



Clinical trial results:

An open label feasibility trial investigating FE 202158 as potential primary vasopressor treatment in patients with vasodilatory hypotension in early septic shock

Summary

EudraCT number	2012-001254-26
Trial protocol	DK BE
Global end of trial date	15 November 2013

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	13 July 2016

Trial information

Trial identification

Sponsor protocol code	000025
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01612676
WHO universal trial number (UTN)	-
Other trial identifiers	FE 202158: 000025

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	Kay Fiskers Plads 11, Copenhagen S, Denmark, 2300
Public contact	Clinical Development Support, Ferring Pharmaceuticals , DK0-Disclosure@fering.com
Scientific contact	Clinical Development Support, Ferring Pharmaceuticals , DK0-Disclosure@fering.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	25 February 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of this study was to investigate if FE 202158 can be used as primary vasopressor treatment in patients with early septic shock.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical study as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture.

Collected personal data and human biological samples were processed in compliance with the Declaration of Helsinki and its amendments in force at the initiation of the trial in compliance with the approved protocol and its amendment, Good Clinical Practice and applicable regulatory requirements of Belgium and Denmark.

During the trial study drug infusion was to be permanently discontinued if any of the following occurred:

- Troponin T or I elevation in combination with other clinical or laboratory findings indicative of myocardial ischemia
- Serious or life-threatening (hemodynamically unstable) cardiac arrhythmias
- Development of 2nd or 3rd degree AV-block without a well-functioning pacemaker
- Suspicions of acute mesenteric or hepatic ischemia
- Clinically relevant digital ischemia
- If the investigator considered this to be in the best interest of the subject, e.g. if a non-allowed treatment is required
- If the norepinephrine requirement during FE 202158 infusion reached 0.6 µg/kg/min or above

Background therapy:

If the highest infusion rate allowed of FE 202158 did not provide adequate vasopressor support, norepinephrine was to be infused as required to maintain the target mean arterial pressure (MAP).

Evidence for comparator: -

Actual start date of recruitment	05 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Denmark: 4
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	11
From 65 to 84 years	18
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited at the respective intensive care units at four centers (3 in Belgium and 1 in Denmark) between 05 Jul 2012 to 15 Nov 2013.

Pre-assignment

Screening details:

Of the 159 subjects screened, 31 subjects were randomised and 30 subjects were dosed. One subject in the 3.75 ng/kg/min dose group did not receive any study treatment due to an adverse event (elevation of troponin) recorded prior to infusion.

Period 1

Period 1 title	Pre-dose period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Infusion Regimen 1: 3.75 ng/kg/min

Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Arm title	Infusion Regimen 2: 5.0 ng/kg/min
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Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 5.0 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Arm title	Infusion Regimen 3: 7.5 ng/kg/min
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Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min adjustable up to a maximum of 7.5 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Arm title	Infusion Regimen 4: modified 3.75 ng/kg/min
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Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min, allowed to be increased to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of infusion. After 1 hour, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Number of subjects in period 1	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min
Started	6	7	5
Completed	5	7	5
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Number of subjects in period 1	Infusion Regimen 4: modified 3.75 ng/kg/min
Started	13
Completed	13
Not completed	0
Adverse event, non-fatal	-

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details: This is an open label study	

Arms

Are arms mutually exclusive?	Yes
Arm title	Infusion Regimen 1: 3.75 ng/kg/min

Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Arm title	Infusion Regimen 2: 5.0 ng/kg/min
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Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 5.0 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Arm title	Infusion Regimen 3: 7.5 ng/kg/min
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Arm description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min adjustable up to a maximum of 7.5 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.

Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Arm title	Infusion Regimen 4: modified 3.75 ng/kg/min
Arm description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min, allowed to be increased to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of infusion. After 1 hour, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Arm type	Experimental
Investigational medicinal product name	FE 202158
Investigational medicinal product code	
Other name	Selepressin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4). FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to a specific dilution protocol.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics were reported for subjects in Full analysis set (FAS). FAS comprised of all subjects who were dosed (N=30). These are mentioned in post-dose period (Period 2).

