Clinical trial results:
A MULTICENTRE, PHASE II, OPEN LABEL, RANDOMISED CONTROLLED TRIAL OF REPEATED AUTOLOGOUS INFUSIONS OF G-CSF MOBILISED CD133+ BONE MARROW STEM CELLS IN PATIENTS WITH CIRRHOSIS

Summary

EudraCT number	2009-010335-41
Trial protocol	GB
Global end of trial date	18 May 2016

Results information

Result version number	v1 (current)
This version publication date	04 May 2019
First version publication date	04 May 2019
Summary attachment (see zip file)	Study Protocol (20140129 realistic protocol V8.0_Clean (2).pdf) Public summary of Results: REALISTIC (REALISTIC Public Summary 29 11 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_09-151

Additional study identifiers

ISRCTN number	ISRCTN91288089
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Room 119, Aston Webb Building,Edgbaston,, Birmingham, United Kingdom, B15 2TT
Public contact	Mr Darren Barton, D3B Trial Management Team Leader CRUK Clinical Trials Unit Birmingham United Kingdom, 44 1213718027, d.barton@bham.ac.uk
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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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2016
Global end of trial reached?	Yes
Global end of trial date	18 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the trial is to examine whether administering either G-CSF alone or G-CSF followed by repeated infusions of stem cells is better than standard supportive care in improving severity of liver disease over 3 months.

Protection of trial subjects:

All adverse events and serious adverse events experienced by participants in the clinical trial were collected by the study team.
Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.
Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or to continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.
The DMC will report directly to the Trial Management Group who will convey the findings of the DMC to the Study Sponsor, the MHRA and Ethics Committee.
The DMC may consider discontinuing the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety.

Background therapy:

see attached protocol

Evidence for comparator:

see attached protocol

Actual start date of recruitment	18 May 2010
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	United Kingdom: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	70
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 3 NHS participating hospitals in the united kingdom. The Recruitment was between 18th May 2010 - 26th Feb 2015. A total of 81 patients were recruited across 3 different treatment groups

Pre-assignment

Screening details:

All screening procedures were performed a maximum of 7 days prior to randomisation and with 14 days of start of treatment

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Control group: standard conservative management

Arm description:

Standard conservative management only

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Group 2: Treatment: GCSF Alone

Arm description:

Standard conservative management + GCSF

Arm type	Experimental
Investigational medicinal product name	Lenograstim
Investigational medicinal product code	
Other name	Granocyte
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage to be used in this study will be 15µg/kg/day. This is higher than the standard dose and has been shown to be safe and more effective in patients with cirrhosis

Arm title	Group 3: GSCF + CD133+ cell infusion (x3)

Arm description:

GCSF followed by Leukapheresis, CD133+ cell isolation and
repeated infusions on days 5/6, 30, 60 via peripheral vein

Arm type	Experimental
Investigational medicinal product name	Lenograstim
Investigational medicinal product code	
Other name	Granocyte
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage to be used in this study will be 15µg/kg/day. This is higher than the standard dose and has been shown to be safe and more effective in patients with cirrhosis

Number of subjects in period 1	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)
Started	27	26	28
Completed	27	26	26
Not completed	0	0	2
Patient did not receive any cell infusions	-	-	1
Patient died before treatment	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: Control group: standard conservative management
Reporting group description:	
Standard conservative management only	
Reporting group title	Group 2: Treatment: GCSF Alone
Reporting group description:	
Standard conservative management + GCSF	
Reporting group title	Group 3: GSCF + CD133+ cell infusion (x3)
Reporting group description:	
GCSF followed by Leukapheresis, CD133+ cell isolation and repeated infusions on days 5/6, 30, 60 via peripheral vein	

Reporting group values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects	27	26	28
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	52.0	54.0	56.5
inter-quartile range (Q1-Q3)	47.0 to 60.0	49.0 to 61.0	47.5 to 62.5
Gender categorical			
Units: Subjects			
Female	14	8	6
Male	13	18	22
Aetiology			
Units: Subjects			
Alcohol related liver disease	12	12	13
Hepatitis C	4	3	3
Other	11	11	12
Centre			
Units: Subjects			
Queen's Medical Centre, Nottingham	1	1	2
The Queen Elizabeth Hospital	20	19	19
Royal Infirmary of Edinburgh	6	6	7

Alcohol related Units: Subjects			
No	15	14	13
Yes	12	12	15
Hep C Units: Subjects			
No	23	23	24
Yes	4	3	4
Hep B Units: Subjects			
No	26	26	28
Yes	1	0	0
Primary biliary cirrhosis Units: Subjects			
No	22	19	25
Yes	5	7	3
Haemochromatosis Units: Subjects			
No	27	26	28
Cryptogenic cirrhosis Units: Subjects			
No	27	25	26
Yes	0	1	2
NAFLD Units: Subjects			
No	21	23	20
Yes	6	3	8
Ascites Units: Subjects			
No	14	16	14
Yes	13	10	14
Variceal Bleeding Units: Subjects			
No	20	15	17
Yes	7	11	11
Encephalopathy Units: Subjects			
No	24	23	21
Yes	3	3	7
Age (years) Units: see title			
median	52.00	54.00	56.50
inter-quartile range (Q1-Q3)	47.00 to 60.00	49.00 to 61.00	47.50 to 62.50
Creatinine (mu mol/L) Units: see title			
median	62.00	63.00	71.00
inter-quartile range (Q1-Q3)	52.00 to 74.00	56.00 to 75.00	64.00 to 90.00
INR Units: see title			
median	1.40	1.20	1.30
inter-quartile range (Q1-Q3)	1.20 to 1.40	1.20 to 1.40	1.20 to 1.40

MELD			
Units: see title			
median	13.12	12.69	13.15
inter-quartile range (Q1-Q3)	12.41 to 13.76	11.98 to 13.09	12.09 to 13.87
UKELD			
Units: see title			
median	51.50	51.14	51.97
inter-quartile range (Q1-Q3)	49.84 to 54.21	49.96 to 52.51	50.89 to 53.46
Haemoglobin (g/dL)			
Units: see title			
median	12.90	13.10	12.95
inter-quartile range (Q1-Q3)	11.80 to 13.80	11.60 to 14.30	12.05 to 14.30
Platelets (*10^9/L)			
Units: see title			
median	77.00	90.50	78.50
inter-quartile range (Q1-Q3)	57.00 to 92.00	54.00 to 116.00	57.00 to 106.50
WBC (*10^9/L)			
Units: see title			
median	4.20	4.30	4.25
inter-quartile range (Q1-Q3)	3.30 to 5.40	3.40 to 5.20	3.30 to 5.35
Bilirubin (mu mol/L)			
Units: see title			
median	38.00	44.00	41.50
inter-quartile range (Q1-Q3)	30.00 to 53.00	34.00 to 53.00	33.00 to 51.00
Urea (mmol/L)			
Units: see title			
median	3.70	3.75	4.75
inter-quartile range (Q1-Q3)	2.70 to 4.20	2.90 to 4.80	3.70 to 5.35
Potassium (mmol/L)			
Units: see title			
median	3.90	3.95	4.10
inter-quartile range (Q1-Q3)	3.70 to 4.40	3.70 to 4.20	3.95 to 4.20
Sodium(mmol/L)			
Units: see title			
median	140.00	140.00	139.00
inter-quartile range (Q1-Q3)	137.00 to 142.00	137.00 to 142.00	137.00 to 140.00
Calcium (U/L)			
Units: see title			
median	2.23	2.19	2.25
inter-quartile range (Q1-Q3)	2.15 to 2.37	2.13 to 2.30	2.13 to 2.30
Magnesium (mmol/L)			
Units: see title			
median	0.73	0.75	0.74
inter-quartile range (Q1-Q3)	0.69 to 0.81	0.70 to 0.79	0.70 to 0.78
AST (U/L)			
Units: see title			
median	44.00	50.50	48.00
inter-quartile range (Q1-Q3)	35.00 to 62.00	37.00 to 82.00	37.00 to 62.00
ALT (U/L)			
Units: see title			
median	28.00	31.50	31.00
inter-quartile range (Q1-Q3)	20.00 to 39.00	21.00 to 54.00	21.50 to 45.00

ALP (U/L)			
Units: see title			
median	160.00	142.50	138.50
inter-quartile range (Q1-Q3)	108.00 to 255.00	118.00 to 282.00	97.50 to 244.00
Bilirubin (mu mol/L)			
Units: see title			
median	38.00	44.00	41.50
inter-quartile range (Q1-Q3)	30.00 to 53.00	34.00 to 53.00	33.00 to 51.00
Albumin (g/L)			
Units: see title			
median	33.00	36.00	35.50
inter-quartile range (Q1-Q3)	30.00 to 37.00	30.00 to 39.00	33.50 to 39.00
GGT(g/dL)			
Units: see title			
median	68.00	86.00	73.00
inter-quartile range (Q1-Q3)	49.00 to 110.00	57.00 to 198.00	41.00 to 188.50
AFP (KU/L)			
Units: see title			
median	3.00	3.00	3.00
inter-quartile range (Q1-Q3)	2.00 to 6.00	2.00 to 5.00	2.00 to 5.00

Reporting group values	Total		
Number of subjects	81		
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			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	28		
Male	53		
Aetiology			
Units: Subjects			
Alcohol related liver disease	37		
Hepatitis C	10		
Other	34		
Centre			
Units: Subjects			

Queen's Medical Centre, Nottingham	4		
The Queen Elizabeth Hospital	58		
Royal Infirmary of Edinburgh	19		
Alcohol related Units: Subjects			
No	42		
Yes	39		
Hep C Units: Subjects			
No	70		
Yes	11		
Hep B Units: Subjects			
No	80		
Yes	1		
Primary biliary cirrhosis Units: Subjects			
No	66		
Yes	15		
Haemochromatosis Units: Subjects			
No	81		
Cryptogenic cirrhosis Units: Subjects			
No	78		
Yes	3		
NAFLD Units: Subjects			
No	64		
Yes	17		
Ascites Units: Subjects			
No	44		
Yes	37		
Variceal Bleeding Units: Subjects			
No	52		
Yes	29		
Encephalopathy Units: Subjects			
No	68		
Yes	13		
Age (years) Units: see title			
median			
inter-quartile range (Q1-Q3)	-		
Creatinine (mu mol/L) Units: see title			
median			
inter-quartile range (Q1-Q3)	-		

INR Units: see title median inter-quartile range (Q1-Q3)	-		
MELD Units: see title median inter-quartile range (Q1-Q3)	-		
UKELD Units: see title median inter-quartile range (Q1-Q3)	-		
Haemoglobin (g/dL) Units: see title median inter-quartile range (Q1-Q3)	-		
Platelets (*10^9/L) Units: see title median inter-quartile range (Q1-Q3)	-		
WBC (*10^9/L) Units: see title median inter-quartile range (Q1-Q3)	-		
Bilirubin (mu mol/L) Units: see title median inter-quartile range (Q1-Q3)	-		
Urea (mmol/L) Units: see title median inter-quartile range (Q1-Q3)	-		
Potassium (mmol/L) Units: see title median inter-quartile range (Q1-Q3)	-		
Sodium(mmol/L) Units: see title median inter-quartile range (Q1-Q3)	-		
Calcium (U/L) Units: see title median inter-quartile range (Q1-Q3)	-		
Magnesium (mmol/L) Units: see title median inter-quartile range (Q1-Q3)	-		
AST (U/L) Units: see title median inter-quartile range (Q1-Q3)	-		

ALT (U/L) Units: see title median inter-quartile range (Q1-Q3)	- -		
ALP (U/L) Units: see title median inter-quartile range (Q1-Q3)	- -		
Bilirubin (mu mol/L) Units: see title median inter-quartile range (Q1-Q3)	- -		
Albumin (g/L) Units: see title median inter-quartile range (Q1-Q3)	- -		
GGT(g/dL) Units: see title median inter-quartile range (Q1-Q3)	- -		
AFP (KU/L) Units: see title median inter-quartile range (Q1-Q3)	- -		

Subject analysis sets	
Subject analysis set title	primary population (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population included all participants who received at least one day of treatment (one day of G-CSF at 15 μg/kg bodyweight in the treatment groups, plus one infusion of at least 0·17×106 cells per kg for the G-CSF plus stem-cell infusion group), with patients retained in their randomly assigned treatment groups, including those who violated the protocol or were ineligible.

Subject analysis set title	trial cohort
Subject analysis set type	Full analysis

Subject analysis set description:

all patient randomised

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

Subject analysis set description:

The per-protocol population was defined as any patients who received 5 days of G-CSF at an average daily dose of at least 12 μg/kg and any patients who received 5 days of G-CSF plus three infusions at a minimum of 0·17×106 cells per kg each. All patients in the control group were included in the mITT and per-protocol populations.

Reporting group values	primary population (mITT)	trial cohort	Per-protocol
Number of subjects	79	81	74
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 inter-quartile range (Q1-Q3)		 54 48 to 61	
Gender categorical Units: Subjects			
Female Male			
Aetiology Units: Subjects			
Alcohol related liver disease Hepatitis C Other		37 10 34	
Centre Units: Subjects			
Queen's Medical Centre, Nottingham The Queen Elizabeth Hospital Royal Infirmary of Edinburgh		4 58 19	
Alcohol related Units: Subjects			
No Yes		42 39	
Hep C Units: Subjects			
No Yes		70 11	
Hep B Units: Subjects			
No Yes		80 1	
Primary biliary cirrhosis Units: Subjects			
No Yes		66 15	
Haemochromatosis Units: Subjects			
No		81	
Cryptogenic cirrhosis Units: Subjects			
No Yes		78 3	
NAFLD Units: Subjects			

No		64	
Yes		17	
Ascites			
Units: Subjects			
No		44	
Yes		37	
Variceal Bleeding			
Units: Subjects			
No		52	
Yes		29	
Encephalopathy			
Units: Subjects			
No		68	
Yes		13	
Age (years)			
Units: see title			
median		54.00	
inter-quartile range (Q1-Q3)	to	48.00 to 61.00	to
Creatinine (mu mol/L)			
Units: see title			
median		66.00	
inter-quartile range (Q1-Q3)	to	58.00 to 77.00	to
INR			
Units: see title			
median		1.30	
inter-quartile range (Q1-Q3)	to	1.20 to 1.40	to
MELD			
Units: see title			
median		12.85	
inter-quartile range (Q1-Q3)	to	12.20 to 13.66	to
UKELD			
Units: see title			
median		51.52	
inter-quartile range (Q1-Q3)	to	50.50 to 53.29	to
Haemoglobin (g/dL)			
Units: see title			
median		12.90	
inter-quartile range (Q1-Q3)	to	11.80 to 14.20	to
Platelets (*10^9/L)			
Units: see title			
median		81.00	
inter-quartile range (Q1-Q3)	to	57.00 to 106.00	to
WBC (*10^9/L)			
Units: see title			
median		4.20	
inter-quartile range (Q1-Q3)	to	3.30 to 5.30	to
Bilirubin (mu mol/L)			
Units: see title			
median		42.00	
inter-quartile range (Q1-Q3)	to	33.00 to 53.00	to
Urea (mmol/L)			

Units: see title			
median		4.00	
inter-quartile range (Q1-Q3)	to	2.90 to 4.90	to
Potassium (mmol/L)			
Units: see title			
median		4.00	
inter-quartile range (Q1-Q3)	to	3.80 to 4.20	to
Sodium(mmol/L)			
Units: see title			
median		140.00	
inter-quartile range (Q1-Q3)	to	137.00 to 141.00	to
Calcium (U/L)			
Units: see title			
median		2.23	
inter-quartile range (Q1-Q3)	to	2.14 to 2.31	to
Magnesium (mmol/L)			
Units: see title			
median		0.75	
inter-quartile range (Q1-Q3)	to	0.70 to 0.79	to
AST (U/L)			
Units: see title			
median		48.00	
inter-quartile range (Q1-Q3)	to	37.00 to 62.00	to
ALT (U/L)			
Units: see title			
median		30.00	
inter-quartile range (Q1-Q3)	to	21.00 to 43.00	to
ALP (U/L)			
Units: see title			
median		147.00	
inter-quartile range (Q1-Q3)	to	108.00 to 255.00	to
Bilirubin (mu mol/L)			
Units: see title			
median		42.00	
inter-quartile range (Q1-Q3)	to	33.00 to 53.00	to
Albumin (g/L)			
Units: see title			
median		35.00	
inter-quartile range (Q1-Q3)	to	30.00 to 39.00	to
GGT(g/dL)			
Units: see title			
median		79.00	
inter-quartile range (Q1-Q3)	to	49.00 to 152.00	to
AFP (KU/L)			
Units: see title			
median		3.00	
inter-quartile range (Q1-Q3)	to	2.00 to 5.00	to

End points

End points reporting groups

Reporting group title	Group 1: Control group: standard conservative management
Reporting group description: Standard conservative management only	
Reporting group title	Group 2: Treatment: GCSF Alone
Reporting group description: Standard conservative management + GCSF	
Reporting group title	Group 3: GSCF + CD133+ cell infusion (x3)
Reporting group description: GCSF followed by Leukapheresis, CD133+ cell isolation and repeated infusions on days 5/6, 30, 60 via peripheral vein	
Subject analysis set title	primary population (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT population included all participants who received at least one day of treatment (one day of G-CSF at 15 µg/kg bodyweight in the treatment groups, plus one infusion of at least 0·17×106 cells per kg for the G-CSF plus stem-cell infusion group), with patients retained in their randomly assigned treatment groups, including those who violated the protocol or were ineligible.	
Subject analysis set title	trial cohort
Subject analysis set type	Full analysis
Subject analysis set description: all patient randomised	
Subject analysis set title	Per-protocol
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol population was defined as any patients who received 5 days of G-CSF at an average daily dose of at least 12 µg/kg and any patients who received 5 days of G-CSF plus three infusions at a minimum of 0·17×106 cells per kg each. All patients in the control group were included in the mITT and per-protocol populations.	

Primary: Change from baseline to day 90 (mITT) MELD

End point title	Change from baseline to day 90 (mITT) MELD
End point description: Non parametric comparison of distributions	
End point type	Primary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	79
Units: see title				
median (inter-quartile range (Q1-Q3))	-0.483 (-1.480 to 1.055)	-0.522 (-1.727 to 0.479)	-0.453 (-1.290 to 1.001)	-0.483 (-1.480 to 0.712)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.718
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.904
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	change point model (group 2 vs 1) mitt

Statistical analysis description:

A model incorporating splines was constructed to assess fit. Model selection was then performed beginning with a mixed-model including just treatment arm (factor) and time (continuous) covariates, and then by iteratively increasing flexibility as required to find the most parsimonious model resulting in approximately optimum fit; polynomial, interaction, and change-point terms were all explored in doing so.

Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.31 [2]
Method	non standard method

Notes:

[1] - The continuous time-scale, representing timing of measurement, was split at 4.3 weeks (30 days) allowing differing trends to be explored both prior to and after this point, hereafter referred to as period 1 and 2 respectively. Splits at 8.6 weeks, and +/- 5 days either side of the particular change-point were also explored but found to fit the data less well. The model also incorporates interactions between time period and group, to allow
for the rate of change to differ between groups.

[2] - period 1, group 2 interaction estimates of 0.14 (p=0. 28), hence no evidence differed from group 1. No evidence of non-zero slope in period 2, with group 2 interaction coefficient -0.066 (p=0.31).

Statistical analysis title	change point model (group 3 vs 1) mitt

Statistical analysis description:

A model incorporating splines was constructed to assess fit. Model selection was then performed beginning with a mixed-model including just treatment arm (factor) and time (continuous) covariates, and then by iteratively increasing flexibility as required to find the most parsimonious model resulting in approximately optimum fit; polynomial, interaction, and change-point terms were all explored in doing so.

Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.94 [4]
Method	non-standard method

Notes:

[3] - The continuous time-scale, representing timing of measurement, was split at 4.3 weeks (30 days) allowing differing trends to be explored both prior to and after this point, hereafter referred to as period 1 and 2 respectively. Splits at 8.6 weeks, and +/- 5 days either side of the particular change-point were also explored but found to fit the data less well. The model also incorporates interactions between time period and group, to allow for the rate of change to differ between groups.

[4] - period 1, group 3 interaction estimates of 0.022 (p=0. 87), hence no evidence differed from group 1. No evidence of non-zero slope in period 2, with group 3 interaction coefficient -0.005 (p=0. 94).

Secondary: Change from baseline to day 90 (mITT) UKELD

End point title	Change from baseline to day 90 (mITT) UKELD

End point description:

Non parametric comparison of distributions

End point type	Secondary

End point timeframe:

Baseline to day 90

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	-0.060 (-3.217 to 1.679)	0.538 (-1.044 to 1.393)	-0.459 (-1.186 to 0.518)	-0.181 (-1.346 to 1.143)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.346
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.689
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Haemoglobin (g/dL)

End point title	Change from baseline to day 90 (mITT) Haemoglobin (g/dL)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.250 (-0.600 to 0.500)	-0.300 (-0.600 to 0.500)	-0.350 (-1.000 to 0.400)	-0.300 (-0.800 to 0.500)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.449
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.175
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) WBC (*10^9/L)	
End point title	Change from baseline to day 90 (mITT) WBC (*10^9/L)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.300 (-0.200 to 0.600)	-0.050 (-0.800 to 0.600)	-0.150 (-1.100 to 0.500)	0.000 (-0.800 to 0.600)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.238
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.102
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Platelets (*10^9/L)	
End point title	Change from baseline to day 90 (mITT) Platelets (*10^9/L)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	-0.500 (-8.000 to 9.000)	0.000 (-8.000 to 7.000)	1.000 (-3.000 to 5.000)	0.000 (-7.000 to 7.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.983
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.548
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) INR	
End point title	Change from baseline to day 90 (mITT) INR
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.000 (-0.100 to 0.100)	0.000 (-0.100 to 0.100)	0.000 (0.000 to 0.000)	0.000 (-0.100 to 0.100)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.859
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.983
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Sodium(mmol/L)	
End point title	Change from baseline to day 90 (mITT) Sodium(mmol/L)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.000 (-2.000 to 3.000)	-1.000 (-2.000 to 1.000)	0.000 (-1.000 to 3.000)	0.000 (-1.000 to 2.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.431
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.231
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Potassium (mmol/L)

End point title	Change from baseline to day 90 (mITT) Potassium (mmol/L)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.075 (-0.100 to 0.300)	0.150 (-0.200 to 0.500)	-0.050 (-0.300 to 0.300)	0.000 (-0.300 to 0.300)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.64
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.323
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Urea (mmol/L)	
End point title	Change from baseline to day 90 (mITT) Urea (mmol/L)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.100 (-0.400 to 1.000)	0.150 (-0.600 to 0.900)	-0.050 (-1.000 to 0.400)	0.100 (-0.600 to 0.900)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.508
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.261
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Creatinine (mu mol/L)

End point title	Change from baseline to day 90 (mITT) Creatinine (mu mol/L)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	1.000 (-2.000 to 10.000)	2.500 (-1.000 to 10.000)	1.500 (-4.000 to 9.000)	2.000 (-3.000 to 10.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.857
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.711
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Bilirubin (mu mol/L)

End point title	Change from baseline to day 90 (mITT) Bilirubin (mu mol/L)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	-5.000 (-12.000 to 3.000)	-6.000 (-12.000 to -1.000)	-2.000 (-9.000 to 7.000)	-5.000 (-10.000 to 5.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.372
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.771
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Albumin (g/L)

End point title	Change from baseline to day 90 (mITT) Albumin (g/L)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	25	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.000 (-3.000 to 1.000)	-2.000 (-3.000 to 0.000)	-1.000 (-4.000 to 2.000)	-1.000 (-3.000 to 1.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.309
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.848
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) AST (U/L)	
End point title	Change from baseline to day 90 (mITT) AST (U/L)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	21	24	23	
Units: see title				
median (inter-quartile range (Q1-Q3))	-2.000 (-6.000 to 4.000)	-4.000 (-13.500 to 4.000)	-2.000 (-9.000 to 1.000)	-2.000 (-9.000 to 4.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.306
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.406
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) ALT (U/L)

End point title	Change from baseline to day 90 (mITT) ALT (U/L)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.000 (-4.000 to 4.000)	-2.000 (-9.000 to 4.000)	-4.500 (-8.000 to 0.000)	-2.000 (-9.000 to 2.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.652
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) ALP (U/L)

End point title	Change from baseline to day 90 (mITT) ALP (U/L)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	26	
Units: see title				
median (inter-quartile range (Q1-Q3))	-4.000 (-20.000 to 11.000)	-5.000 (-16.000 to 7.000)	1.500 (-10.000 to 24.000)	-3.000 (-17.000 to 16.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.912
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.346
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) GGT(g/dL)	
End point title	Change from baseline to day 90 (mITT) GGT(g/dL)
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	25	
Units: see title				
median (inter-quartile range (Q1-Q3))	-1.000 (-10.000 to 9.000)	-10.000 (-42.500 to 0.500)	-3.000 (-18.000 to 1.000)	-3.000 (-19.500 to 3.500)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.099
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.363
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) AFP (KU/L)

End point title	Change from baseline to day 90 (mITT) AFP (KU/L)
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	19	21	18	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.000 (-1.000 to 1.000)	0.000 (-1.000 to 0.000)	0.000 (-1.000 to 0.000)	0.000 (-1.000 to 0.000)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.31
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) Overall QoL

End point title	Change from baseline to day 90 (mITT) Overall QoL
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	25	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.183 (-0.137 to 0.603)	-0.076 (-0.354 to 0.275)	0.029 (-0.192 to 0.231)	0.035 (-0.229 to 0.443)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.144
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.489
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) QoL: Abdominal symptoms	
End point title	Change from baseline to day 90 (mITT) QoL: Abdominal symptoms
End point description:	
Non parametric comparison of distributions	
End point type	Secondary
End point timeframe:	
Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	25	24	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.000 (-0.667 to 0.000)	0.000 (-1.000 to 0.667)	0.000 (0.000 to 0.500)	0.000 (-0.667 to 0.333)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.178
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) QoL: Fatigue	
End point title	Change from baseline to day 90 (mITT) QoL: Fatigue
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	25	25	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.400 (-0.600 to 0.800)	0.000 (-0.800 to 0.400)	0.200 (-0.400 to 0.600)	0.200 (-0.400 to 0.600)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.451
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.193
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) QoL: Systemic

End point title	Change from baseline to day 90 (mITT) QoL: Systemic
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	25	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.400 (-0.200 to 0.800)	0.000 (-0.400 to 0.400)	0.000 (-0.400 to 0.400)	0.000 (-0.400 to 0.400)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.324
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.263
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) QoL: Activity	
End point title	Change from baseline to day 90 (mITT) QoL: Activity
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	25	24	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.333 (0.000 to 0.667)	0.000 (-0.333 to 0.667)	-0.167 (-0.667 to 0.667)	0.000 (-0.333 to 0.667)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.117
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) QoL: Emotional function

End point title	Change from baseline to day 90 (mITT) QoL: Emotional function

End point description:

Non parametric comparison of distributions

End point type	Secondary

End point timeframe:

Baseline to day 90

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	25	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.125 (-0.125 to 0.375)	-0.063 (-0.438 to 0.313)	0.125 (-0.250 to 0.500)	0.125 (-0.250 to 0.375)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.392
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.648
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (mITT) QoL: Worry	
End point title	Change from baseline to day 90 (mITT) QoL: Worry
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	primary population (mITT)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	25	
Units: see title				
median (inter-quartile range (Q1-Q3))	0.200 (0.000 to 1.000)	0.000 (-0.400 to 0.600)	0.200 (-0.400 to 0.800)	0.200 (-0.400 to 0.800)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.151
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.584
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (PP) MELD

End point title	Change from baseline to day 90 (PP) MELD
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	Per-protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	21	
Units: see title				
median (inter-quartile range (Q1-Q3))	-0.483 (-1.480 to 1.055)	-0.522 (-1.727 to 0.479)	-0.708 (-1.054 to 0.734)	-0.508 (-1.357 to 0.602)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.718
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.897
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline to day 90 (PP) UKELD

End point title	Change from baseline to day 90 (PP) UKELD
End point description: Non parametric comparison of distributions	
End point type	Secondary
End point timeframe: Baseline to day 90	

End point values	Group 1: Control group: standard conservative management	Group 2: Treatment: GCSF Alone	Group 3: GSCF + CD133+ cell infusion (x3)	Per-protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	26	21	
Units: see title				
median (inter-quartile range (Q1-Q3))	-0.060 (-3.217 to 1.679)	0.538 (-1.044 to 1.393)	-0.181 (-0.907 to 0.518)	-0.140 (-1.316 to 1.203)

Statistical analyses

Statistical analysis title	Standard Care vs G-CSF
Comparison groups	Group 1: Control group: standard conservative management v Group 2: Treatment: GCSF Alone

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.346
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Standard Care vs G-CSF + Cells
Comparison groups	Group 1: Control group: standard conservative management v Group 3: GSCF + CD133+ cell infusion (x3)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.916
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Date of consent - Day 360	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4
Reporting groups	
Reporting group title	Standard Care
Reporting group description: safety reporting period is up to 1 year after randomisation	
Reporting group title	G-CSF + CD133 + cell infusion
Reporting group description: safety reporting period is up to 1 year after randomisation	
Reporting group title	G-CSF only
Reporting group description: safety reporting period is up to 1 year after randomisation	

Serious adverse events	Standard Care	G-CSF + CD133 + cell infusion	G-CSF only
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	8 / 26 (30.77%)	3 / 27 (11.11%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events	1	0	0
Vascular disorders			
Esophageal hemorrhage			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Heart failure			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (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			
Encephalopathy			

subjects affected / exposed	0 / 28 (0.00%)	3 / 26 (11.54%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (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			
Ascites			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (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
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (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
Metabolism and nutrition disorders			
Edema limbs			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (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
Hypoglycemia			

subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard Care	G-CSF + CD133 + cell infusion	G-CSF only
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 28 (96.43%)	26 / 26 (100.00%)	27 / 27 (100.00%)
Vascular disorders			
Esophageal varices hemorrhage			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Oral hemorrhage			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Portal vein thrombosis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Skin ulceration			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Hematoma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)	3 / 26 (11.54%)	0 / 27 (0.00%)
occurrences (all)	0	3	0
Hypotension			

subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Edema trunk			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	13 / 28 (46.43%)	9 / 26 (34.62%)	10 / 27 (37.04%)
occurrences (all)	13	10	13
Fever			
subjects affected / exposed	2 / 28 (7.14%)	3 / 26 (11.54%)	1 / 27 (3.70%)
occurrences (all)	2	3	1
Flu like symptoms			
subjects affected / exposed	1 / 28 (3.57%)	14 / 26 (53.85%)	7 / 27 (25.93%)
occurrences (all)	1	16	8
Malaise			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	2 / 27 (7.41%)
occurrences (all)	0	1	3
Pain			
subjects affected / exposed	6 / 28 (21.43%)	1 / 26 (3.85%)	3 / 27 (11.11%)
occurrences (all)	6	1	3
Lethargy			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Immune system disorders			
Allergic rhinitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 26 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	2	1
Respiratory, thoracic and mediastinal disorders			
Bronchial infection			

subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Lung infection			
subjects affected / exposed	2 / 28 (7.14%)	2 / 26 (7.69%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Upper respiratory infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Dyspnea			
subjects affected / exposed	4 / 28 (14.29%)	2 / 26 (7.69%)	4 / 27 (14.81%)
occurrences (all)	4	2	5
Cough			
subjects affected / exposed	1 / 28 (3.57%)	4 / 26 (15.38%)	3 / 27 (11.11%)
occurrences (all)	1	4	4
Hypoxia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pleuritic pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Sore throat			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Psychiatric disorders			
Somnolence			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Confusion			
subjects affected / exposed	3 / 28 (10.71%)	4 / 26 (15.38%)	2 / 27 (7.41%)
occurrences (all)	4	4	4

Depression			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	4 / 28 (14.29%)	8 / 26 (30.77%)	10 / 27 (37.04%)
occurrences (all)	7	8	14
Alanine aminotransferase increased			
subjects affected / exposed	7 / 28 (25.00%)	9 / 26 (34.62%)	13 / 27 (48.15%)
occurrences (all)	11	12	22
Alkaline phosphatase increased			
subjects affected / exposed	15 / 28 (53.57%)	15 / 26 (57.69%)	21 / 27 (77.78%)
occurrences (all)	16	17	30
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 28 (53.57%)	15 / 26 (57.69%)	18 / 27 (66.67%)
occurrences (all)	16	24	30
Blood bilirubin increased			
subjects affected / exposed	24 / 28 (85.71%)	23 / 26 (88.46%)	25 / 27 (92.59%)
occurrences (all)	44	44	68
Cardiac troponin I increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Creatinine increased			
subjects affected / exposed	3 / 28 (10.71%)	6 / 26 (23.08%)	2 / 27 (7.41%)
occurrences (all)	3	7	2
GGT increased			
subjects affected / exposed	17 / 28 (60.71%)	16 / 26 (61.54%)	21 / 27 (77.78%)
occurrences (all)	24	21	32
Haptoglobin decreased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Hemoglobin increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
INR increased			

subjects affected / exposed	10 / 28 (35.71%)	10 / 26 (38.46%)	12 / 27 (44.44%)
occurrences (all)	12	14	16
Lymphocyte count decreased			
subjects affected / exposed	9 / 28 (32.14%)	8 / 26 (30.77%)	8 / 27 (29.63%)
occurrences (all)	15	16	27
Lymphocyte count increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	3 / 27 (11.11%)
occurrences (all)	0	1	3
Neutrophil count decreased			
subjects affected / exposed	11 / 28 (39.29%)	12 / 26 (46.15%)	17 / 27 (62.96%)
occurrences (all)	16	22	29
Platelet count decreased			
subjects affected / exposed	22 / 28 (78.57%)	22 / 26 (84.62%)	24 / 27 (88.89%)
occurrences (all)	32	41	41
Weight loss			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
White blood cell decreased			
subjects affected / exposed	16 / 28 (57.14%)	16 / 26 (61.54%)	15 / 27 (55.56%)
occurrences (all)	27	31	48
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Fracture			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Heart failure			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Palpitations			

subjects affected / exposed	3 / 28 (10.71%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	3	1	1
Presyncope			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 28 (0.00%)	2 / 26 (7.69%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Fecal incontinence			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Generalized muscle weakness			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Akathisia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Amnesia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Concentration impairment			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Depressed level of consciousness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Encephalopathy			
subjects affected / exposed	2 / 28 (7.14%)	4 / 26 (15.38%)	2 / 27 (7.41%)
occurrences (all)	2	8	2
Headache			
subjects affected / exposed	0 / 28 (0.00%)	11 / 26 (42.31%)	13 / 27 (48.15%)
occurrences (all)	0	14	13

Memory impairment			
subjects affected / exposed	0 / 28 (0.00%)	2 / 26 (7.69%)	3 / 27 (11.11%)
occurrences (all)	0	3	3
Paresthesia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 28 (7.14%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Seizure			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Tremor			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Trigeminal nerve disorder			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	3 / 28 (10.71%)	1 / 26 (3.85%)	5 / 27 (18.52%)
occurrences (all)	3	1	5
Urinary incontinence			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	12 / 28 (42.86%)	15 / 26 (57.69%)	15 / 27 (55.56%)
occurrences (all)	17	21	28
Leukocytosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	8 / 28 (28.57%)	8 / 26 (30.77%)	12 / 27 (44.44%)
occurrences (all)	9	9	13
Bloating			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Constipation			
subjects affected / exposed	3 / 28 (10.71%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	3	1	0
Diarrhea			
subjects affected / exposed	2 / 28 (7.14%)	4 / 26 (15.38%)	3 / 27 (11.11%)
occurrences (all)	2	4	3
Dry mouth			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	3 / 28 (10.71%)	3 / 26 (11.54%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Gastritis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	10 / 26 (38.46%)	6 / 27 (22.22%)
occurrences (all)	1	10	6
Oral pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Rectal hemorrhage			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1

Toothache			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Stomach pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)	4 / 26 (15.38%)	3 / 27 (11.11%)
occurrences (all)	2	5	3
Gum infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	1 / 28 (3.57%)	8 / 26 (30.77%)	4 / 27 (14.81%)
occurrences (all)	1	11	8
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 28 (10.71%)	4 / 26 (15.38%)	4 / 27 (14.81%)
occurrences (all)	4	6	4
Skin hyperpigmentation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hematuria			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Renal calculi			

subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Urinary tract pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypercalcemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Gynecomastia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 26 (7.69%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 28 (10.71%)	3 / 26 (11.54%)	2 / 27 (7.41%)
occurrences (all)	3	3	2
Arthritis			
subjects affected / exposed	3 / 28 (10.71%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	3	1	1
Back pain			
subjects affected / exposed	3 / 28 (10.71%)	2 / 26 (7.69%)	4 / 27 (14.81%)
occurrences (all)	3	2	6
Bone pain			
subjects affected / exposed	0 / 28 (0.00%)	14 / 26 (53.85%)	15 / 27 (55.56%)
occurrences (all)	0	15	15
Musculoskeletal deformity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Pain in extremity			

subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	5 / 27 (18.52%)
occurrences (all)	0	1	5
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Lip infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Mucosal infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	4 / 28 (14.29%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	4	0	2
Metabolism and nutrition disorders			
Edema limbs			
subjects affected / exposed	9 / 28 (32.14%)	12 / 26 (46.15%)	5 / 27 (18.52%)
occurrences (all)	9	15	5
Anorexia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 26 (7.69%)	2 / 27 (7.41%)
occurrences (all)	1	2	3
Dehydration			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hyperglycemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Hyperkalemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	2 / 27 (7.41%)
occurrences (all)	1	2	3
Hypermagnesemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 26 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Hypernatremia			

subjects affected / exposed	1 / 28 (3.57%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Hyperuricemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminemia			
subjects affected / exposed	13 / 28 (46.43%)	14 / 26 (53.85%)	15 / 27 (55.56%)
occurrences (all)	19	19	33
Hypocalcemia			
subjects affected / exposed	9 / 28 (32.14%)	7 / 26 (26.92%)	13 / 27 (48.15%)
occurrences (all)	11	9	26
Hypoglycemia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	3	0	3
Hypokalemia			
subjects affected / exposed	5 / 28 (17.86%)	5 / 26 (19.23%)	4 / 27 (14.81%)
occurrences (all)	7	5	9
Hypomagnesemia			
subjects affected / exposed	11 / 28 (39.29%)	8 / 26 (30.77%)	9 / 27 (33.33%)
occurrences (all)	16	13	14
Hyponatremia			
subjects affected / exposed	2 / 28 (7.14%)	6 / 26 (23.08%)	4 / 27 (14.81%)
occurrences (all)	3	9	8
Hypophosphatemia			
subjects affected / exposed	5 / 28 (17.86%)	1 / 26 (3.85%)	8 / 27 (29.63%)
occurrences (all)	6	1	12
Osteoporosis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2009	Protocol version 2.0 : substantial amendment: a) Section 3.2 - Further Exclusion Criteria added b) Section 7.4, 7.5 - Addition of Treatment Day 4 Blood Test c) Section 7.9 - Lenograstim Discontinuation Criteria added
05 November 2009	Protocol V3.0 Substantial Amendment a) Section 3.2 - Further detail added to Exclusion Criteria. b) Section 7.1 – Change to study administration (all drug will be administered by suitable qualified medical staff only). c) Section 7.2 – Dose modification and toxicity management recommendations (new section). d) Section 8.0 – Additional information added to adverse event reporting section, clarification of SAE reporting period and procedures. e) Section 13.0 Additional information added to power calculations, Interim and final analysis sections f) Section 14.1 Change in sponsor details : single sponsor to Co-sponsorship g) Appendix 2 – change to questionnaire layout. A number of minor amendments have been made throughout the protocol. Which include change in study personnel, Use of µg to replace mcg
06 July 2011	Protocol version 4.0 Substantial Amendment a) Section 3.1 amended inclusion MELD range b) Section 4 changed wording to say multi centre c) Section 5.3, 7.4, 7.5, 7.6: Increased ELF testing frequency A number of minor changes have been made through the protocol, which includes change in study personnel.
22 February 2012	Protocol v5.0 Substantial Amendment a) Changes to inclusion criteria and addition of new inclusion criteria • Alpha-1 Antitrypsin Deficiency • Changes to some diagnostic requirements relating to aetiology of the liver disease. b) Change to wording of exclusion criteria • The requirement (time scales) for Ascites, Portal hypertensive bleeding and Encephalopathy (requiring treatment or hospitalisation) free period prior to randomisation has been reduced from 6 months to 3 months. A number of minor changes have been made throughout the protocol, which includes change in study personnel.
24 May 2012	Protocol V6.0 Substantial Amendment a) Change of sponsor details from co-sponsor to single sponsor b) Change to IMP label c) update to UKELD information
07 November 2012	Protocol V7.0 Substantial Amendment a) Change to inclusion criteria (MELD range) b) Change to inclusion criteria (Age range) A number of minor changes have been made throughout the protocol, which includes change in study personnel and information on eRDC.

05 March 2015	Protocol v8.0 Substantial Amendment A number of minor changes to the protocol. Section 11 : Statistical Considerations Changes to the primary statistical analysis to include MELD measurements at baseline, 30, 60 and 90 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25795699

http://www.ncbi.nlm.nih.gov/pubmed/29127060