Clinical trial results:
An open label trial evaluating the pharmacokinetics and safety of an intravenously administered single dose of Feramyl® 200 mg, 500 mg or 1500 mg vs. Ferinject® 500 mg in patients suffering from anaemia following cardiac surgery.

Summary

EudraCT number	2015-003069-28
Trial protocol	DK
Global end of trial date	14 October 2016

Results information

Result version number	v1 (current)
This version publication date	28 October 2017
First version publication date	28 October 2017

Trial information

Trial identification

Sponsor protocol code	SWB0115

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Serumwerk Bernburg AG
Sponsor organisation address	Hallesche Landstrasse 105 b, Bernburg, Germany, 06406
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 October 2016
Global end of trial reached?	Yes
Global end of trial date	14 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective is to evaluate dose proportionality of single dose Feramyl® given as 200 mg, 500 mg and 1500 mg i.v. infusion in terms of total iron in plasma.
Secondary objectives are:
- To evaluate general safety and tolerability of Feramyl® given as 200 mg, 500 mg and 1500 mg i.v. infusion to that of 500 mg Ferinject® i.v. infusion.
- To evaluate the early phase iron parameters of Feramyl® given as 200 mg, 500 mg and 1500 mg i.v. infusion and compare Feramyl® 500 mg i.v. infusion to that of 500 mg Ferinject® i.v. infusion.
- To evaluate urine iron parameters of Feramyl® given as 200 mg, 500 mg and 1500 mg i.v. infusion and compare Feramyl® 500 mg i.v. infusion to that of 500 mg Ferinject® i.v. infusion.
- To characterize the pharmacokinetic parameters of Feramyl® given as 200 mg, 500 mg and 1500 mg i.v. infusion and compare Feramyl® 500 mg i.v. infusion to that of 500 mg Ferinject® i.v. infusion in terms of total iron in plasma.

Protection of trial subjects:

The DSMB had their first meeting before trial start to decide on meeting frequency and format, the degree, form and frequency of the information neede din oter to monitor trial safety. In addition, the DSMB met prior to start of the 500 mg and 1500 mg dosing groups to evaluate whether or not it was safe to proceed to the next dose level.
The DSMB's tasks were to:
- Monitor safety data
- Assess any critical adverse event (CAE) occuring during the trial
- Assess safety profile after each dose level
- Evaluate PK and urine data
- Evaluate specific rat study before start of the 1500 mg feramyl(R) treatment group

Background therapy: -

Evidence for comparator:

Ferinject (comparator) is an iron-containing nanoparticle, where the shielding sugar is carboxymaltose, which is less antigenic than the sugars in other iron containing drugs based on dextran as the sugar moity.

Actual start date of recruitment	06 November 2015
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	Denmark: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

8 subjects were enrolled in cohort 1 from 06-Nov-2015 to 11-Dec-2015, 18 were enrolled in cohort 2 from 23-Feb-2016 to 04-Jun-2016 (one was not treated due to withdrawal of consent) and 8 subjects were enrolled into cohort 3 from 21-Jun-2016 to 14-Oct-2016.

Pre-assignment

Screening details:

79 subjects were screened before cardiac surgery and reevaluated for particiation after surgery depedning on 1) low mortality risk, 2) severity of anaemia and 3) blood pressure.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinding was used as endpoints are based on lab values.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Subjects in cohort 1 received 200 mg Feramyl.

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

Dosage and administration details:

200 mg Feramyl was administered as single i.v. infusion over a period of 15 minutes by use of an infusion pump.

Arm title	Cohort 2 - experimental

Arm description:

Subjects in cohort 2 were randomized to either receive 500 mg Feramyl or 500 mg Ferinject.

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

Dosage and administration details:

500 mg Feramyl was administered as single i.v. infusion over a period of 15 minutes by use of an infusion pump.

Arm title	Cohort 2 - comparator

Arm description:

Subjects in cohort 2 were randomized to either receive 500 mg Feramyl or 500 mg Ferinject.

Arm type	Active comparator

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

Dosage and administration details:

500 mg Ferinject was administered as single i.v. infusion over a period of 15 minutes by use of an infusion pump.

Arm title	Cohort 3

Arm description:

Subjects in cohort 3 received 1500 mg Feramyl.

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

Dosage and administration details:

1500 mg Feramyl was administered as single i.v. infusion over a period of 15 minutes by use of an infusion pump.

Number of subjects in period 1	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator
Started	8	9	8
per cohort	8	9	8
Completed	7	9	8
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

Number of subjects in period 1	Cohort 3
Started	8
per cohort	8
Completed	8
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	33	33	
Age categorical			
One subject withdrew consent before randomisation. This subject is not included in the age listing.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	22	22	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	33	33	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects in cohort 1 received 200 mg Feramyl.	
Reporting group title	Cohort 2 - experimental
Reporting group description: Subjects in cohort 2 were randomized to either receive 500 mg Feramyl or 500 mg Ferinject.	
Reporting group title	Cohort 2 - comparator
Reporting group description: Subjects in cohort 2 were randomized to either receive 500 mg Feramyl or 500 mg Ferinject.	
Reporting group title	Cohort 3
Reporting group description: Subjects in cohort 3 received 1500 mg Feramyl.	

Primary: Total Iron in Plasma AUC(0-infinity)

End point title	Total Iron in Plasma AUC(0-infinity)[1]

End point description:

The primary objective of the trial was examined by the co-primary endpoints: AUC(0-infinity) and Cmax of total iron in plasma following infusion calculated for subjects exposed to Feramyl® treatment. AUC(0-infinity) is the area under the concentration time curve for plasma total iron from time 0 (start of infusion) to infinity and Cmax the maximum concentration of the same profile.

Dose proportionality could not be claimed for Feramyl, as the 90% CI for both co-primary endpoints was not entirely contained within the limits 0.80 – 1.25. The 90% CI for AUC(0-infinity) ranged between 1.05 – 1.39. Scatterplot of AUC(0-infinity) did however show dose dependency.

End point type	Primary

End point timeframe:

72 hours

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: The primary objective of the trial is examined by the co-primary endpoints: AUC(0-infinity) and Cmax of total iron in plasma following infusion calculated for subjects exposed to treatment with Feramyl. AUC(0-infinity) is the area under the concentration time curve for plasma total iron from time 0 (start of infusion) to infinity and Cmax the maximum concentration of the same profile.
The resuluts will be used for comparison between the 4 groups. No statistical analysis is performed.

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: microgram(s)*hour/millilitre				
geometric mean (full range (min-max))	123.19 (94.6 to 147.1)	426.7 (246.7 to 625.5)	1873.46 (1194.8 to 2567.0)	1204.70 (441.5 to 3423.1)

Statistical analyses

No statistical analyses for this end point

Primary: Total Iron in Plasma C(max)

End point title	Total Iron in Plasma C(max)[2]

End point description:

The primary objective of the trial was examined by the co-primary endpoints: AUC(0-infinity) and Cmax of total iron in plasma following infusion calculated for subjects exposed to Feramyl® treatment. AUC(0-infinity)) is the area under the concentration time curve for plasma total iron from time 0 (start of infusion) to infinity and Cmax the maximum concentration of the same profile.

Dose proportionality could not be claimed for Feramyl, as the 90% CI for both co-primary endpoints was not entirely contained within the limits 0.80 – 1.25. The 90% CI for Cmax ranged between 0.78 – 1.01. Scatterplot Cmax did however show dose dependency.

End point type	Primary

End point timeframe:

72 hours

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: The primary objective of the trial is examined by the co-primary endpoints: AUC(0-infinity) and Cmax of total iron in plasma following infusion calculated for subjects exposed to treatment with Feramyl. AUC(0-infinity) is the area under the concentration time curve for plasma total iron from time 0 (start of infusion) to infinity and Cmax the maximum concentration of the same profile.
The resuluts will be used for comparison between the 4 groups. No statistical analysis is performed.

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: microgram(s)/millilitre				
geometric mean (full range (min-max))	61.20 (40.25 to 73.73)	147.60 (101.66 to 199.50)	128.08 (107.75 to 155.75)	333.94 (189.07 to 598.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Infusion site reactions, hypersensitivity reactions, all-cause mortality. For hypersensitivity reactions blood preasure and heart rate will be evaluated at t=15 minutes (end of infusion), 30 minutes and 60 minutes following infusion.

End point type	Secondary

End point timeframe:

60 minutes following infusion

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: Hypersensitivy reactions				
15 min	0	0	0	0
30 min	0	0	0	0
60 min	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Transferrin Saturation (TSAT)

End point title	Transferrin Saturation (TSAT)

End point description:

Transferrin saturation (TSAT) is a measurement of how much iron is bound and will be shown as a ratio.

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[3]	9[4]	8[5]	8[6]
Units: ratio				
geometric mean (standard deviation)				
Screening	0.206 (± 0.083)	0.272 (± 0.05)	0.293 (± 0.074)	0.174 (± 0.066)
Post-operation and pre-infusion	0.083 (± 0.036)	0.091 (± 0.033)	0.099 (± 0.039)	0.079 (± 0.019)
8 hours	0.083 (± 0.016)	0.124 (± 0.043)	0.649 (± 0.223)	0.367 (± 0.191)
24 hours	0.101 (± 0.020)	0.177 (± 0.084)	0.354 (± 0.193)	0.246 (± 0.104)
48 hours	0.123 (± 0.043)	0.183 (± 0.071)	0.184 (± 0.024)	0.205 (± 0.057)
72 hours	0.124 (± 0.033)	0.209 (± 0.096)	0.154 (± 0.033)	0.231 (± 0.084)

Notes:

[3] - For timeponint "post-operation and pre-infusion" N=8

[4] - At screening N=5

[5] - At screening N=6

[6] - At screening and 24 hours N=7

Statistical analyses

No statistical analyses for this end point

Secondary: Haemoglobin

End point title	Haemoglobin
End point description: haemoglobin (mmol/L)	
End point type	Secondary
End point timeframe: 72 hours	

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[7]	9	8	8[8]
Units: millimole(s)/litre				
geometric mean (standard deviation)				
Screening	8.30 (± 1.05)	8.77 (± 0.94)	9.35 (± 0.62)	7.89 (± 0.75)
Post-operation and pre-infusion	6.19 (± 0.62)	6.86 (± 0.82)	7.09 (± 0.73)	5.78 (± 0.38)
8 hours	5.78 (± 0.71)	6.50 (± 0.71)	6.86 (± 0.80)	5.71 (± 0.54)
24 hours	5.77 (± 0.57)	6.33 (± 0.89)	6.69 (± 0.64)	5.51 (± 0.34)
48 hours	5.71 (± 0.79)	6.13 (± 0.92)	6.68 (± 0.47)	5.36 (± 0.40)
72 hours	5.80 (± 0.78)	6.47 (± 0.73)	6.70 (± 0.65)	5.30 (± 0.55)

Notes:

[7] - At screening and post-operation and pre-infusion N=8
At 8 hours N=6
[8] - At 24 hours N=7

Statistical analyses

No statistical analyses for this end point

Secondary: Ferritin

End point title	Ferritin
End point description: ferritin (µg/L)	
End point type	Secondary
End point timeframe: 72 hours	

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[9]	9	8	8[10]
Units: microgram(s)/litre				
geometric mean (standard deviation)				
Screening	162.9 (± 100.2)	281.3 (± 353.8)	271.4 (± 107.3)	187.6 (± 127.1)
Post-operation and pre-infusion	259.5 (± 98.3)	333.4 (± 334.7)	334.4 (± 99.6)	294.9 (± 191.5)

8 hours	259.6 (± 91.8)	360.3 (± 320.1)	342.8 (± 83.4)	311.1 (± 180.2)
24 hours	298.7 (± 104.8)	458.6 (± 272.8)	493.5 (± 84.0)	549.4 (± 240.7)
48 hours	386.7 (± 167.4)	659.0 (± 334.5)	809.0 (± 104.3)	876.3 (± 411.5)
72 hours	480.6 (± 227.0)	1418.9 (± 2027.3)	1003.9 (± 174.0)	1103.9 (± 515.5)

Notes:

[9] - At post-operation and pre-infusion N=8

[10] - At 24 hours N=7

Statistical analyses

No statistical analyses for this end point

Secondary: Urine Iron Excretion

End point title	Urine Iron Excretion

End point description:

Summary of urine iron excretion (mg) by time period reported as number of patients with urinary iron above lower limit of quantification (LLQ) per patients observed.