Number of subjects in period 2^[2]	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min
Started	5	7	5
Completed	4	3	4
Not completed	1	4	1
Adverse event, non-fatal	1	3	1
Protocol deviation	-	1	-

Number of subjects in period 2^[2]	Infusion Regimen 4: modified 3.75 ng/kg/min
Started	13
Completed	10
Not completed	3
Adverse event, non-fatal	3
Protocol deviation	-

Notes:

[2] - 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: Out of the 31 subjects randomised in the trial, 30 subjects were dosed and comprised Full analysis set (FAS). One subject in the 3.75 ng/kg/min dose group did not receive any study treatment due to an adverse event (elevation of troponin) recorded prior to infusion.

Baseline characteristics

Reporting groups

Reporting group title	Infusion Regimen 1: 3.75 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 2: 5.0 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 5.0 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 3: 7.5 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min adjustable up to a maximum of 7.5 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 4: modified 3.75 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min, allowed to be increased to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of infusion. After 1 hour, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	

Reporting group values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min
Number of subjects	5	7	5
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69	67.9	64.8
standard deviation	± 12.7	± 13.7	± 10.1
Gender categorical Units: Subjects			
Female	1	2	2
Male	4	5	3
Septic shock characteristic: Primary infection type Units: Subjects			

Bacterial	4	6	3
Unknown	0	1	1
Other	1	0	1
Septic shock characteristic: Primary infection location Units: Subjects			
Abdominal cavity	1	5	3
Lung	1	1	0
Urinary tract	0	1	1
Other	3	0	1
Unknown	0	0	0
Weight Units: kg			
arithmetic mean	66.6	74.7	81.3
standard deviation	± 13.5	± 17.7	± 8
Total Sequential Organ Failure Assessment Score Units: Score on scale			
arithmetic mean	11	10	8.8
standard deviation	± 3.32	± 2.31	± 3.19
Norepinephrine infusion rate at baseline Units: µg/kg/min			
arithmetic mean	0.789	0.291	0.412
standard deviation	± 0.724	± 0.174	± 0.438

Reporting group values	Infusion Regimen 4: modified 3.75 ng/kg/min	Total	
Number of subjects	13	30	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	67.6	-	
standard deviation	± 13.2		
Gender categorical Units: Subjects			
Female	5	10	
Male	8	20	
Septic shock characteristic: Primary infection type Units: Subjects			
Bacterial	12	25	

Unknown	1	3	
Other	0	2	
Septic shock characteristic: Primary infection location Units: Subjects			
Abdominal cavity	6	15	
Lung	1	3	
Urinary tract	4	6	
Other	1	5	
Unknown	1	1	
Weight Units: kg arithmetic mean standard deviation	78.9 ± 15.3	-	
Total Sequential Organ Failure Assessment Score Units: Score on scale arithmetic mean standard deviation	9.31 ± 3.01	-	
Norepinephrine infusion rate at baseline Units: µg/kg/min arithmetic mean standard deviation	0.291 ± 0.18	-	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis data set (FAS) comprises data from all dosed subjects.	

Reporting group values	Full analysis set		
Number of subjects	30		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	67.4 ± 12.2		

Gender categorical Units: Subjects			
Female	10		
Male	20		
Septic shock characteristic: Primary infection type Units: Subjects			
Bacterial	25		
Unknown	3		
Other	2		
Septic shock characteristic: Primary infection location Units: Subjects			
Abdominal cavity	15		
Lung	3		
Urinary tract	6		
Other	5		
Unknown	1		
Weight Units: kg			
arithmetic mean	76.3		
standard deviation	± 14.8		
Total Sequential Organ Failure Assessment Score Units: Score on scale			
arithmetic mean	9.67		
standard deviation	± 2.88		
Norepinephrine infusion rate at baseline Units: $\mu\text{g}/\text{kg}/\text{min}$			
arithmetic mean			
standard deviation	$\pm$		

End points

End points reporting groups

Reporting group title	Infusion Regimen 1: 3.75 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 2: 5.0 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 5.0 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 3: 7.5 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min adjustable up to a maximum of 7.5 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 4: modified 3.75 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min, allowed to be increased to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of infusion. After 1 hour, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 1: 3.75 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 2: 5.0 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 5.0 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 3: 7.5 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min adjustable up to a maximum of 7.5 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Reporting group title	Infusion Regimen 4: modified 3.75 ng/kg/min
Reporting group description: FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min, allowed to be increased to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of infusion. After 1 hour, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min. Each subject received FE 202158 until recovered from the shock, however for not more than 7 days.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis data set (FAS) comprises data from all dosed subjects.	

