Clinical trial results:
A Multicenter Study on Regenerative Effects of Erythropoitin (LDE) in Burn and Scaled Injuries

Summary

EudraCT number	2006-002886-38
Trial protocol	DE
Global end of trial date	06 June 2014

Results information

Result version number	v1 (current)
This version publication date	03 April 2021
First version publication date	03 April 2021
Summary attachment (see zip file)	EPO (EPO_CSR.pdf)

Trial information

Trial identification

Sponsor protocol code	0506

Additional study identifiers

ISRCTN number	ISRCTN95777824
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	BMC: doi:10.1186/1745-6215-14-124

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaningerstr. 22, München, Germany, 81675
Public contact	Professor Dr. med. Hans-Günther Machens, Klinikum rechts der Isar der TU München, Klinik und Poliklinik für Plastische Chirurgie, 49 4140 2171, Hans-Guenther.Machens@mri.tum.de
Scientific contact	Professor Dr. med. Hans-Günther Machens, Klinikum rechts der Isar der TU München, Klinik und Poliklinik für Plastische Chirurgie, 49 4140 2171, Hans-Guenther.Machens@mri.tum.de

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	28 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2014
Global end of trial reached?	Yes
Global end of trial date	06 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Time until complete reepithelialization of skin graft donor sites (thickness 0.3 mm) at a definite location on the lateral upper thigh (Primary endpoint)

- To prove a cytoprotective and regenerative effect of erythropoietin in thermally injured patients in terms of reduced morbidity and mortality
- To better understand the cellular mechanisms of erythropoietin in Skin Graft Donor Sites (SGDS) and Second Degree Wounds (SDW)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP).
Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
The study was regularly monitored by the Sponsor and additionally a Data Safety Monitoring Board was set up. All investigators connected to the study were GCP trained.

Background therapy:

Erythropoietin application will be the only change of standard therapy protocol in all patients.
Every subject had received a state of the art Treatment for burn or scald injury during study. These concomitant Treatments had been doccumented appropriately in the Standard patients´chart documentation flow sheets. All Treatments had been taken by the subjects at any time during the study in addition to the investigational product were regarded as concomitant treatments.

Evidence for comparator:

Comparator(s) not applicable.

Actual start date of recruitment	09 January 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	72
From 65 to 84 years	11
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted multicentric in Germany between 09.01.2009 (first patient recruited) and 09.07.2013 (last patient completed).

Pre-assignment

Screening details:

Each potential patient was examined before the start of the study to determine their eligibility for participation. Patients must have all screening evaluations performed prior to the first dose of study drug and must meet all inclusion and none of the exclusion criteria.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Erythropoietin

Arm description:

Erythropoietin (EPO, Neorecormon 50.000 IE Multidose) application: The amount of EPO given to the patients was 150 IU/kg body weight/application every second day over 21 days after randomization, injected subcutaneously in the caudal third of the abdominal wall, if not injured. EPO will be applied as NeoRecormon from multidosage vials containing 50,000 IU EPO.

Arm type	Experimental
Investigational medicinal product name	NeoRecormon
Investigational medicinal product code	ATC code B03XA
Other name	Epoetin Beta, Erythropoietin, Epo
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

150/KG IU every second day over 21 days after randomization, injected subcutaneously

Arm title	Placebo

Arm description:

Placebo Group: Each patient will receive a placebo carrier substance (without EPO) every second day over 21 days after randomization, injected subcutaneously in the caudal third of the abdominal wall, if not injured.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In the control group placebo was given to the patients every second day over 3 weeks after randomization, injected subcutaneously in the caudal third of the abdominal wall, if not injured.

Number of subjects in period 1	Erythropoietin	Placebo
Started	45	39
Completed	23	19
Not completed	22	20
Adverse event, serious fatal	3	1
Consent withdrawn by subject	1	4
Adverse event, non-fatal	1	-
Lost to follow-up	14	14
personal reasons	2	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	84	84	
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			
median	47.5		
full range (min-max)	18 to 87	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	66	66	

Subject analysis sets

Subject analysis set title	PP-EPO
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set contains all patients in the pp-set, who were in the EPO arm.

Subject analysis set title	PP-Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set contains all patients in the pp-set, who were in the Placebo arm.

Reporting group values	PP-EPO	PP-Placebo	
Number of subjects	29	24	
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			
median	51	43	
full range (min-max)	19 to 87	18 to 74	
Gender categorical Units: Subjects			
Female	8	2	
Male	21	22	

End points

End points reporting groups

Reporting group title	Erythropoietin

Reporting group description:

Erythropoietin (EPO, Neorecormon 50.000 IE Multidose) application: The amount of EPO given to the patients was 150 IU/kg body weight/application every second day over 21 days after randomization, injected subcutaneously in the caudal third of the abdominal wall, if not injured. EPO will be applied as NeoRecormon from multidosage vials containing 50,000 IU EPO.

Reporting group title	Placebo

Reporting group description:

Placebo Group: Each patient will receive a placebo carrier substance (without EPO) every second day over 21 days after randomization, injected subcutaneously in the caudal third of the abdominal wall, if not injured.

Subject analysis set title	PP-EPO
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set contains all patients in the pp-set, who were in the EPO arm.

Subject analysis set title	PP-Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set contains all patients in the pp-set, who were in the Placebo arm.

Primary: Time to complete reepithelialization

End point title	Time to complete reepithelialization

End point description:

The primary endpoint analysis was performed by a two-sided van Elteren's test with ABSI score (<7 versus ≥7) as strata on a confirmatory 5% significance level using the ITT population. Missing values were imputed according to the „worst-case scenario".

End point type	Primary

End point timeframe:

Time from study begin to complete reepithelialization

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	39		
Units: day				
arithmetic mean (standard deviation)				
ABSI <7	24.1 (± 10.1)	12.6 (± 4.0)		
ABSI >=7	28.7 (± 6.2)	14.6 (± 3.4)		

Statistical analyses

Statistical analysis title	Difference between groups

Statistical analysis description:

Using the Van Elteren Test there was a statistically significant difference between the two groups (ITT) in favor of the placebo group, which was mainly due to the

imputation of missing values because of the conservative substitution.

Comparison groups	Placebo v Erythropoietin
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Van Elteren Test

Notes:

[1] - The Van Elteren test stratified by ABSI score (<7 or >=7) was used.

Primary: Grade of re-epithelialization

End point title	Grade of re-epithelialization

End point description:

Sensitivity analysis of the primary endpoint. Since wound healing was recorded as ordinal data in the CRF (values: 0%; 1-25%, 26-50%, 51-75%, 76-99%, 100%), the last recorded value for re-epithelialization was compared between treatment groups using number and percent for each re-epithelialization value and an exploratory Mann-Whitney-U test as sensitivity analysis.

End point type	Primary

End point timeframe:

End of study

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[2]	37[3]		
Units: Patients				
26-50%	1	2		
51-75%	8	4		
76-99%	22	20		
100%	9	11		

Notes:

[2] - 5 patients with missing values

[3] - 2 patients with missing values

Statistical analyses

Statistical analysis title	Comparison of grade of re-epithelialization
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to complete wound healing of type 2a SDW

End point title	Time to complete wound healing of type 2a SDW

End point description:

End point type	Secondary

End point timeframe:
from start of treatment until study end

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	45	39	29	24
Units: day				
arithmetic mean (standard deviation)	27.3 (± 7.7)	25.9 (± 8.5)	27.1 (± 7.8)	24.6 (± 9.5)

Statistical analyses

Statistical analysis title	Comparison complete wound healing type 2a SDW ITT

Statistical analysis description:
Comparison of time to complete wound healing type 2a SDW on the ITT set.

Comparison groups	Placebo v Erythropoietin
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.401
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison complete wound healing type 2a SDW PP

Statistical analysis description:
Comparison of time to complete wound healing type 2a SDW on the PP set.

Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.278
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to complete wound healing of TDW

End point title	Time to complete wound healing of TDW

End point description:
Time until complete wound healing of skin graft

End point type	Secondary

End point timeframe:
From study begin to end of study

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	45	39	29	24
Units: day				
arithmetic mean (standard deviation)	26.4 (± 8.2)	23.1 (± 9.9)	27.2 (± 7.6)	23.1 (± 10.6)

Statistical analyses

Statistical analysis title	Difference in TDW on ITT
Statistical analysis description: Difference in time to complete wound healing of skin graft on the ITT set.	
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Difference in TDW on PP
Statistical analysis description: Difference in time to complete wound healing of skin graft on the PP set.	
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of scar formation on type 2a SDW	
End point title	Quality of scar formation on type 2a SDW
End point description: Quality of scar formation on type 2a SDW at day 42 - Vancouver Scar Scale	
End point type	Secondary
End point timeframe: Day 42	

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	18[4]	13[5]	13[6]	10[7]
Units: points				
arithmetic mean (standard deviation)	2.7 (± 1.4)	2.9 (± 1.6)	2.9 (± 1.4)	2.7 (± 1.5)

Notes:

[4] - Available for 18 patients at day 42

[5] - Available for 13 patients at day 42

[6] - Available for 13 patients at day 42.

[7] - Available for 10 patients at day 42.

Statistical analyses

Statistical analysis title	Comparison SDW quality of scar score ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.838
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SDW quality of scar score PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.678
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of scar formation on TDW

End point title	Quality of scar formation on TDW
End point description:	
Quality of scar formation on TDW - Vancouver Scar Scale	
End point type	Secondary
End point timeframe:	
day 42	

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	26[8]	18[9]	19[10]	14[11]
Units: points				
arithmetic mean (standard deviation)	5.0 (± 2.0)	3.7 (± 1.7)	5.1 (± 2.1)	3.4 (± 1.5)

Notes:
[8] - Values available for 26 patients.
[9] - Values available for 18 patients.
[10] - Values available for 19 patients.
[11] - Values available for 14 patients.

Statistical analyses

Statistical analysis title	Comparison TDW quality of scar score ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison TDW quality of scar score PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of scar formation on SGDS	
End point title	Quality of scar formation on SGDS
End point description: Quality of scar formation on skin graft donor site (SGDS) at day 42 – Vancouver Scar Scale	
End point type	Secondary
End point timeframe: day 42	

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	27[12]	18[13]	20[14]	14[15]
Units: points				
arithmetic mean (standard deviation)	3.1 (± 1.3)	3.6 (± 1.6)	3.2 (± 1.2)	3.1 (± 1.6)

Notes:
[12] - Values available for 27 patients only.
[13] - Values available for 18 patients only.
[14] - Values available for 20 patients only.
[15] - Values available for 14 patients only.

Statistical analyses

Statistical analysis title	Comparison SGDS quality of scar score ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SGDS quality of scar score PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.719
Method	Wilcoxon (Mann-Whitney)

Secondary: Red cells	
End point title	Red cells
End point description: Number of packed red cell units, which are transfused during the treatment.	
End point type	Secondary
End point timeframe: Throughout the study	

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	43[16]	38[17]	27[18]	23[19]
Units: Packs				
arithmetic mean (standard deviation)	6.9 (± 11.9)	7.1 (± 9.0)	6.7 (± 7.8)	9.3 (± 10.1)

Notes:

[16] - Values available for 43 patients only.

[17] - Values available for 38 patients only.

[18] - Values available for 27 patients only.

[19] - Values available for 23 patients only.

Statistical analyses

Statistical analysis title	Comparison of red cell units on ITT
Comparison groups	Erythropoietin v Placebo

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison of red cell units on PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	Wilcoxon (Mann-Whitney)

Secondary: Respiratory SOFA score Day 7

End point title	Respiratory SOFA score Day 7

End point description:

End point type	Secondary

End point timeframe:

Measured on day 7.

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[20]	37[21]		
Units: points				
arithmetic mean (standard deviation)	0.6 (± 1.0)	1.1 (± 1.3)		

Notes:

[20] - Values available for 40 patients only.

[21] - Values available for 37 patients only.

Statistical analyses

Statistical analysis title	Comparison Resp. SOFA Day 7
Comparison groups	Placebo v Erythropoietin
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Wilcoxon (Mann-Whitney)

Secondary: Respiratory SOFA score Day 14

End point title	Respiratory SOFA score Day 14

End point description:

End point type	Secondary

End point timeframe:

Measured on day 14.

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[22]	35[23]		
Units: points				
arithmetic mean (standard deviation)	0.5 (± 0.8)	0.7 (± 0.9)		

Notes:

[22] - Values available for 39 patients only.

[23] - Values available for 35 patients only.

Statistical analyses

Statistical analysis title	Comparison Resp. SOFA Day 14
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.145
Method	Wilcoxon (Mann-Whitney)

Secondary: Cardiovascular SOFA day 7

End point title	Cardiovascular SOFA day 7

End point description:

Cardiovascular SOFA score on day 7

End point type	Secondary

End point timeframe:

Measured on day 7.

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[24]	37[25]		
Units: points				
arithmetic mean (standard deviation)	0.5 (± 1.1)	0.6 (± 1.2)		

Notes:
[24] - Values available for 40 patients only.
[25] - Values available for 37 patients only.

Statistical analyses

Statistical analysis title	Comparison Cardio SOFA Day 7
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.678
Method	Wilcoxon (Mann-Whitney)

Secondary: Cardiovascular SOFA day 14

End point title	Cardiovascular SOFA day 14
End point description: Cardiovascular SOFA score measured on day 14.	
End point type	Secondary
End point timeframe: Measured on day 14	

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[26]	35[27]		
Units: points				
arithmetic mean (standard deviation)	0.2 (± 0.7)	0.8 (± 1.3)		

Notes:
[26] - Values available for 39 patients only.
[27] - Values available for 35 patients only.

