actual start date of recruitment	28 November 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Belgium: 117
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 29
Country: Number of subjects enrolled	France: 171
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	361
EEA total number of subjects	358

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)	106
From 65 to 84 years	255
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from 14/11/2019 to 11/04/2022 in hospital ICU.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	361
Number of subjects completed	355

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious fatal: 3
Reason: Number of subjects	Withdrawal of consent: 1
Reason: Number of subjects	Other: 2

Period 1

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

Blinding implementation details:

The study was conducted in a double-blind fashion, whereby patients and clinical study site staff were blinded to study drug assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Control group

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Patients would be randomized to one of three treatment arms. Patients would then either receive a 6.66 mg/kg/h loading dose (LD) of nangibotide over 15 minutes followed by a continuous intravenous (i.v.) infusion of nangibotide 0.3 mg/kg/h or a 20 mg/kg/h LD of nangibotide over 15 minutes followed by a continuous i.v. infusion of nangibotide 1.0 mg/kg/h or a matching placebo.
Patients would be treated for at least 3 days (72 ±2 hours) with study drug. After the first 3 days of treatment, patients still requiring vasopressor would be treated until 24 (±2) hours after vasopressor withdrawal with a maximum treatment duration of 5 days (120 ±2 hours).

Arm title	Nangibotide low dose

Arm description:

0.3 mg/kg/h

Arm type	Experimental
Investigational medicinal product name	Nangibotide
Investigational medicinal product code	LR12
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Patients would be randomized to one of three treatment arms. Patients would then either receive a 6.66 mg/kg/h loading dose (LD) of nangibotide over 15 minutes followed by a continuous intravenous (i.v.) infusion of nangibotide 0.3 mg/kg/h or a 20 mg/kg/h LD of nangibotide over 15 minutes followed by a continuous i.v. infusion of nangibotide 1.0 mg/kg/h or a matching placebo.
Patients would be treated for at least 3 days (72 ±2 hours) with study drug. After the first 3 days of treatment, patients still requiring vasopressor would be treated until 24 (±2) hours after vasopressor withdrawal with a maximum treatment duration of 5 days (120 ±2 hours).

Arm title	Nangibotide high dose

Arm description:

1 mg/kg/h

Arm type	Experimental
Investigational medicinal product name	Nangibotide
Investigational medicinal product code	LR12
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Patients would be randomized to one of three treatment arms. Patients would then either receive a 6.66 mg/kg/h loading dose (LD) of nangibotide over 15 minutes followed by a continuous intravenous (i.v.) infusion of nangibotide 0.3 mg/kg/h or a 20 mg/kg/h LD of nangibotide over 15 minutes followed by a continuous i.v. infusion of nangibotide 1.0 mg/kg/h or a matching placebo.
Patients would be treated for at least 3 days (72 ±2 hours) with study drug. After the first 3 days of treatment, patients still requiring vasopressor would be treated until 24 (±2) hours after vasopressor withdrawal with a maximum treatment duration of 5 days (120 ±2 hours).

Number of subjects in period 1[1]	Placebo	Nangibotide low dose	Nangibotide high dose
Started	116	118	121
Completed	84	72	85
Not completed	32	46	36
Adverse event, serious fatal	28	35	28
Adverse event, non-fatal	1	3	1
Other	3	7	5
Withdrawal of consent	-	1	2

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: 361 subjects were randomized in the study. 355 subjects received at least one dose of study drug and were analyzed.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Control group	
Reporting group title	Nangibotide low dose
Reporting group description: 0.3 mg/kg/h	
Reporting group title	Nangibotide high dose
Reporting group description: 1 mg/kg/h	

Reporting group values	Placebo	Nangibotide low dose	Nangibotide high dose
Number of subjects	116	118	121
Age categorical Units: Subjects			
Adults (18-64 years)	36	40	29
From 65-84 years	80	78	92
Age continuous Units: years			
arithmetic mean	66.7	67.4	69.2
standard deviation	± 12.94	± 12.68	± 10.69
Gender categorical Units: Subjects			
Female	37	41	78
Male	79	77	43
sTREM-1 Units: Subjects			
Subjects with elevated sTREM-1 (≥400 pg/mL)	75	90	88
Subjects with not elevated sTREM-1 (<400 pg/mL)	41	28	33
sTREM-1 Units: pg/mL			
arithmetic mean	663.81	768.69	716.20
standard deviation	± 425.87	± 478.88	± 460.96

Reporting group values	Total		
Number of subjects	355		
Age categorical Units: Subjects			
Adults (18-64 years)	105		
From 65-84 years	250		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	156		
Male	199		
sTREM-1 Units: Subjects			
Subjects with elevated sTREM-1 (≥400 pg/mL)	253		
Subjects with not elevated sTREM-1 (<400 pg/mL)	102		
sTREM-1 Units: pg/mL arithmetic mean standard deviation	- -		

Subject analysis sets

Subject analysis set title	mItT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent to treat analysis set (Patients in ITT set who received treatment)

Reporting group values	mItT		
Number of subjects	355		
Age categorical Units: Subjects			
Adults (18-64 years)	105		
From 65-84 years	250		
Age continuous Units: years arithmetic mean standard deviation	 67.8 ± 12.14		
Gender categorical Units: Subjects			
Female	121		
Male	234		
sTREM-1 Units: Subjects			
Subjects with elevated sTREM-1 (≥400 pg/mL)	253		
Subjects with not elevated sTREM-1 (<400 pg/mL)	102		
sTREM-1 Units: pg/mL arithmetic mean standard deviation	 716.53 ± 456.687		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Control group	
Reporting group title	Nangibotide low dose
Reporting group description: 0.3 mg/kg/h	
Reporting group title	Nangibotide high dose
Reporting group description: 1 mg/kg/h	
Subject analysis set title	mItT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intent to treat analysis set (Patients in ITT set who received treatment)	

Primary: Delta Sofa score

End point title	Delta Sofa score
End point description: Change of total SOFA score (improvement of organ dysfunction) from baseline to day 5 (in the subgroup defined by patients with elevated sTREM-1 baseline levels and in the overall population)	
End point type	Primary
End point timeframe: From baseline to day 5	

End point values	Placebo	Nangibotide low dose	Nangibotide high dose	mItT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	116	118	121	355
Units: units				
least squares mean (standard error)	-2.05 (± 0.468)	-2.26 (± 0.463)	-3.11 (± 0.460)	-2.68 (± 0.326)

Statistical analyses

Statistical analysis title	Analysis of the Primary Endpoint Change Low dose

Statistical analysis description:

Low Dose vs Placebo
Analysis of the Primary Endpoint Change from Baseline in Total SOFA Score to Day 5 With Last Observation Carried Forward (LOCF) and Penalty Points (4 points) for Patient Deaths, Analysis of Covariance (ANCOVA) by Visit, Overall and by sTREM-1 Level Subgroup mITT Set

Comparison groups	Placebo v Nangibotide low dose

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.38 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.658

Notes:

[1] - This study aims at:
• Assessing the safety and tolerability of two doses of nangibotide
• Assessing the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints
• Determining the best cut-off for baseline sTREM1 as a predictive biomarker.
[2] - One-sided p-value of difference from Placebo is reported.

Statistical analysis title	Analysis of the Primary Endpoint Change High dose

Statistical analysis description:

High Dose vs Placebo
Analysis of the Primary Endpoint Change from Baseline in Total SOFA Score to Day 5 With Last Observation Carried Forward (LOCF) and Penalty Points (4 points) for Patient Deaths, Analysis of Covariance (ANCOVA) by Visit, Overall and by sTREM-1 Level Subgroup mITT Set

Comparison groups	Placebo v Nangibotide high dose
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.054 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	2.35
Variability estimate	Standard error of the mean
Dispersion value	0.658

Notes:

[3] - This study aims at:
• Assessing the safety and tolerability of two doses of nangibotide
• Assessing the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints
• Determining the best cut-off for baseline sTREM1 as a predictive biomarker.

[4] - One-sided p-value of difference from Placebo is reported.

Secondary: All-Cause Mortality at D5 and D28

End point title	All-Cause Mortality at D5 and D28

End point description:

All-Cause Mortality at day 5 and day 28 (in the subgroup defined by patients with elevated sTREM-1

baseline levels and in the overall population)

End point type	Secondary

End point timeframe:

From baseline to day 28

End point values	Placebo	Nangibotide low dose	Nangibotide high dose	mItT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	116	118	121	355
Units: events				
All-cause mortality on D5	16	21	13	50
All-cause mortality on D28	29	38	30	97

Statistical analyses

Statistical analysis title	Logistic Regression for All-Cause Mortality mITT

Statistical analysis description:

Logistic Regression for All-Cause Mortality mITT Set (Low Dose vs Placebo on D5)
This study aims at:
- Assessing the safety and tolerability of two doses of nangibotide
- Assessing the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints
- Determining the best cut-off for baseline sTREM1 as a predictive biomarker.

Comparison groups	Nangibotide low dose v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.729 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.59

Notes:

[5] - Patients lost to follow-up before Day 5/28 without known survival status on Day 5/28 were not included in the Day 5/28 analyses respectively.
[6] - Odds of dead/alive in Nangibotide versus placebo and one-sided p-value from a logistic regression model with terms for treatment and baseline SOFA score.

Statistical analysis title	Logistic Regression for All-Cause Mortality mITT

Statistical analysis description:

Logistic Regression for All-Cause Mortality mITT Set (Low Dose vs Placebo on D28)
This study aims at:
- Assessing the safety and tolerability of two doses of nangibotide
- Assessing the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints
- Determining the best cut-off for baseline sTREM1 as a predictive biomarker.

Comparison groups	Placebo v Nangibotide low dose

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.856 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.45

Notes:

[7] - Patients lost to follow-up before Day 5/28 without known survival status on Day 5/28 were not included in the Day 5/28 analyses respectively.
[8] - Odds of dead/alive in Nangibotide versus placebo and one-sided p-value from a logistic regression model with terms for treatment and baseline SOFA score.

Statistical analysis title	Logistic Regression for All-Cause Mortality mITT

Statistical analysis description:

Logistic Regression for All-Cause Mortality mITT Set (High Dose vs Placebo on D5)
This study aims at:
- Assessing the safety and tolerability of two doses of nangibotide
- Assessing the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints
- Determining the best cut-off for baseline sTREM1 as a predictive biomarker.

Comparison groups	Placebo v Nangibotide high dose
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.153 [10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.46

Notes:

[9] - Patients lost to follow-up before Day 5/28 without known survival status on Day 5/28 were not included in the Day 5/28 analyses respectively.
[10] - Odds of dead/alive in Nangibotide versus placebo and one-sided p-value from a logistic regression model with terms for treatment and baseline SOFA score.

Statistical analysis title	Logistic Regression for All-Cause Mortality mITT

Statistical analysis description:

Logistic Regression for All-Cause Mortality mITT Set (High Dose vs Placebo on D28)
This study aims at:
- Assessing the safety and tolerability of two doses of nangibotide
- Assessing the efficacy of two doses of nangibotide on the primary and secondary efficacy endpoints
- Determining the best cut-off for baseline sTREM1 as a predictive biomarker.

Comparison groups	Placebo v Nangibotide high dose

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.381 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.66

Notes:

[11] - Patients lost to follow-up before Day 5/28 without known survival status on Day 5/28 were not included in the Day 5/28 analyses respectively.
[12] - Odds of dead/alive in Nangibotide versus placebo and one-sided p-value from a logistic regression model with terms for treatment and baseline SOFA score.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Onset Date occurring from D0 to D28

Adverse event reporting additional description:

Within Safety Set population (n=355). Any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Control group

Reporting group title	Nangibotide low dose

Reporting group description:

0.3 mg/kg/h

Reporting group title	Nangibotide high dose

Reporting group description:

1 mg/kg/h

Serious adverse events	Placebo	Nangibotide low dose	Nangibotide high dose
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 116 (24.14%)	26 / 118 (22.03%)	31 / 121 (25.62%)
number of deaths (all causes)	29	38	30
number of deaths resulting from adverse events	11	10	17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma recurrent			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			

subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastatic neoplasm			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour budding			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	1 / 116 (0.86%)	2 / 118 (1.69%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Pelvic venous thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 116 (0.00%)	2 / 118 (1.69%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Shock haemorrhagic			

subjects affected / exposed	2 / 116 (1.72%)	1 / 118 (0.85%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Subclavian vein thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	6 / 116 (5.17%)	7 / 118 (5.93%)	7 / 121 (5.79%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 6	0 / 7	0 / 7
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bronchoplegia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchospasm			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 116 (1.72%)	0 / 118 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia aspiration			

subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory fatigue			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
Cytomegalovirus test positive			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyperkalaemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fascial rupture			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma necrosis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatic leak			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous haematoma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Ehlers-Danlos syndrome			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac disorders			
Bradyarrhythmia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 116 (0.00%)	2 / 118 (1.69%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cardiac failure			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardio-respiratory arrest			
subjects affected / exposed	1 / 116 (0.86%)	3 / 118 (2.54%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Mitral valve incompetence			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nervous system disorders			
Brain stem syndrome			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	1 / 116 (0.86%)	2 / 118 (1.69%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Nerve degeneration			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolic encephalopathy			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer perforation			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			

subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fistula			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	2 / 116 (1.72%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	1 / 116 (0.86%)	3 / 118 (2.54%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2
Oesophageal fistula			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic fistula			

subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peritonitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal ischaemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal syndrome			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute hepatic failure			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain abscess			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Coronavirus infection			
subjects affected / exposed	2 / 116 (1.72%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infected skin ulcer			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infective aneurysm			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 116 (4.31%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 116 (0.86%)	2 / 118 (1.69%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Septic shock			
subjects affected / exposed	7 / 116 (6.03%)	12 / 118 (10.17%)	3 / 121 (2.48%)
occurrences causally related to treatment / all	0 / 7	0 / 12	0 / 3
deaths causally related to treatment / all	0 / 7	0 / 12	0 / 3
Skin infection			

subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic candida			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombophlebitis septic			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

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

Non-serious adverse events	Placebo	Nangibotide low dose	Nangibotide high dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 116 (94.83%)	113 / 118 (95.76%)	115 / 121 (95.04%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences (all)	12	13	17
Hypotension			
subjects affected / exposed	6 / 116 (5.17%)	5 / 118 (4.24%)	7 / 121 (5.79%)
occurrences (all)	8	6	10
General disorders and administration site conditions			

Multiple organ dysfunction syndrome			
subjects affected / exposed	6 / 116 (5.17%)	7 / 118 (5.93%)	7 / 121 (5.79%)
occurrences (all)	6	7	7
Oedema peripheral			
subjects affected / exposed	2 / 116 (1.72%)	7 / 118 (5.93%)	8 / 121 (6.61%)
occurrences (all)	2	7	8
Pyrexia			
subjects affected / exposed	5 / 116 (4.31%)	7 / 118 (5.93%)	4 / 121 (3.31%)
occurrences (all)	5	7	5
Generalised oedema			
subjects affected / exposed	4 / 116 (3.45%)	2 / 118 (1.69%)	5 / 121 (4.13%)
occurrences (all)	4	2	6
Hyperthermia			
subjects affected / exposed	2 / 116 (1.72%)	2 / 118 (1.69%)	5 / 121 (4.13%)
occurrences (all)	2	2	6
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	8 / 116 (6.90%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences (all)	8	12	11
Acute respiratory distress syndrome			
subjects affected / exposed	8 / 116 (6.90%)	4 / 118 (3.39%)	5 / 121 (4.13%)
occurrences (all)	8	4	5
Respiratory failure			
subjects affected / exposed	4 / 116 (3.45%)	4 / 118 (3.39%)	7 / 121 (5.79%)
occurrences (all)	4	4	7
Pneumothorax			
subjects affected / exposed	4 / 116 (3.45%)	0 / 118 (0.00%)	5 / 121 (4.13%)
occurrences (all)	5	0	5
Psychiatric disorders			
Agitation			
subjects affected / exposed	6 / 116 (5.17%)	5 / 118 (4.24%)	7 / 121 (5.79%)
occurrences (all)	6	6	8
Delirium			
subjects affected / exposed	8 / 116 (6.90%)	4 / 118 (3.39%)	6 / 121 (4.96%)
occurrences (all)	8	4	7
Confusional state			

subjects affected / exposed	5 / 116 (4.31%)	5 / 118 (4.24%)	6 / 121 (4.96%)
occurrences (all)	5	5	6
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 116 (3.45%)	3 / 118 (2.54%)	2 / 121 (1.65%)
occurrences (all)	5	3	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 116 (1.72%)	2 / 118 (1.69%)	2 / 121 (1.65%)
occurrences (all)	22	20	19
Tachycardia			
subjects affected / exposed	4 / 116 (3.45%)	3 / 118 (2.54%)	4 / 121 (3.31%)
occurrences (all)	4	3	4
Bradycardia			
subjects affected / exposed	3 / 116 (2.59%)	3 / 118 (2.54%)	4 / 121 (3.31%)
occurrences (all)	3	3	4
Cardiac arrest			
subjects affected / exposed	1 / 116 (0.86%)	3 / 118 (2.54%)	5 / 121 (4.13%)
occurrences (all)	1	3	6
Nervous system disorders			
Intensive care unit acquired weakness			
subjects affected / exposed	5 / 116 (4.31%)	2 / 118 (1.69%)	6 / 121 (4.96%)
occurrences (all)	5	2	6
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 116 (2.59%)	2 / 118 (1.69%)	2 / 121 (1.65%)
occurrences (all)	36	21	30
Thrombocytopenia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences (all)	14	14	19
Coagulopathy			
subjects affected / exposed	4 / 116 (3.45%)	2 / 118 (1.69%)	4 / 121 (3.31%)
occurrences (all)	4	2	5
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	6 / 116 (5.17%)	1 / 118 (0.85%)	9 / 121 (7.44%)
occurrences (all)	6	10	9
Constipation			
subjects affected / exposed	6 / 116 (5.17%)	3 / 118 (2.54%)	1 / 121 (0.83%)
occurrences (all)	6	3	11
Vomiting			
subjects affected / exposed	2 / 116 (1.72%)	4 / 118 (3.39%)	6 / 121 (4.96%)
occurrences (all)	3	4	8
Ascites			
subjects affected / exposed	4 / 116 (3.45%)	4 / 118 (3.39%)	2 / 121 (1.65%)
occurrences (all)	4	4	2
Nausea			
subjects affected / exposed	2 / 116 (1.72%)	3 / 118 (2.54%)	5 / 121 (4.13%)
occurrences (all)	2	3	5
Intestinal ischaemia			
subjects affected / exposed	1 / 116 (0.86%)	5 / 118 (4.24%)	3 / 121 (2.48%)
occurrences (all)	1	5	3
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	9 / 116 (7.76%)	7 / 118 (5.93%)	7 / 121 (5.79%)
occurrences (all)	9	7	7
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	4 / 116 (3.45%)	6 / 118 (5.08%)	3 / 121 (2.48%)
occurrences (all)	4	7	3
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 116 (7.76%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences (all)	9	13	11
Renal failure			
subjects affected / exposed	2 / 116 (1.72%)	2 / 118 (1.69%)	4 / 121 (3.31%)
occurrences (all)	2	3	4
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences (all)	17	16	11
Septic shock			

subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	6 / 121 (4.96%)
occurrences (all)	13	13	6
Bacteraemia			
subjects affected / exposed	5 / 116 (4.31%)	0 / 118 (0.00%)	5 / 121 (4.13%)
occurrences (all)	5	0	5
Coronavirus infection			
subjects affected / exposed	4 / 116 (3.45%)	2 / 118 (1.69%)	2 / 121 (1.65%)
occurrences (all)	5	2	2
Oral herpes			
subjects affected / exposed	3 / 116 (2.59%)	4 / 118 (3.39%)	2 / 121 (1.65%)
occurrences (all)	3	4	2
Tracheobronchitis			
subjects affected / exposed	4 / 116 (3.45%)	1 / 118 (0.85%)	3 / 121 (2.48%)
occurrences (all)	4	1	4
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 116 (1.72%)	1 / 118 (0.85%)	2 / 121 (1.65%)
occurrences (all)	29	26	29
Hypophosphataemia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 118 (0.85%)	1 / 121 (0.83%)
occurrences (all)	12	18	15
Hypernatraemia			
subjects affected / exposed	1 / 116 (0.86%)	9 / 118 (7.63%)	10 / 121 (8.26%)
occurrences (all)	11	9	10
Hyperglycaemia			
subjects affected / exposed	6 / 116 (5.17%)	8 / 118 (6.78%)	1 / 121 (0.83%)
occurrences (all)	6	10	10
Hyperkalaemia			
subjects affected / exposed	5 / 116 (4.31%)	5 / 118 (4.24%)	8 / 121 (6.61%)
occurrences (all)	5	6	9
Hypoglycaemia			
subjects affected / exposed	3 / 116 (2.59%)	8 / 118 (6.78%)	5 / 121 (4.13%)
occurrences (all)	3	8	6
Hypomagnesaemia			
subjects affected / exposed	6 / 116 (5.17%)	6 / 118 (5.08%)	3 / 121 (2.48%)
occurrences (all)	6	6	3

Hypoalbuminaemia			
subjects affected / exposed	2 / 116 (1.72%)	4 / 118 (3.39%)	7 / 121 (5.79%)
occurrences (all)	2	4	7
Hypocalcaemia			
subjects affected / exposed	3 / 116 (2.59%)	4 / 118 (3.39%)	3 / 121 (2.48%)
occurrences (all)	4	4	3
Hypervolaemia			
subjects affected / exposed	9 / 116 (7.76%)	6 / 118 (5.08%)	10 / 121 (8.26%)
occurrences (all)	9	6	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2019	Amended protocol v2.0: • Addition of an additional interim analysis and DMC review of safety data after 112 (25%) of patients randomized (section 8.5) • Addition of exclusion criteria "history of prosthetic heart valves" and "Prolonged QT syndrome" • Addition of daily ECG measurements until end of study drug infusion • Clarification of section "12.14 Study Drug Infusion and End of Vasopressor Definition", cross-reference with section 10.3 added • Reference to summary of product characteristics added for concomitant medications in sections 10.7 and 11.5 • Clarification of section "9.5 Withdrawal of Patients" and addition of the need for a concomitant medication representing a risk to the patient as criterion for withdrawal • Clarification of adaptive features (section 8.3) regarding DMC and DAC • Addition of paragraphs relating to data safety, accessibility and portability and feedback on incidental findings have been added to section 17 • Assessment of secondary infections stopped at day 28 • Assessment of disseminated intravascular coagulation (DIC) removed • Change of address for ABF Pharmaceutical Services GmbH • Minor corrections and clarifications
16 September 2019	Protocol amendment 2.1: • Addition of an additional interim analysis and DMC review of safety data after 112 (25%) of patients randomized (section 8.5) • Addition of exclusion criteria "history of prosthetic heart valves" and "Prolonged QT syndrome" • Addition of daily ECG measurements until end of study drug infusion • Clarification of section "12.14 Study Drug Infusion and End of Vasopressor Definition", cross-reference with section 10.3 added • Reference to summary of product characteristics added for concomitant medications in sections 10.7 and 11.5 • Clarification of section "9.5 Withdrawal of Patients" and addition of the need for a concomitant medication representing a risk to the patient as criterion for withdrawal • Clarification of adaptive features (section 8.3) regarding DMC and DAC • Addition of paragraphs relating to data safety, accessibility and portability and feedback on incidental findings have been added to section 17 • Assessment of disseminated intravascular coagulation (DIC) removed • Assessment of secondary infections stopped at day 28 • Change of address for ABF Pharmaceutical Services GmbH • Changes requested by ANSM, applicable to sites in France: o Measurements of interferon-γ o Additional timepoint for the measurement of anti-drug antibodies on day 10 o Direct antibody test (direct Coombs) at baseline (pre-dose), days 10 and 28 o Addition of free bilirubin to the biochemistry laboratory parameters o Update of SUSAR reporting requirements for France • Minor corrections and clarifications

04 February 2020	Protocol amendment 3.0, 04/02/2020 and 3.1, 03/02/2020 (France only): • Assessment of primary endpoint changed from day 3 to day 5: "Change of total SOFA score (improvement of organ dysfunction) from baseline to day 5 (in the subgroup defined by patients with elevated sTREM-1 baseline levels and in the overall population)" • The handling of missing data was updated • Assessment of body temperature updated • Treatment regimen clarified (section 10.3) • Assessment of vital signs, ECG and SOFA score at screening clarified (section 11.3.1) • Reporting of overdosing added • Minor corrections and clarifications • Addresses of INOTREM and Stragen Services updated
25 March 2020	Protocol amendment 4.0 and 4.1 (France only): • Accommodation of possibly limited blood sampling in patients with a concomitant diagnosis of Covid-19 (section 12.19.6) • Assessment of EQ5D for visit a day 28 updated
14 January 2022	Protocol amendment 5.0 and 5.1 (France only): • PK sampling becomes optional as sufficient samples have been collected to support pharmacokinetic studies and in order to ease recruitment since the pharmacokinetic sampling procedure is technically difficult and not always easy to conduct at sites. • Modification of the sample size according to the proportion of patients in the high sTREM-1 group

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported