Clinical trial results:
Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 3 Doses of MOTREM in Patients with Septic Shock. A Randomised, Double-blind, Two-stage, Placebo Controlled Study.

Summary

EudraCT number	2016-005032-14
Trial protocol	BE NL ES
Global end of trial date	13 June 2018

Results information

Result version number	v1 (current)
This version publication date	20 March 2022
First version publication date	20 March 2022

Trial information

Trial identification

Sponsor protocol code	MOT-C-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03158948
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	INOTREM SA
Sponsor organisation address	54 rue de Ponthieu, Paris, France, 75008
Public contact	Executive VP Research and Medical Sciences, INOTREM S.A., +33 (0)6 30 62 86 51, jjg@inotrem.com
Scientific contact	Executive VP Research and Medical Sciences, INOTREM S.A., +33 (0)6 30 62 86 51, jjg@inotrem.com

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	20 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2018
Global end of trial reached?	Yes
Global end of trial date	13 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of MOTREM in patients with septic shock

Protection of trial subjects:

The study was performed in accordance with the Declaration of Helsinki and International Council on Harmonization Good Clinical Practice, and approved by the South Central – Berkshire B Research Ethics Committee, UK. The written informed consent for patient was obtained from relative or independent clinicians before the enrolment when the patient was unable to consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	France: 13
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	23
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled from 03 July 2017 (first patient first visit) to 11 June 2018 (last patient last visit) in 11 centers in 4 countries (Belgium, France, Spain, The Netherlands). 50 patients were included and randomized. 49 (98.0%) patients received the IMP and one patient died before IMP administration.

Pre-assignment

Screening details:

The duration of this study for each patient was a maximum of 13 weeks (including screening, up to 5 days of treatment and follow-up assessments 28 and 90 days after randomization). The purpose of the screening phase was to confirm patient eligibility for enrolment in the study based on the inclusion and exclusion criteria and to obtain written ICF.

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

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. The pharmacy staff or any other dedicated person preparing the investigational products was not blinded to study drug assignment and was responsible for the blinding of the study drug. During the study, the randomization codes were kept in the site's clinical trials pharmacy, accessible to the pharmacy personnel or any other dedicated person only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Commercial saline solution (i.e. NaCl 0.9%)

Arm title	0.3 mg/kg/h

Arm description: -

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

Dosage and administration details:

5.0 mg/kg i.v. (loading dose) for 15 minutes followed by a maintenance dose of 0.3 mg/kg/h for up to 5 days

Arm title	1.0 mg/kg/h

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nangibotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5.0 mg/kg i.v. (loading dose) for 15 minutes followed by a maintenance dose of 1.0 mg/kg/h for up to 5 days

Arm title	3.0 mg/kg/h
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nangibotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5.0 mg/kg i.v. (loading dose) for 15 minutes followed by a maintenance dose of 3.0 mg/kg/h for up to 5 days

Number of subjects in period 1	Placebo	0.3 mg/kg/h	1.0 mg/kg/h
Started	12	13	12
Completed	9	12	11
Not completed	3	1	1
Adverse event, serious fatal	2	1	1
Investigator decision	1	-	-

Number of subjects in period 1	3.0 mg/kg/h
Started	12
Completed	9
Not completed	3
Adverse event, serious fatal	3
Investigator decision	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	0.3 mg/kg/h
Reporting group description: -	
Reporting group title	1.0 mg/kg/h
Reporting group description: -	
Reporting group title	3.0 mg/kg/h
Reporting group description: -	

Reporting group values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h
Number of subjects	12	13	12
Age categorical Units: Subjects			
Adults (18-64 years)	5	8	3
From 65-84 years	7	5	9
Age continuous Units: years			
arithmetic mean	66	63	65
full range (min-max)	47 to 80	38 to 80	40 to 77
Gender categorical Units: Subjects			
Female	4	6	5
Male	8	7	7

Reporting group values	3.0 mg/kg/h	Total	
Number of subjects	12	49	
Age categorical Units: Subjects			
Adults (18-64 years)	7	23	
From 65-84 years	5	26	
Age continuous Units: years			
arithmetic mean	62		
full range (min-max)	22 to 79	-	
Gender categorical Units: Subjects			
Female	4	19	
Male	8	30	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	0.3 mg/kg/h
Reporting group description: -	
Reporting group title	1.0 mg/kg/h
Reporting group description: -	
Reporting group title	3.0 mg/kg/h
Reporting group description: -	

Primary: Adverse Events

End point title	Adverse Events[1]

End point description:

End point type	Primary

End point timeframe:

Adverse events experienced until D28 (End of study visit)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: Number of subjects experiencing AEs	10	13	12	11

Attachments (see zip file)	Summary of adverse event by patient/Summary of adverse Summary of TEAEs/Summary of TEAEs.PNG

Statistical analyses

No statistical analyses for this end point

Primary: Systolic Blood Pressure

End point title	Systolic Blood Pressure[2]

End point description:

Mean SBP at each visit is summarized by treatment group. No obvious difference between treatment groups was shown.

End point type	Primary

End point timeframe:

Vital signs were assessed each day from D0 (before IMP initiation) to D5 (EOI) and on D28 (EOS).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p- values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[3]	13[4]	12[5]	12[6]
Units: mmHg				
arithmetic mean (standard deviation)				
D0	118.8 (± 22.2)	109.8 (± 14.5)	119.2 (± 11.4)	116.3 (± 22.3)
D1	108.8 (± 19.1)	121.8 (± 18.0)	112.1 (± 9.1)	114.3 (± 16.7)
D2	107.0 (± 4.2)	118.8 (± 21.6)	120.2 (± 9.4)	116.6 (± 17.0)
D3	94.0 (± 9.9)	126.5 (± 3.5)	110.0 (± 13.3)	112.5 (± 8.7)
D4	108.0 (± 5.7)	133.0 (± 0)	110.3 (± 12.9)	107.0 (± 10.1)
D5/EOI	110.4 (± 19.5)	120.3 (± 23.1)	120.2 (± 19.9)	107.9 (± 15.4)
D28/EOS	132.3 (± 24.3)	116.6 (± 14.8)	117.0 (± 21.2)	109.0 (± 8.9)

Notes:

[3] - D0: N=10
D1: N=8
D2: N=2
D3: N=2
D4: N=2
D5/EOI: N=10
D29/EOS: N=9
[4] - D0: N=13
D1: N=9
D2: N=4
D3: N=2
D4: N=1
D5/EOI: N=13
D29/EOS: N=11
[5] - D0: N=12
D1: N=10
D2: N=5
D3: N=4
D4: N=3
D5/EOI: N=12
D29/EOS: N=11
[6] - D0: N=12
D1: N=11
D2: N=7
D3: N=4
D4: N=4
D5/EOI: N=12
D29/EOS: N=9

Statistical analyses

No statistical analyses for this end point

Primary: Diastolic Blood Pressure

End point title	Diastolic Blood Pressure[7]

End point description:

Mean DBP at each visit is summarized by treatment group. No obvious difference between treatment groups was shown.

End point type	Primary

End point timeframe:

Vital signs were assessed each day from D0 (before IMP initiation) to D5 (EOI) and on D28 (EOS).

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[8]	13[9]	12[10]	12[11]
Units: mmHg				
arithmetic mean (standard deviation)				
D0	56.1 (± 11.3)	56.9 (± 11.0)	61.1 (± 9.1)	56.3 (± 7.5)
D1	59.4 (± 10.3)	56.4 (± 13.7)	67.7 (± 22.9)	59.2 (± 11.0)
D2	61.0 (± 7.1)	65.8 (± 6.4)	65.4 (± 6.3)	66.6 (± 14.7)
D3	58.5 (± 12.0)	60.5 (± 0.7)	53.3 (± 9.8)	60.0 (± 10.4)
D4	61.5 (± 9.2)	64.0 (± 0)	54.3 (± 2.1)	56.3 (± 7.6)
D5/EOI	55.7 (± 6.5)	60.4 (± 15.0)	59.3 (± 12.5)	54.4 (± 13.8)
D28/EOS	67.3 (± 14.0)	66.9 (± 14.4)	60.9 (± 13.8)	68.2 (± 7.2)

Notes:

[8] - D0: N=10
D1: N=8
D2: N=2
D3: N=2
D4: N=2
D5/EOI: N=10
D29/EOS: N=9
[9] - D0: N=13
D1: N=9
D2: N=4
D3: N=2
D4: N=1
D5/EOI: N=13
D29/EOS: N=11
[10] - D0: N=12
D1: N=10
D2: N=5
D3: N=4
D4: N=3
D5/EOI: N=12
D29/EOS: N=11
[11] - D0: N=12
D1: N=11
D2: N=7
D3: N=4
D4: N=4
D5/EOI: N=12
D29/EOS: N=9

Statistical analyses

No statistical analyses for this end point

Primary: Mean Arterial Pressure

End point title	Mean Arterial Pressure[12]

End point description:

MAP at each visit is summarized by treatment group. No obvious difference between treatment groups

was shown.

End point type	Primary

End point timeframe:

Vital signs were assessed each day from D0 (before IMP initiation) to D5 (EOI) and on D28 (EOS).

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[13]	13[14]	12[15]	12[16]
Units: mmHg				
arithmetic mean (standard deviation)				
D0	75.4 (± 13.8)	74.7 (± 10.8)	80.6 (± 9.2)	77.9 (± 14.0)
D1	76.1 (± 13.8)	79.0 (± 13.8)	73.8 (± 9.5)	77.1 (± 10.9)
D2	76.0 (± 9.9)	86.8 (± 12.6)	76.8 (± 14.3)	80.6 (± 11.2)
D3	71.0 (± 12.7)	84.5 (± 0.7)	70.5 (± 12.2)	79.0 (± 7.3)
D4	76.5 (± 10.6)	92.0 (± 0)	71.3 (± 2.5)	75.8 (± 4.3)
D5/EOI	74.2 (± 7.4)	80.7 (± 18.3)	80.2 (± 14.0)	70.7 (± 15.6)
D28/EOS	86.1 (± 12.7)	84.3 (± 15.0)	80.0 (± 15.8)	80.3 (± 8.3)

Notes:

[13] - D0: N=10
D1: N=8
D2: N=2
D3: N=2
D4: N=2
D5/EOI: N=10
D29/EOS: N=8
[14] - D0: N=13
D1: N=9
D2: N=4
D3: N=2
D4: N=1
D5/EOI: N=13
D29/EOS: N=10
[15] - D0: N=12
D1: N=10
D2: N=5
D3: N=4
D4: N=3
D5/EOI: N=12
D29/EOS: N=11
[16] - D0: N=12
D1: N=11
D2: N=7
D3: N=4
D4: N=4
D5/EOI: N=12
D29/EOS: N=9

Statistical analyses

No statistical analyses for this end point

Primary: Heart Rate

End point title	Heart Rate[17]

End point description:

Mean DBP at each visit is summarized by treatment group. No obvious difference between treatment groups was shown.

End point type	Primary

End point timeframe:

Vital signs were assessed each day from D0 (before IMP initiation) to D5 (EOI).

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[18]	13[19]	12[20]	12[21]
Units: bpm				
arithmetic mean (standard deviation)				
D0	90.2 (± 26.8)	97.2 (± 17.7)	101.8 (± 24.2)	106.4 (± 22.7)
D1	94.4 (± 30.9)	90.2 (± 18.1)	94.1 (± 19.4)	103.3 (± 18.7)
D2	74.0 (± 19.8)	88.8 (± 11.2)	108.0 (± 15.7)	94.4 (± 35.1)
D3	95.0 (± 35.4)	60.5 (± 3.5)	96.8 (± 26.8)	85.3 (± 17.0)
D4	75.0 (± 7.1)	61.0 (± 0)	125.7 (± 28.3)	82.8 (± 14.2)
D5/EOI	90.9 (± 20.6)	90.6 (± 19.5)	89.5 (± 15.7)	92.7 (± 14.9)

Notes:

[18] - D0: N=10
D1: N=8
D2: N=2
D3: N=2
D4: N=2
D5/EOI: N=10
[19] - D0: N=13
D1: N=9
D2: N=4
D3: N=2
D4: N=1
D5/EOI: N=13
[20] - D0: N=12
D1: N=10
D2: N=5
D3: N=4
D4: N=3
D5/EOI: N=12
[21] - D0: N=12
D1: N=11
D2: N=7
D3: N=4
D4: N=4
D5/EOI: N=12

Statistical analyses

No statistical analyses for this end point

Primary: Temperature

End point title	Temperature[22]

End point description:

Mean DBP at each visit is summarized by treatment group. No obvious difference between treatment groups was shown.

End point type	Primary

End point timeframe:

Vital signs were assessed each day from D0 (before IMP initiation) to D5 (EOI).

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[23]	13[24]	12[25]	12[26]
Units: °C				
arithmetic mean (standard deviation)				
D0	37.1 (± 1.5)	36.9 (± 1.1)	37.0 (± 0.6)	37.1 (± 1.4)
D1	37.1 (± 1.8)	36.3 (± 1.5)	36.9 (± 0.7)	37.1 (± 1.0)
D2	36.1 (± 0.8)	36.3 (± 0.6)	36.7 (± 0.6)	37.0 (± 1.5)
D3	36.6 (± 0.8)	36.3 (± 0.9)	36.8 (± 0.7)	37.3 (± 1.1)
D4	36.1 (± 0.1)	36.1 (± 0)	37.0 (± 0.4)	36.7 (± 0.5)
D5/EOI	36.7 (± 0.6)	36.7 (± 0.9)	36.8 (± 1.1)	36.6 (± 1.2)

Notes:

[23] - D0: N=10
D1: N=8
D2: N=2
D3: N=2
D4: N=2
D5/EOI: N=10
[24] - D0: N=13
D1: N=9
D2: N=4
D3: N=2
D4: N=1
D5/EOI: N=13
[25] - D0: N=12
D1: N=10
D2: N=5
D3: N=4
D4: N=3
D5/EOI: N=12
[26] - D0: N=12
D1: N=11
D2: N=7
D3: N=4
D4: N=4
D5/EOI: N=11

Statistical analyses

No statistical analyses for this end point

Primary: Electrocardiogram

End point title	Electrocardiogram[27]

End point description:

There was no obvious dose effect in the frequency of abnormal CS ECG in nangibotide groups, and no obvious difference with the placebo group.
Based, on Listing of ECG abnormalities:
- 13 patients had abnormal CS ECG (emergent or not): 3 patients in the nangibotide group 0.3 mg/kg/h, 2 patients in the nangibotide group 1.0 mg/kg/h, 4 patients in the nangibotide group 3.0 mg/kg/h and 2 patients in the placebo group.

- 4 patients had emergent (i.e. not reported at baseline) abnormal clinically significant ECG during the study: 1 patient in the nangibotide group 0.3 mg/kg/h, 1 patient in the nangibotide group 1.0 mg/kg/h, 2 patients in the nangibotide group 3.0 mg/kg/h and none in the placebo group.

End point type	Primary

End point timeframe:

Electrocardiogram was performed each day from D0 (before IMP initiation) to D5 (EOI) and on D28 (EOS).

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: Number of subjects				
abnormal CS ECG	2	3	2	4
emergent abnormal clinically significant ECG	1	1	2	0

Attachments (see zip file)	Electrocardiogram/Electrocardiogram.PNG

Statistical analyses

No statistical analyses for this end point

Primary: Anti-Drug Antibodies (ADA Dimer)

End point title	Anti-Drug Antibodies (ADA Dimer)[28]

End point description:

Anti-Drug Antibodies test were negative at D0 and D28 in all patients.

End point type	Primary

End point timeframe:

Anti-Drug Antibodies test were done at D0, D10 and D28 in all patients.

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[29]	13[30]	12[31]	12[32]
Units: ADA DIMER				
Missing	3	4	2	3
Negative	9	9	10	9

Notes:

[29] - Results for D28 represented

[30] - Results for D28 represented

[31] - Results for D28 represented

[32] - Results for D28 represented

Statistical analyses

No statistical analyses for this end point

Primary: Anti-Drug Antibodies (ADA Monomer)

End point title	Anti-Drug Antibodies (ADA Monomer)[33]

End point description:

Anti-Drug Antibodies test were negative at D0 and D28 in all patients.

End point type	Primary

End point timeframe:

Anti-Drug Antibodies test were measured at D0, D10 and D28.

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the primary endpoints in this study are safety endpoints concerning primarily adverse events, statistics for the aforementioned do not contain p-values. For this reason statistical analysis is not provided here.

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[34]	13[35]	12[36]	12[37]
Units: ADA Monomer				
Missing	3	5	2	3
Negative	9	8	10	9

Notes:

[34] - Values are presented for D28

[35] - Values are presented for D28

[36] - Values are presented for D28

[37] - Values are presented for D28

Statistical analyses

No statistical analyses for this end point

Secondary: PK (Cmax)

End point title	PK (Cmax)

End point description:

End point type	Secondary

End point timeframe:

Baseline: pre-dose sample at Day 0 (D0)
Daily up to Day 5 (D5) (or the last day in the study/EOI)
If possible, at D5/EOI:
- 15 min before end of infusion (EOI)
- 10 min after EOI
- 30 min after EOI
- 2h after EOI

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[38]	13	12	12
Units: ng/mL				
median (full range (min-max))	(to)	71.2 (20.0 to 219)	234 (71.3 to 514)	914 (502 to 6095)

Notes:

[38] - PK not analyzed for placebo

Statistical analyses

No statistical analyses for this end point

Secondary: PK (tmax)

End point title	PK (tmax)

End point description:

End point type	Secondary

End point timeframe:

Baseline: pre-dose sample at Day 0 (D0)
Daily up to Day 5 (D5) (or the last day in the study/EOI)
If possible, at D5/EOI:
- 15 min before end of infusion (EOI)
- 10 min after EOI
- 30 min after EOI
- 2h after EOI

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[39]	13	12	12
Units: hour				
median (full range (min-max))	(to)	22.7 (14.3 to 76.0)	25.4 (9.25 to 118)	36.0 (9.00 to 75.8)

Notes:

[39] - PK not analyzed for placebo

Statistical analyses

No statistical analyses for this end point

Secondary: PK (AUC0-last)

End point title	PK (AUC0-last)

End point description:

End point type	Secondary

End point timeframe:

Baseline: pre-dose sample at Day 0 (D0)
Daily up to Day 5 (D5) (or the last day in the study/EOI)
If possible, at D5/EOI:
- 15 min before end of infusion (EOI)
- 10 min after EOI
- 30 min after EOI
- 2h after EOI

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[40]	13	12	12
Units: ng*h/mL				
median (full range (min-max))	(to)	1722 (360 to 5243)	7579 (668 to 45189)	47320 (3830 to 393506)

Notes:

[40] - PK not analyzed for placebo

Statistical analyses

No statistical analyses for this end point

Secondary: PK (Cavg)

End point title	PK (Cavg)

End point description:

End point type	Secondary

End point timeframe:

Baseline: pre-dose sample at Day 0 (D0)
Daily up to Day 5 (D5) (or the last day in the study/EOI)
If possible, at D5/EOI:
- 15 min before end of infusion (EOI)
- 10 min after EOI
- 30 min after EOI
- 2h after EOI

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[41]	13	12	12
Units: ng/mL				
median (full range (min-max))	(to)	67.6 (20.0 to 219)	223 (71.3 to 418)	729 (93.9 to 3778)

Notes:

[41] - PK not analyzed for placebo

Statistical analyses

No statistical analyses for this end point

Secondary: PK (CL)

End point title	PK (CL)

End point description:

End point type	Secondary

End point timeframe:

Baseline: pre-dose sample at Day 0 (D0)
Daily up to Day 5 (D5) (or the last day in the study/EOI)
If possible, at D5/EOI:
- 15 min before end of infusion (EOI)
- 10 min after EOI
- 30 min after EOI
- 2h after EOI

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[42]	13	12	12
Units: L/h/kg				
median (full range (min-max))	(to)	4.52 (1.36 to 15.3)	4.50 (2.39 to 14.0)	4.12 (0.794 to 25.0)

Notes:

[42] - PK not analyzed for placebo

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker- Ang-1)

End point title	PD (Biomarker- Ang-1)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: ng/mL				
arithmetic mean (standard deviation)	3.6 (± 6.1)	7.8 (± 16.6)	3.1 (± 3.5)	3.1 (± 2.3)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker- Ang-2)

End point title	PD (Biomarker- Ang-2)

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: ng/mL				
arithmetic mean (standard deviation)	29.7 (± 33.3)	20.4 (± 15.2)	18.6 (± 9.1)	25.3 (± 19.7)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker- CCL-2 [MCP-1])

End point title	PD (Biomarker- CCL-2 [MCP-1])

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: pg/ml				
arithmetic mean (standard deviation)	3643 (± 4177)	2839 (± 3023)	5505 (± 10947)	22427 (± 22738)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker-INF gamma)

End point title	PD (Biomarker-INF gamma)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[43]	5	6
Units: pg/ml				
arithmetic mean (standard deviation)	1.6 (± 0)	()	35.8 (± 26.0)	15.9 (± 17.6)

Notes:

[43] - INF gamma not analyzed for this group

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker IL-10)

End point title	PD (Biomarker IL-10)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: pg/mL				
arithmetic mean (standard deviation)	261 (± 364)	123 (± 81)	2102 (± 4436)	1650 (± 4565)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker IL-6)

End point title	PD (Biomarker IL-6)

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: pg/mL				
arithmetic mean (standard deviation)	6549 (± 11639)	3255 (± 6285)	19060 (± 55879)	27774 (± 52882)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker IL-8)

End point title	PD (Biomarker IL-8)

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: pg/mL				
arithmetic mean (standard deviation)	1551 (± 2888)	984 (± 2259)	3490 (± 11177)	10742 (± 27964)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker TNF alpha)

End point title	PD (Biomarker TNF alpha)

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: pg/mL				
arithmetic mean (standard deviation)	397 (± 538)	313 (± 303)	551 (± 674)	614 (± 548)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker VCAM-1)

End point title	PD (Biomarker VCAM-1)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: ng/mL				
arithmetic mean (standard deviation)	5010 (± 3600)	4616 (± 3538)	5363 (± 3756)	3606 (± 2059)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker VEGFR-1)

End point title	PD (Biomarker VEGFR-1)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: ng/mL				
arithmetic mean (standard deviation)	0.74 (± 0.53)	1.46 (± 2.28)	3.07 (± 6.85)	3.20 (± 5.06)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker sCD62E)

End point title	PD (Biomarker sCD62E)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: ng/mL				
arithmetic mean (standard deviation)	101.9 (± 86.8)	93.8 (± 96.7)	148.9 (± 145.4)	169.4 (± 212.1)

Statistical analyses

No statistical analyses for this end point

Secondary: PD (Biomarker sTREM-1)

End point title	PD (Biomarker sTREM-1)

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	0.3 mg/kg/h	1.0 mg/kg/h	3.0 mg/kg/h
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	12
Units: pg/mL				
arithmetic mean (standard deviation)	676 (± 622)	474 (± 221)	519 (± 306)	616 (± 365)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline until D28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	0.3 mg/kg/h
Reporting group description: -	
Reporting group title	1.0 mg/kg/h
Reporting group description: -	
Reporting group title	3.0 mg/kg/h
Reporting group description: -	

Serious adverse events	Placebo	0.3 mg/kg/h	1.0 mg/kg/h
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	4 / 13 (30.77%)	2 / 12 (16.67%)
number of deaths (all causes)	2	4	2
number of deaths resulting from adverse events	2	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (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
Injury, poisoning and procedural complications			
Mechanical ventilation complication			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (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	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (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
Sinus tachycardia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (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
Ischaemic stroke			

subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple Organ Failure syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory fatigue			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (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
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	0 / 12 (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
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	0 / 12 (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
Cardiac infection			

subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (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

Serious adverse events	3.0 mg/kg/h		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Mechanical ventilation complication			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Shock			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple Organ Failure syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory fatigue			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Encephalitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	0.3 mg/kg/h	1.0 mg/kg/h
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)	12 / 13 (92.31%)	12 / 12 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 12 (8.33%)	5 / 13 (38.46%)	2 / 12 (16.67%)
occurrences (all)	1	5	2
Arrhythmia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Nervous system disorders			
Confusional state			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 12 (25.00%)	3 / 13 (23.08%)	2 / 12 (16.67%)
occurrences (all)	3	3	2
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Intra-Abdominal Fluid Collection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	2 / 12 (16.67%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	2	1	2
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	3 / 12 (25.00%)
occurrences (all)	0	1	3
Pneumothorax			

subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Oral Fungal Infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Infectious Pleural Effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Septic Shock			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypophosphataemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2

Non-serious adverse events	3.0 mg/kg/h		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Vascular disorders			
Hypotension			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Cardiac disorders Atrial Fibrillation subjects affected / exposed occurrences (all) Arrhythmia subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3 2 / 12 (16.67%) 2		
Nervous system disorders Confusional state subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3 4 / 12 (33.33%) 4		
Gastrointestinal disorders Intra-Abdominal Fluid Collection subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Pleural Effusion subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Pneumothorax subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 2 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1		
Psychiatric disorders			

Agitation subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Renal and urinary disorders Renal Failure subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infections and infestations Oral Fungal Infection subjects affected / exposed occurrences (all) Infectious Pleural Effusion subjects affected / exposed occurrences (all) Septic Shock subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2 2 / 12 (16.67%) 2 0 / 12 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2017	• Addition of blood samples for DNA analyses related to the TREM-1 signalling pathway • Changes requested by the ethics committee in the Netherlands and implemented in the country specific amendment 1.1 • Change of the lower age limit to 16 years (applicable only for sites in the Netherlands) • Addition of a paragraph detailing the analysis and storage of blood samples • Blood levels of sTLT-1 will not be analysed • Name change of IMP management provider implemented • Rating of Adverse Events updated for consistency with eCRF • Minor corrections and clarifications
08 January 2018	• Addition of an interim analysis (section 15.4) • Clarification of concomitant medication recording • Minor corrections and clarifications.

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/32468087