Primary: Proportion of subjects maintaining target/adequate mean arterial pressure (MAP>60 mmHg) without norepinephrine

End point title	Proportion of subjects maintaining target/adequate mean arterial pressure (MAP>60 mmHg) without norepinephrine ^[1]
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End point description:

Mean arterial pressure (MAP) was measured intra-arterially on a continuous basis. Proportion of subjects (success percentage) was presented.

End point type	Primary
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End point timeframe:

Day 1 up to Day 7

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: Due to the highly explorative nature of the trial, proportion of subjects maintaining MAP>60 mmHg was summarised using 60% confidence interval (CI) based on Clopper-Pearson (exact statistics).

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: proportion of subjects				
number (confidence interval 60%)				
Day 1 (Post 1 h)	20 (4.4 to 49)	42.9 (22.8 to 65)	60 (32.7 to 83.1)	7.7 (1.7 to 21.3)
Day 1 (Post 3 h)	20 (4.4 to 49)	14.3 (3.1 to 37.1)	60 (32.7 to 83.1)	53.8 (38.7 to 68.4)
Day 1 (Post 6 h)	25 (5.4 to 58.2)	14.3 (3.1 to 37.1)	80 (51 to 95.6)	76.9 (61.6 to 88)
Day 1 (Post 12 h)	60 (32.7 to 83.1)	28.6 (12 to 51.7)	80 (51 to 95.6)	53.8 (38.7 to 68.4)
Day 1 (Post 18 h)	60 (32.7 to 83.1)	42.9 (22.8 to 65)	80 (51 to 95.6)	66.7 (50.3 to 80.2)
Day 1 (Post 24 h)	80 (51 to 95.6)	42.9 (22.8 to 65)	80 (51 to 95.6)	61.5 (46.1 to 75.2)
Day 2 (Post 48 h)	80 (51 to 95.6)	50 (26.9 to 73.1)	80 (51 to 95.6)	76.9 (61.6 to 88)
Day 3 (Post 72 h)	80 (51 to 95.6)	66.7 (41.5 to 86)	80 (51 to 95.6)	69.2 (53.7 to 81.8)
Day 5 (Post 120 h)	80 (51 to 95.6)	80 (51 to 95.6)	80 (51 to 95.6)	84.6 (69.9 to 93.6)
Day 7 (Post 168 h)	80 (51 to 95.6)	80 (51 to 95.6)	80 (51 to 95.6)	76.9 (61.6 to 88)

Attachments (see zip file)	Subject proportion (60% CI) maintaining target
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Statistical analyses

No statistical analyses for this end point

Primary: Cumulative dose of FE 202158

End point title	Cumulative dose of FE 202158 ^[2]
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End point description:

Cumulative dose of FE 202158 was calculated from Day 1 up to Day 7.

End point type	Primary
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End point timeframe:

Day 1 up to Day 7

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: Due to the highly explorative nature of the trial, confidence interval was displayed with 60% coverage. Cumulative dose of FE 202158 was presented using descriptive statistics and graphical representation.

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: ng/kg				
arithmetic mean (confidence interval 60%)				
Day 1 (12 h)	2451 (2226.3 to 2675.8)	3276.3 (2941.3 to 3611.3)	2946 (2426.2 to 3465.8)	2377 (2220.2 to 2533.7)
Day 1 (24 h)	4217.4 (3736.5 to 4698.3)	5502.2 (4698.7 to 6305.7)	4927.3 (4064.8 to 5789.8)	3818.8 (3429.6 to 4208)
Day 2 (36 h)	4463.9 (3877 to 5050.7)	7535.9 (6206.2 to 8865.7)	5842 (4554.6 to 7129.4)	4619.2 (4005 to 5233.4)
Day 2 (48 h)	4523.9 (3900.8 to 5146.9)	9185 (7405.2 to 10963.9)	6716 (4674.3 to 8757.6)	5225 (4401.7 to 6048.3)
Day 3 (72 h)	4523.9 (3900.8 to 5146.9)	11511.4 (9096.1 to 13926.7)	7902 (4758.8 to 11045.1)	5860.1 (4763.9 to 6956.4)
Day 4 (96 h)	4523.9 (3900.8 to 5146.9)	12204.6 (9365.7 to 15043.4)	7999.8 (4765.3 to 11234.3)	6298.6 (4939.5 to 7657.7)
Day 5 (120 h)	4523.9 (3900.8 to 5146.9)	12865.3 (9561.7 to 16168.9)	7999.8 (4765.3 to 11234.3)	6621.8 (5033.5 to 8210.1)
Day 6 (144 h)	4523.9 (3900.8 to 5146.9)	13543.7 (9724 to 17363.3)	7999.8 (4765.3 to 11234.3)	6696.5 (5052.9 to 8340.1)
Day 7 (168 h)	4523.9 (3900.8 to 5146.9)	13543.7 (9724 to 17363.3)	7999.8 (4765.3 to 11234.3)	7003.7 (5126 to 8881.5)

Attachments (see zip file)	Mean (60% CI) cumulative dose of FE 202158 (FAS)/Mean
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Statistical analyses

No statistical analyses for this end point

Primary: Infusion rate of FE 202158

End point title	Infusion rate of FE 202158 ^[3]
End point description: Infusion rate of FE 202158 was presented from Day 1 up to Day 7.	
End point type	Primary
End point timeframe: Day 1 up to Day 7	

Notes:

[3] - 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: Due to the highly explorative nature of the trial, confidence interval was displayed with 60% coverage. Infusion rate for FE 202158 was presented using descriptive statistics and graphical representation.

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: ng/kg/min				
arithmetic mean (standard deviation)				
Day 1 (12 h)	3.25 (± 1.29)	4.13 (± 2.09)	3.08 (± 2.56)	2.43 (± 1.41)
Day 1 (24 h)	0.94 (± 1.88)	3.39 (± 2.37)	1.59 (± 2.19)	1.39 (± 1.65)
Day 2 (36 h)	0.23 (± 0.47)	2.66 (± 2.27)	2.08 (± 2.77)	1.25 (± 1.76)
Day 2 (48 h)	0 (± 0)	2.51 (± 2.29)	1.79 (± 3.57)	0.69 (± 1.28)
Day 3 (72 h)	0 (± 0)	0.82 (± 2.02)	0.61 (± 1.22)	0.39 (± 1.08)
Day 5 (120 h)	0 (± 0)	0.99 (± 2.21)	0 (± 0)	0 (± 0)
Day 7 (168 h)	0 (± 0)	0 (± 0)	0 (± 0)	0.33 (± 1.08)

Attachments (see zip file)	Mean (60% CI) infusion rate of FE 202158 (FAS)/Mean infusion
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Statistical analyses

No statistical analyses for this end point

Primary: Cumulative dose of norepinephrine

End point title	Cumulative dose of norepinephrine ^[4]
End point description: Cumulative dose of norepinephrine was calculated from Day 1 up to Day 7.	
End point type	Primary
End point timeframe: Day 1 up to Day 7	

Notes:

[4] - 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: Due to the highly explorative nature of the trial, confidence interval was displayed with 60% coverage. Cumulative dose of norepinephrine was presented using descriptive statistics and graphical representation.

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	4	13
Units: µg/kg				
arithmetic mean (confidence interval 60%)				
Day 1 (12 h)	358.1 (91.8 to 624.3)	172.1 (96.5 to 247.8)	118 (12.7 to 223.3)	73.1 (47.2 to 99)
Day 1 (24 h)	720.8 (131.8 to 1309.7)	338 (171.5 to 504.6)	357.5 (17.8 to 697.2)	149.5 (90.4 to 208.6)
Day 2 (36 h)	720.8 (131.8 to 1309.7)	406.2 (214.7 to 597.6)	778.2 (26.9 to 1529.5)	197.8 (111.4 to 284.2)
Day 2 (48 h)	720.8 (131.8 to 1309.7)	495.5 (296.4 to 694.5)	778.4 (27.2 to 1529.7)	232.8 (120.6 to 345.1)
Day 3 (72 h)	720.8 (131.8 to 1309.7)	669 (390.8 to 947.2)	778.4 (27.2 to 1529.7)	279.1 (129.5 to 428.7)
Day 4 (96 h)	720.8 (131.8 to 1309.7)	829.6 (438.1 to 1221.1)	778.4 (27.2 to 1529.7)	303.1 (133.6 to 472.6)
Day 5 (120 h)	720.8 (131.8 to 1309.7)	1039.5 (473.7 to 1605.2)	778.4 (27.2 to 1529.7)	307.8 (134.4 to 481.2)
Day 6 (144 h)	720.8 (131.8 to 1309.7)	1152 (489.2 to 1814.7)	778.4 (27.2 to 1529.7)	307.8 (134.4 to 481.2)
Day 7 (168 h)	720.8 (131.8 to 1309.7)	1152 (489.2 to 1814.7)	778.4 (27.2 to 1529.7)	311.1 (134.9 to 487.2)

Attachments (see zip file)	Mean (60% CI) cumulative dose-norepinephrine (FAS)/Mean
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Statistical analyses

No statistical analyses for this end point

Primary: Infusion rate of norepinephrine

End point title	Infusion rate of norepinephrine ^[5]
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End point description:

Infusion rate of FE 202158 was presented from Day 1 up to Day 7.

End point type	Primary
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End point timeframe:

Day 1 up to Day 7

Notes:

[5] - 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: Due to the highly explorative nature of the trial, confidence interval was displayed with 60% coverage. Infusion rate of norepinephrine was presented using descriptive statistics and graphical representation.

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: µg/kg/min				
arithmetic mean (standard deviation)				
Day 1 (12 h)	0.341 (± 0.691)	0.281 (± 0.444)	0.215 (± 0.405)	0.111 (± 0.197)
Day 1 (24 h)	0.01 (± 0.02)	0.222 (± 0.402)	0.639 (± 1.28)	0.089 (± 0.188)
Day 2 (36 h)	0 (± 0)	0.049 (± 0.101)	0 (± 0)	0.061 (± 0.171)
Day 2 (48 h)	0 (± 0)	0.105 (± 0.215)	0.004 (± 0.008)	0.057 (± 0.188)
Day 3 (72 h)	0 (± 0)	0.12 (± 0.27)	0 (± 0)	0.024 (± 0.079)
Day 4 (96 h)	0 (± 0)	0.184 (± 0.411)	0 (± 0)	0.005 (± 0.016)
Day 5 (120 h)	0 (± 0)	0.172 (± 0.385)	0 (± 0)	0 (± 0)
Day 6 (144 h)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Day 7 (168 h)	0 (± 0)	0 (± 0)	0 (± 0)	0.006 (± 0.021)

Statistical analyses

No statistical analyses for this end point

Primary: Time to septic shock resolution

End point title	Time to septic shock resolution ^[6]
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End point description:

Time to (first) septic shock resolution was defined as time of end of infusion regimen. Intermittent off treatment periods were regarded as part of the shock duration.

End point type	Primary
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End point timeframe:

Day 1 up to Day 28

Notes:

[6] - 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: Due to the highly explorative nature of the trial, confidence interval was displayed with 60% coverage. Time to septic shock resolution was displayed graphically by Kaplan-Meier (KM) plots.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	30 ^[7]			
Units: probability (%)				
number (confidence interval 60%)				
3.75 ng/kg/min:Period 0-≤47 h	0 (0 to 0)			
5.0 ng/kg/min:Period 0-≤136 h	0 (0 to 0)			
7.5 ng/kg/min:Period 0-≤79 h	0 (0 to 0)			

Modified 3.75 ng/kg/min:Period 0-≤168 h	7.7 (3 to 15.4)			
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Notes:

[7] - 3.75 ng/kg/min, n=5; 5.0 ng/kg/min, n=7; 7.5 ng/kg/min, n=5; modified 3.75 ng/kg/min, n=13

Attachments (see zip file)	KM estimation of time to septic shock resolution /KM estimation
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Statistical analyses

No statistical analyses for this end point

Secondary: Urinary output

End point title	Urinary output
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End point description:

The urinary output was recorded every 24 hours up to Day 7, or as long as the subject was in intensive care unit.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 7

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: mL/kg				
arithmetic mean (confidence interval 60%)				
Day 1 (24 h)	24.9 (16 to 33.8)	21.8 (16.4 to 27.2)	36 (27 to 45.1)	24.1 (20.2 to 28)
Day 2 (48 h)	42.9 (26.7 to 59.1)	31 (23.9 to 38)	55.9 (41.8 to 69.9)	48.1 (36.6 to 59.5)
Day 3 (72 h)	57.3 (32.3 to 82.3)	43.2 (32.3 to 54.1)	79.2 (58 to 100.4)	72.3 (53.7 to 91)
Day 4 (96 h)	68 (37.6 to 98.4)	58.8 (42.1 to 75.4)	100.5 (74.4 to 126.7)	94 (69.4 to 118.7)
Day 5 (120 h)	74.3 (42.3 to 106.3)	73.3 (51.1 to 95.6)	125.2 (94.3 to 156.1)	106.2 (79.2 to 133.2)
Day 6 (144 h)	81.8 (46.6 to 116.9)	85.9 (58.2 to 113.5)	139.8 (104.7 to 175)	111.9 (84.8 to 139.1)
Day 7 (168 h)	82 (46.8 to 117.2)	96.1 (64.2 to 128)	144.7 (108.2 to 181.2)	115.1 (87.7 to 142.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid balance

End point title	Fluid balance
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End point description:

The fluid balance (accumulated input/output) was recorded in 24-hour collecting periods when the subject was in the intensive care unit and during the infusion of FE 202158.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 7

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: mL/kg				
arithmetic mean (confidence interval 60%)				
Day 1 (24 h)	50 (23 to 77)	72 (60 to 85)	62 (50 to 74)	61 (52 to 69)
Day 2 (48 h)	69 (34 to 103)	128 (103 to 153)	96 (78 to 113)	75 (66 to 85)
Day 3 (72 h)	75 (32 to 118)	173 (141 to 206)	115 (94 to 135)	72 (61 to 83)
Day 4 (96 h)	76 (30 to 122)	189 (153 to 226)	107 (90 to 124)	68 (57 to 79)
Day 5 (120 h)	80 (31 to 130)	209 (172 to 247)	90 (78 to 102)	69 (57 to 81)
Day 6 (144 h)	84 (31 to 138)	209 (166 to 252)	88 (75 to 100)	76 (61 to 91)
Day 7 (168 h)	90 (33 to 147)	220 (174 to 267)	98 (77 to 119)	78 (62 to 95)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of investigator reported outcomes

End point title	Summary of investigator reported outcomes
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End point description:

Investigator reported outcome on FE 202158 performance. Answers were graded on a visual analogue scale (VAS) from 0 to 10, 0 being the worst and 10 being the best outcome.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 2

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: Score on scale				
arithmetic mean (standard deviation)				
Q1: Onset of action adequate to reach target MAP	4.4 (± 3.78)	3.57 (± 2.51)	9 (± 1.22)	7.85 (± 2.54)
Q2: MAP maintained within desired boundaries, Day 1	6.8 (± 2.77)	3.86 (± 2.67)	9 (± 1.22)	7.69 (± 3.66)
Q3: MAP maintained within desired boundaries, Day 2	10 (± 0)	4 (± 2.35)	8.75 (± 1.26)	6.71 (± 3.77)
Q4: Confidence to use FE 202158 primary treatment	6.5 (± 1.91)	5.5 (± 2.43)	9.5 (± 0.577)	8.18 (± 2.44)

Statistical analyses

No statistical analyses for this end point

Secondary: Morbidity assessment

End point title	Morbidity assessment
End point description: Collection of data on morbidity (proportion of subjects) was performed on Day 28 in addition to the collection of data on time of stay in intensive care unit and hospital.	
End point type	Secondary
End point timeframe: Day 1 up to Day 28	

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: percentage				
arithmetic mean (standard deviation)				
Days alive and out of intensive care unit	51.6 (± 47.4)	31.4 (± 43.2)	61.2 (± 35.9)	58.8 (± 37.2)
Days alive and out of hospital	12.8 (± 20.1)	3.6 (± 8.05)	17.8 (± 24.4)	26.2 (± 33.2)
Days alive and free of dialysis	60 (± 54.8)	38.6 (± 52.9)	80 (± 44.7)	76.7 (± 43.7)
Days alive and free of ventilation	58.8 (± 53.7)	39.6 (± 54.2)	75.6 (± 42.5)	73.9 (± 42.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse effects on lab parameters, vital signs and electrocardiogram

End point title	Adverse effects on lab parameters, vital signs and electrocardiogram
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End point description:

Significant changes for vital signs (blood pressure, heart rate, mean arterial pressure), electrocardiogram (ECG), and laboratory parameters (clinical chemistry, haematology, haemostasis, and urinary parameters).

End point type	Secondary
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End point timeframe:

Day 1 up to Day 7, and at follow-up assessments performed 24-72 hours after end of IMP infusion

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: subjects				
subjects with adverse effects on lab parameters	0	0	0	0
subjects with adverse effects on vital signs	0	0	0	0
subjects with adverse effects on electrocardiogram	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Graded morbidity

End point title	Graded morbidity
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End point description:

Collection of data on graded morbidity was performed on Day 28 in addition to the collection of data on time of stay in intensive care unit and hospital.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 28

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: Subjects				
Alive and out of hospital	2	0	2	6
In hospital (not intensive care unit)	1	2	2	4

In intensive care unit	1	1	0	0
Dead	1	2	1	3

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality
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End point description:

Collection of data on mortality was performed on Day 28 in addition to the collection of data on time of stay in intensive care unit and hospital.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 28

End point values	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min	Infusion Regimen 4: modified 3.75 ng/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	13
Units: subjects				
Alive	4	3	4	10
Dead	1	2	1	3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator monitored the condition of the subject throughout the trial from the time of obtaining informed consent until the end-of-trial visit or end of follow-up period as applicable.

Adverse event reporting additional description:

Collection of adverse events comprised the subject's positive response to questions about their health, symptoms spontaneously reported by the subject, and clinically relevant changes and abnormalities observed by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Infusion Regimen 1: 3.75 ng/kg/min
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Reporting group description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 3.75 ng/kg/min

Reporting group title	Infusion Regimen 2: 5.0 ng/kg/min
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Reporting group description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5 ng/kg/min, adjustable up to 5.0 ng/kg/min

Reporting group title	Infusion Regimen 3: 7.5 ng/kg/min
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Reporting group description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min adjustable up to a maximum of 7.5 ng/kg/min

Reporting group title	Infusion Regimen 4: modified 3.75 ng/kg/min
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Reporting group description:

FE 202158 0.1 mg/mL (10 mM acetate buffer, pH 4) was administered at initial infusion rate of 2.5-3.75 ng/kg/min, allowed to be increased to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of infusion. After 1 hour, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min

Reporting group title	Total
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Reporting group description:

Summation of adverse events in all arms.

Serious adverse events	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	4 / 7 (57.14%)	2 / 5 (40.00%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events	0	0	1
Vascular disorders			
Distributive shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Peripheral ischemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Cardiogenic shock			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (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
Myocardial ischemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Surgical and medical procedures			
Colostomy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (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

Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Gastrointestinal disorders			
Intestinal ischemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Hepatobiliary disorders			
Hepatic congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endocarditis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (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
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (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

Serious adverse events	Infusion Regimen 4: modified 3.75	Total	
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	ng/kg/min		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)	10 / 30 (33.33%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Distributive shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Peripheral ischemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Right ventricular failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 13 (0.00%) 0 / 0 0 / 0	1 / 30 (3.33%) 1 / 1 0 / 0	
Surgical and medical procedures Colostomy subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 13 (0.00%) 0 / 0 0 / 0	1 / 30 (3.33%) 0 / 1 0 / 0	
Nervous system disorders Cerebral haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 13 (7.69%) 0 / 1 0 / 1	1 / 30 (3.33%) 0 / 1 0 / 1	
Gastrointestinal disorders Intestinal ischemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 13 (0.00%) 0 / 0 0 / 0	1 / 30 (3.33%) 1 / 1 0 / 0	
Rectal haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 13 (7.69%) 0 / 1 0 / 0	2 / 30 (6.67%) 1 / 2 0 / 0	
Hepatobiliary disorders Hepatic congestion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 13 (0.00%) 0 / 0 0 / 0	1 / 30 (3.33%) 0 / 1 0 / 0	
Respiratory, thoracic and mediastinal disorders Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 13 (0.00%) 0 / 0 0 / 0	1 / 30 (3.33%) 1 / 1 0 / 0	
Infections and infestations Endocarditis			

subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Infusion Regimen 1: 3.75 ng/kg/min	Infusion Regimen 2: 5.0 ng/kg/min	Infusion Regimen 3: 7.5 ng/kg/min
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	7 / 7 (100.00%)	4 / 5 (80.00%)
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Peripheral coldness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Peripheral ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Atelectasis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Hypoventilation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Laryngospasm subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Lung infiltration subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Pleural effusion subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Pulmonary hypertension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Respiratory failure subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	1 / 5 (20.00%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Confusional state			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Investigations			
Blood potassium decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Troponin increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Injury, poisoning and procedural complications			
Overdose subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Post procedural complication subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 7 (28.57%) 2	0 / 5 (0.00%) 0
Cardiac failure subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Cyanosis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Myocardial depression subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Supraventricular tachycardia			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Impaired gastric emptying			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Intestinal ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Mouth haemorrhage			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oesophageal perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cytolytic hepatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatic congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Fluid overload			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Medical device complication			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoalbuminaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
occurrences (all)	1	2	1
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Metabolic alkalosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Infusion Regimen 4: modified 3.75 ng/kg/min	Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	27 / 30 (90.00%)	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Peripheral coldness			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Peripheral ischaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 30 (6.67%) 2	
General disorders and administration site conditions			
Hypothermia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Atelectasis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Hypoventilation subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Laryngospasm subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Lung infiltration subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Pleural effusion subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Pulmonary hypertension			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Respiratory failure subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	2 / 30 (6.67%) 2	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 30 (6.67%) 2	
Confusional state subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Investigations Blood potassium decreased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Troponin increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Injury, poisoning and procedural complications Overdose subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Post procedural complication subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	3 / 30 (10.00%) 3	
Cardiac failure subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	

Cyanosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Myocardial depression			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Thrombocytopenia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Duodenal ulcer			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastritis			

subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Impaired gastric emptying			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Intestinal ischaemia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Mouth haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 13 (15.38%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Oesophageal perforation			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Cytolytic hepatitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hepatic congestion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 13 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Fluid overload			
subjects affected / exposed	1 / 13 (7.69%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Infections and infestations			

Medical device complication subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	
Pneumonia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Metabolism and nutrition disorders			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	5 / 30 (16.67%) 5	
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 30 (3.33%) 1	
Metabolic acidosis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	2 / 30 (6.67%) 2	
Metabolic alkalosis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 30 (3.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2013	The amendment described changes to inclusion criterion 5 (inclusion of subject with septic shock requiring 0.6 µg/kg/min norepinephrine vasopressor support), and changes in the infusion rate of FE 202158 (introduction of modified regimen). In order to lower the risk of over-treatment with vasopressor, the norepinephrine requirement prior to start of FE 202158 was limited to 0.6 µg/kg/min, and the administration of IMP at an initial infusion rate of 2.5-3.75 ng/kg/min was allowed to be increased above 3.75 ng/kg/min up to a maximum of 7.5 ng/kg/min if needed, with a maximum duration of 1 hour, during the first 6 hours of FE 202158 infusion. When 1 hour had elapsed, or beyond the initial 6 hours, the infusion rate could not exceed 3.75 ng/kg/min. If the NE requirement increased above 0.6 µg/kg/min, infusion of FE 202158 should be terminated. The amendment required changes to the CRF and the IMP Administration Guideline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 November 2012	Safety reason	11 April 2013

Notes:

Limitations and caveats

None reported