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9[11]	8	8
Units: Patients				
0-8 hours	0	0	8	1
8-24 hours	0	0	5	1
24-48 hours	0	1	0	1
48-72 hours	0	0	0	1

Notes:

[11] - At t=48-72 N=8

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax

End point title	Tmax

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: minute				
geometric mean (full range (min-max))	17.1 (15 to 30)	24.0 (15 to 63)	47.6 (15 to 120)	15.0 (15 to 15)

Statistical analyses

No statistical analyses for this end point

Secondary: T(half)

End point title	T(half)

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: hour				
geometric mean (full range (min-max))	1.58 (1.16 to 2.29)	1.25 (0.79 to 2.01)	8.96 (7.48 to 10.70)	1.08 (0.42 to 1.92)

Statistical analyses

No statistical analyses for this end point

Secondary: Clearence

End point title	Clearence

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: Litre(s)/hour				
geometric mean (full range (min-max))	1.623 (1.36 to 2.11)	1.179 (0.80 to 2.03)	0.267 (0.19 to 0.42)	1.245 (0.44 to 3.40)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Iron in Plasma AUC(0-72)

End point title	Total Iron in Plasma AUC(0-72)

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: hour/litre				
geometric mean (full range (min-max))	120.69 (93.8 to 144.6)	418.02 (246.6 to 613.9)	1782.42 (1161.3 to 2237.1)	1174.21 (435.8 to 3180.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Lambda(z)

End point title	Lambda(z)

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: 1/hour				
geometric mean (full range (min-max))	0.44 (0.30 to 0.60)	0.56 (0.35 to 0.88)	0.08 (0.07 to 0.09)	0.64 (0.36 to 1.67)

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution(z)

End point title	Volume of Distribution(z)

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	8	8
Units: litre(s)				
geometric mean (full range (min-max))	3.70 (2.80 to 5.36)	2.12 (1.40 to 3.19)	3.45 (2.49 to 6.18)	1.94 (0.97 to 6.35)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period begins from screening until the subject terminates the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cohort 1
Reporting group description: -	
Reporting group title	Cohort 2 - experimental
Reporting group description: -	
Reporting group title	Cohort 2 - comparator

Reporting group description:

One subject randomized withdrew his consent before dosing. This subjects did not experience any adverse events and is not included in the summary below (as he withdrew right after screening).

Reporting group title	Cohort 3

Reporting group description: -

Serious adverse events	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Haemorrhage	Additional description: Surgical bleeding		
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (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	Cohort 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Haemorrhage	Additional description: Surgical bleeding		

subjects affected / exposed	0 / 8 (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: 0 %

Non-serious adverse events	Cohort 1	Cohort 2 - experimental	Cohort 2 - comparator
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	5 / 9 (55.56%)	3 / 8 (37.50%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 8 (37.50%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	3	1	0
Atrioventricular block			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Respiratory failure			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 8 (12.50%)	3 / 9 (33.33%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Hypovolaemia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Atrioventricular block			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hypovolaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2016	Substantial amendment specifying that anesthesia was not required to be transcribed from source data to the eCRF, as the operation was not considered trial related. In addition, the amendment covered a specification of inclusion criteria no 4 (level of anaemia) for the 1500 mg treatment group.
28 June 2016	Opening of an extra site in Århus as recruitment for the 1500 mg treatment group was significantly delayed at Rigshospitalet. The delay was due to the severe anaemia required for subjects to qualify for the 1500 mg treatment group. This amendment never came into force as the subjects became available at Rigshospitalet.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported