



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 |
| Scientific contact | Prof Philip Newsome, Director of Centre for Liver research University of Birmingham Birmingham United Kingdom, 44 1214145614, p.n.newsone@bham.ac.uk |

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 |

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

| | | | |
|--|----------------------------|----------------------------|---------------------------|
| ALP (U/L) Units: see title median inter-quartile range (Q1-Q3) | 160.00 108.00 to 255.00 | 142.50 118.00 to 282.00 | 138.50 97.50 to 244.00 |
| Bilirubin (mu mol/L) Units: see title median inter-quartile range (Q1-Q3) | 38.00 30.00 to 53.00 | 44.00 34.00 to 53.00 | 41.50 33.00 to 51.00 |
| Albumin (g/L) Units: see title median inter-quartile range (Q1-Q3) | 33.00 30.00 to 37.00 | 36.00 30.00 to 39.00 | 35.50 33.50 to 39.00 |
| GGT(g/dL) Units: see title median inter-quartile range (Q1-Q3) | 68.00 49.00 to 110.00 | 86.00 57.00 to 198.00 | 73.00 41.00 to 188.50 |
| AFP (KU/L) Units: see title median inter-quartile range (Q1-Q3) | 3.00 2.00 to 6.00 | 3.00 2.00 to 5.00 | 3.00 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 inter-quartile range (Q1-Q3) | to | 4.00 2.90 to 4.90 | to |
| Potassium (mmol/L) Units: see title median inter-quartile range (Q1-Q3) | to | 4.00 3.80 to 4.20 | to |
| Sodium(mmol/L) Units: see title median inter-quartile range (Q1-Q3) | to | 140.00 137.00 to 141.00 | to |
| Calcium (U/L) Units: see title median inter-quartile range (Q1-Q3) | to | 2.23 2.14 to 2.31 | to |
| Magnesium (mmol/L) Units: see title median inter-quartile range (Q1-Q3) | to | 0.75 0.70 to 0.79 | to |
| AST (U/L) Units: see title median inter-quartile range (Q1-Q3) | to | 48.00 37.00 to 62.00 | to |
| ALT (U/L) Units: see title median inter-quartile range (Q1-Q3) | to | 30.00 21.00 to 43.00 | to |
| ALP (U/L) Units: see title median inter-quartile range (Q1-Q3) | to | 147.00 108.00 to 255.00 | to |
| Bilirubin (mu mol/L) Units: see title median inter-quartile range (Q1-Q3) | to | 42.00 33.00 to 53.00 | to |
| Albumin (g/L) Units: see title median inter-quartile range (Q1-Q3) | to | 35.00 30.00 to 39.00 | to |
| GGT(g/dL) Units: see title median inter-quartile range (Q1-Q3) | to | 79.00 49.00 to 152.00 | to |
| AFP (KU/L) Units: see title median inter-quartile range (Q1-Q3) | to | 3.00 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: GCSF + 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 0.17×10 ⁶ 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 0.17×10 ⁶ 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: GCSF + 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 (*10⁹/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 (*10⁹/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 occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 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 occurrences (all) | 1 / 28 (3.57%) 1 | 1 / 26 (3.85%) 1 | 2 / 27 (7.41%) 2 |
| Investigations | | | |
| Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) | 4 / 28 (14.29%) 7 | 8 / 26 (30.77%) 8 | 10 / 27 (37.04%) 14 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 28 (25.00%) 11 | 9 / 26 (34.62%) 12 | 13 / 27 (48.15%) 22 |
| Alkaline phosphatase increased subjects affected / exposed occurrences (all) | 15 / 28 (53.57%) 16 | 15 / 26 (57.69%) 17 | 21 / 27 (77.78%) 30 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 15 / 28 (53.57%) 16 | 15 / 26 (57.69%) 24 | 18 / 27 (66.67%) 30 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 24 / 28 (85.71%) 44 | 23 / 26 (88.46%) 44 | 25 / 27 (92.59%) 68 |
| Cardiac troponin I increased subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Creatinine increased subjects affected / exposed occurrences (all) | 3 / 28 (10.71%) 3 | 6 / 26 (23.08%) 7 | 2 / 27 (7.41%) 2 |
| GGT increased subjects affected / exposed occurrences (all) | 17 / 28 (60.71%) 24 | 16 / 26 (61.54%) 21 | 21 / 27 (77.78%) 32 |
| Haptoglobin decreased subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 1 |
| Hemoglobin increased subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| INR increased | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 10 / 28 (35.71%) 12 | 10 / 26 (38.46%) 14 | 12 / 27 (44.44%) 16 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 9 / 28 (32.14%) 15 | 8 / 26 (30.77%) 16 | 8 / 27 (29.63%) 27 |
| Lymphocyte count increased subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 3 / 27 (11.11%) 3 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 11 / 28 (39.29%) 16 | 12 / 26 (46.15%) 22 | 17 / 27 (62.96%) 29 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 22 / 28 (78.57%) 32 | 22 / 26 (84.62%) 41 | 24 / 27 (88.89%) 41 |
| Weight loss subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 1 |
| White blood cell decreased subjects affected / exposed occurrences (all) | 16 / 28 (57.14%) 27 | 16 / 26 (61.54%) 31 | 15 / 27 (55.56%) 48 |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Fracture subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Cardiac disorders | | | |
| Cardiac arrest subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Heart failure subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 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 occurrences (all) | 0 / 28 (0.00%) 0 | 2 / 26 (7.69%) 3 | 3 / 27 (11.11%) 3 |
| Paresthesia subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 1 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Seizure subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Tremor subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Trigeminal nerve disorder subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 28 (10.71%) 3 | 1 / 26 (3.85%) 1 | 5 / 27 (18.52%) 5 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) | 12 / 28 (42.86%) 17 | 15 / 26 (57.69%) 21 | 15 / 27 (55.56%) 28 |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 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 occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Stomach pain subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | 4 / 26 (15.38%) 5 | 3 / 27 (11.11%) 3 |
| Gum infection subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Hepatobiliary disorders Gallbladder obstruction subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Ascites subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | 8 / 26 (30.77%) 11 | 4 / 27 (14.81%) 8 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 3 / 28 (10.71%) 4 | 4 / 26 (15.38%) 6 | 4 / 27 (14.81%) 4 |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Hematuria subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 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 occurrences (all) | 0 / 28 (0.00%) 0 | 1 / 26 (3.85%) 1 | 5 / 27 (18.52%) 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>