Statistical analyses

Statistical analysis title	Comparison Cardio SOFA Day 14
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-36, physical functioning

End point title	SF-36, physical functioning

End point description:

End point type	Secondary

End point timeframe:

At 12 months post trauma.

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	13[28]	12[29]	10	10
Units: points				
arithmetic mean (standard deviation)	83.5 (± 23.3)	77.5 (± 16.6)	79.0 (± 25.0)	75.0 (± 17.0)

Notes:

[28] - Values available for 13 patients only.

[29] - Values available for 12 patients only.

Statistical analyses

Statistical analysis title	Comparison SF-36, physical functioning, ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.467
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SF-36, physical functioning, PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.682
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-36, physical role functioning

End point title	SF-36, physical role functioning

End point description:

End point type	Secondary

End point timeframe:

At 12 months post trauma.

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12[30]	12[31]	9	10
Units: points				
arithmetic mean (standard deviation)	52.1 (± 44.5)	33.3 (± 45.6)	38.9 (± 43.5)	27.5 (± 44.8)

Notes:

[30] - Values available for 12 patients only.

[31] - Values available for 12 patients only.

Statistical analyses

Statistical analysis title	Comparison SF-36, physical role functioning, ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SF-36, physical role functioning, PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-36, emotional role functioning

End point title	SF-36, emotional role functioning

End point description:

End point type	Secondary

End point timeframe:

At 12 months post trauma.

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12[32]	12[33]	9	10
Units: points				
arithmetic mean (standard deviation)	77.8 (± 41.0)	79.2 (± 33.4)	77.8 (± 41.0)	79.2 (± 33.4)

Notes:

[32] - Values available for 12 patients only.

[33] - Values available for 12 patients only.

Statistical analyses

Statistical analysis title	Comparison SF-36, emotional role functioning, ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.928
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SF-36, emotional role functioning, PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.809
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-36, mental health

End point title	SF-36, mental health

End point description:

End point type	Secondary

End point timeframe:

At 12 months post trauma.

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[34]	12[35]		
Units: points				
arithmetic mean (standard deviation)	81.5 (± 17.3)	78.0 (± 14.2)		

Notes:

[34] - Values available for 13 patients only.

[35] - Values available for 12 patients only.

Statistical analyses

Statistical analysis title	Comparison SF-36, mental health
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.581
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-36, vitality

End point title	SF-36, vitality

End point description:

End point type	Secondary

End point timeframe:

At 12 months post trauma.

End point values	Erythropoietin	Placebo	PP-EPO	PP-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	13[36]	12[37]	10	10
Units: points				
arithmetic mean (standard deviation)	71.9 (± 17.9)	62.9 (± 19.8)	69.0 (± 19.6)	61.5 (± 21.6)

Notes:

[36] - Values available for 13 patients only.

[37] - Values available for 12 patients only.

Statistical analyses

Statistical analysis title	Comparison SF-36, vitality, ITT
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison SF-36, vitality, PP
Comparison groups	PP-EPO v PP-Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-36, general health

End point title	SF-36, general health

End point description:

End point type	Secondary

End point timeframe:

At 12 months post trauma.

End point values	Erythropoietin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[38]	12[39]		
Units: points				
arithmetic mean (standard deviation)	79.8 (± 20.8)	75.5 (± 17.2)		

Notes:

[38] - Values available for 13 patients only.

[39] - Values available for 12 patients only.

Statistical analyses

Statistical analysis title	Comparison SF-36, general health
Comparison groups	Erythropoietin v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.578
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1
Reporting groups	
Reporting group title	All patients
Reporting group description:	
Adverse events analysis was conducted on the ITT set.	

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 84 (22.62%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood culture positive			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood urea increased			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Thrombosis				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ischaemic cerebral infarction				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytosis				
subjects affected / exposed	3 / 84 (3.57%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Multi-organ failure				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sudden cardiac death				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Systemic inflammatory response syndrome				

subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Enterococcal sepsis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	3 / 84 (3.57%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 84 (3.57%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pseudomonal sepsis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection staphylococcal			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 84 (45.24%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	10 / 84 (11.90%)		
occurrences (all)	12		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 84 (7.14%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	12 / 84 (14.29%)		
occurrences (all)	19		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 84 (11.90%)		
occurrences (all)	16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30429786