



## Clinical trial results:

**Myeloma X Relapse (Intensive) - A randomised controlled trial to determine the role of a second autologous stem cell transplant as consolidation therapy in patients with relapsed multiple myeloma following prior high-dose chemotherapy and autologous stem cell rescue.**

### Summary

EudraCT number	2006-005890-24
Trial protocol	GB
Global end of trial date	16 November 2016

### Results information

Result version number	v1 (current)
This version publication date	30 November 2017
First version publication date	30 November 2017

### Trial information

#### Trial identification

Sponsor protocol code	HM05/7287
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#### Additional study identifiers

ISRCTN number	ISRCTN60123120
ClinicalTrials.gov id (NCT number)	NCT00747877
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Leeds Teaching Hospitals NHS Trust - Research & Innovation Department
Sponsor organisation address	Research & Innovation Centre, St James's University Hospital, Beckett Street, Leeds, United Kingdom, LS9 7TF
Public contact	Regulatory Affairs and Governance Manager, CTRU QA Department, 0113 3431477, medctrug@leeds.ac.uk
Scientific contact	Regulatory Affairs and Governance Manager, CTRU QA Department, 0113 3431477, medctrug@leeds.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 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	20 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2016
Global end of trial reached?	Yes
Global end of trial date	16 November 2016
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine the effect on freedom-from disease progression of a second autologous stem cell transplant (ASCT) compared with low-dose consolidation, following re-induction chemotherapy, in patients with relapsed myeloma previously treated with high-dose chemotherapy and ASCT.

Protection of trial subjects:

Safety analyses will summarise the adverse event rates and serious adverse events separately for each of the re-induction and consolidation treatments. Safety data will be presented for patients receiving any of the relevant study treatment by treatment group and relationship to study treatment.

Background therapy:

All trial participants received re-induction therapy of 2-4 cycles of PAD (Bortezomib, doxorubicin, dexamethasone) before proceeding to peripheral blood stem cell (PBSC) mobilisation and harvesting. Cyclophosphamide and granulocyte colony stimulating factor (G-CSF) were suggested for mobilisation. Mobilisation and harvest was optional for patients who already had sufficient stem cells stored from a previous harvest. Patients with an adequate number of PBSC collected were then randomised to the two different treatment arms.

Evidence for comparator:

The trial will identify whether a second course of high dose melphalan and ASCT performed at relapse in myeloma patients results in an improved duration of response and survival outcome compared to a less intensive, alkylating agent therapy of cyclophosphamide-weekly. No RCTs have been done to assess the outcome of a second autologous transplant at relapse. Some patients will have achieved a good remission following their original ASCT and a second similar procedure undertaken following relapse may be an effective form of therapy.

Together with pain and Quality of Life (QoL) assessments, it is proposed that the full effect of the differing treatment strategies on time to disease progression, key symptoms and QoL will assist in the development of an evidence based management plan for treatment of relapse in these patients and allow the best use of available resources.

Actual start date of recruitment	16 April 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 297
Worldwide total number of subjects	297
EEA total number of subjects	297

Notes:

<b>Subjects enrolled per age group</b>	
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)	206
From 65 to 84 years	91
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial opened at 51 centres across the United Kingdom. Between April 16 2008 and November 19 2012, 297 patients were registered and 174 were randomised. On the grounds of efficacy data reviewed by the DMEC, the trial was closed to recruitment on 21 November 2012.

### Pre-assignment

Screening details:

Patients with multiple myeloma previously treated with standard chemotherapy and autologous stem cell transplant.

Patients requiring therapy for first Progressive Disease & 12 months since 1st transplant.

Written informed consent.

### Pre-assignment period milestones

Number of subjects started	297
Number of subjects completed	293

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Received no treatment: 1

### Period 1

Period 1 title	Re-Induction PAD and PBSC Harvest
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Re-induction PAD and PBSC Harvest
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Arm description:

All patients will be registered at trial entry and will receive re-induction therapy with 2-4 cycles of PAD. Following completion of re-induction therapy, the disease response will be re-assessed and all patients without progressive disease will then proceed to PBSC mobilisation and harvesting. Mobilisation and harvest is encouraged in all patients without progressive disease, but is optional in patients who have sufficient stem cells stored from a previous harvest.

Those patients with an adequate number of PBSC (including those who do not mobilise or who were not mobilised but have stored PBSC from prior mobilisations) will be randomised.

Arm type	Re-induction
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Bortezomib is supplied as a 3.5 mg powder for solution for injection. It is administered as an intravenous bolus at a maximum dose of 1.3mg/m<sup>2</sup> per day of treatment. Treatment days are days 1, 4, 8 and 11 of a 21 day cycle. A minimum of 2 cycles and a maximum of 4 cycles are given.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use
Dosage and administration details:	
Doxorubicin is administered as a continuous intravenous infusion at a dose of 9mg/m <sup>2</sup> /day on days 1 to 4 of a 21 day cycle. A minimum of 2 cycles and a maximum of 4 cycles are given.	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone is in the form of tablets containing 2.0mg dexamethasone. It is administered at a dose of 40mg/day on days 1 to 4 of a 21 day cycle, for a minimum of 2 cycles and maximum of 4 cycles. It is also given on days 8-11 and 15-18 in cycle 1.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide is in the form of powder for solution for injection. Each vial contains cyclophosphamide monohydrate equivalent to 1000mg anhydrous cyclophosphamide. For stem cell mobilisation, it is administered as an intravenous infusion at a dose of 1.5-3g/m<sup>2</sup> on day 0.

Investigational medicinal product name	G-CSF
Investigational medicinal product code	
Other name	Granulocyte cell stimulating factor
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

G-CSF is administered at a dose of 5-10µg/kg/day, subcutaneously, from day +1 to time of stem cell harvest.

Number of subjects in period 1	Re-induction PAD and PBSC Harvest
Started	293
Completed	174
Not completed	119
Adverse event, serious fatal	29
Consent withdrawn by subject	19
Physician decision	34
Did not mobilise sufficient stem cells	30
Progressive disease	4
Protocol deviation	3

**Period 2**

Period 2 title	Consolidation Randomisation
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	C-weekly

Arm description:

Oral cyclophosphamide 400 mg/m<sup>2</sup> per week for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

For the C-weekly regimen, cyclophosphamide tablets, containing 50mg anhydrous cyclophosphamide, is administered orally at 400mg/m<sup>2</sup> weekly for 12 weeks. Alternatively, cyclophosphamide may be administered at a dose of 300mg/m<sup>2</sup> intravenously, weekly for 12 weeks.

<b>Arm title</b>	High dose melphalan and ASCT
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Arm description:

Single infusion of intravenous melphalan 200 mg/m<sup>2</sup> followed by ASCT after 24–48 h.

Arm type	Experimental
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

High-dose melphalan is given as a 200mg/m<sup>2</sup> short infusion (as per local protocol) in 100ml NaCL 0.9%.

Notes:

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

Justification: Period 1 relates to the trial treatment received prior to randomisation. Period 2 is the period following randomisation. In alliance with the publications this has been defined as our baseline period.

<b>Number of subjects in period 2<sup>[2]</sup></b>	C-weekly	High dose melphalan and ASCT
Started	85	89
Completed	84	83
Not completed	1	6
Physician decision	1	1
Consent withdrawn by subject	-	1
Lost to follow-up	-	1
Progressive disease	-	3

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Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled relates to the total number registered onto the trial. The baseline period relates to the total number randomised. As the trial had registration and randomisation stages these numbers are not identical.

## Baseline characteristics

### Reporting groups

Reporting group title	C-weekly
Reporting group description: Oral cyclophosphamide 400 mg/m <sup>2</sup> per week for 12 weeks.	
Reporting group title	High dose melphalan and ASCT
Reporting group description: Single infusion of intravenous melphalan 200 mg/m <sup>2</sup> followed by ASCT after 24–48 h.	

Reporting group values	C-weekly	High dose melphalan and ASCT	Total
Number of subjects	85	89	174
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	61	61	
full range (min-max)	40 to 73	40 to 73	-
Gender categorical Units: Subjects			
Female	24	24	48
Male	61	65	126
Haemoglobin at randomisation Units: g/dL			
arithmetic mean	11.6	11.5	
standard deviation	± 1.14	± 1.41	-
Calcium at randomisation Units: mmol/L			
arithmetic mean	2.3	2.3	
standard deviation	± 0.12	± 0.12	-
Time from previous autograft to first progression/relapse Units: Years			
arithmetic mean	2.8	3.2	
standard deviation	± 1.3	± 2.11	-
Beta-2 microglobulin at registration Units: mg/L			
arithmetic mean	3.0	3.1	



standard deviation	± 1.11	± 1.64	-
Serum creatinine at randomisation			
Units: umol/L			
arithmetic mean	82	79.8	
standard deviation	± 20.78	± 19.45	-

## End points

### End points reporting groups

Reporting group title	Re-induction PAD and PBSC Harvest
Reporting group description:	
All patients will be registered at trial entry and will receive re-induction therapy with 2-4 cycles of PAD. Following completion of re-induction therapy, the disease response will be re-assessed and all patients without progressive disease will then proceed to PBSC mobilisation and harvesting. Mobilisation and harvest is encouraged in all patients without progressive disease, but is optional in patients who have sufficient stem cells stored from a previous harvest.	
Those patients with an adequate number of PBSC (including those who do not mobilise or who were not mobilised but have stored PBSC from prior mobilisations) will be randomised.	
Reporting group title	C-weekly
Reporting group description:	
Oral cyclophosphamide 400 mg/m <sup>2</sup> per week for 12 weeks.	
Reporting group title	High dose melphalan and ASCT
Reporting group description:	
Single infusion of intravenous melphalan 200 mg/m <sup>2</sup> followed by ASCT after 24–48 h.	

### Primary: Time to disease progression

End point title	Time to disease progression
End point description:	
Time to disease progression is defined as time from randomisation to first documented evidence of disease progression.	
Documented evidence of progression is defined as:	
<ul style="list-style-type: none"><li>- Progression confirmed by central review (blind to treatment) by the central reviewer.</li><li>- Progression unconfirmed by central review if central review unable to determine whether or not a patient suffered progression</li><li>- Death primarily due to progression</li></ul>	
Patients who die prior to documentation of disease progression will be censored in the analysis. Patients not reaching disease progression at the time of analysis will be censored at the last date known to be progression-free. Patients dying from causes not primarily due to progression will also be censored in the disease progression analysis.	
The results of this endpoint are based on the final data download on 20/01/2017.	
End point type	Primary
End point timeframe:	
Time to disease progression is defined as time from randomisation to first documented evidence of disease progression.	

End point values	C-weekly	High dose melphalan and ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: Months				
median (confidence interval 95%)	11 (9 to 12)	19 (16 to 26)		

## Statistical analyses

<b>Statistical analysis title</b>	Time to disease progression
Statistical analysis description:	
Cox regression will be used to analyse time to progression accounting for the stratification factors (length of first remission or plateau and response to PAD re-induction therapy), and whether or not mobilisation therapy was received. Patients not reaching disease progression at the time of analysis will be censored at the last date known to be progression-free. Patients dying from causes not primarily due to progression will also be censored.	
Comparison groups	High dose melphalan and ASCT v C-weekly
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.56

## Secondary: Response rate to PAD

<b>End point title</b>	Response rate to PAD
End point description:	
Response to treatment will be assessed according to the international uniform response criteria for multiple myeloma.	
For all analyses, responses will be categorised into the following five groups: Complete Response (sCR and CR), Partial Response (VGPR and PR), Stable Disease (SD), Progressive Disease (PD) and early death.	
For response rate to PAD, early death is defined as death between registration and up to and including 21 days post date last PAD cycle started.	
Results for this endpoint are based on the first data cut off of 9/7/2013.	
<b>End point type</b>	Secondary
End point timeframe:	
This is measured following re-induction treatment with PAD.	

<b>End point values</b>	Re-induction PAD and PBSC Harvest			
Subject group type	Reporting group			
Number of subjects analysed	293			
Units: Participants				
Complete Response	49			
Partial Response	186			
Stable Disease	44			
Progressive Disease	2			
Early Death	2			
Response not available	10			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall response rate following randomised treatments

End point title	Overall response rate following randomised treatments
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End point description:

Response to treatment will be assessed according to the international uniform response criteria for multiple myeloma.

For all analyses, responses will be categorised into the following five groups: Complete Response (sCR and CR), Partial Response (VGPR and PR), Stable Disease (SD), Progressive Disease (PD) and early death.

At 100 days post transplant or 30 days post end of C-weekly treatment, early death is defined as death between randomisation and up to and including 100 days post randomisation.

Results for this endpoint are based on the first data cut off of 9/7/2013.

End point type	Secondary
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End point timeframe:

Response rate is measured following the completion of the randomised treatments (100 days post transplant or 30 days post end of C-weekly treatment).

End point values	C-weekly	High dose melphalan and ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: Participants				
Complete Response	19	35		
Partial Response	45	39		
Stable Disease	2	4		
Progressive Disease	15	2		
Early Death	0	1		
Response not available	3	2		
No treatment received	1	6		

## Statistical analyses

Statistical analysis title	Overall response rate
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Statistical analysis description:

Treatment groups will be compared using ordinal logistic regression to adjust for the stratification factors (length of first remission or plateau and response to PAD re-induction therapy) and whether or not mobilisation therapy was received.

Comparison groups	High dose melphalan and ASCT v C-weekly
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Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.79

## Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival is defined as the time from randomisation to death from any cause. If a patient is still alive at the time of analysis or lost to follow-up, they will be treated as censored at the date last known to be alive.	
The analysis of this end point is based off data from the final download 20/1/2017.	
The upper 95% confidence interval limit was not reached for the median survival time in the high dose melphalan and ASCT arm, this has been indicated by 999.	
End point type	Secondary
End point timeframe:	
Overall survival is defined as the time from randomisation to death from any cause.	

End point values	C-weekly	High dose melphalan and ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: Months				
median (confidence interval 95%)	55 (44 to 67)	67 (59 to 999)		

## Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Cox regression analysis will be used to analyse overall survival accounting for the stratification factors (length of first remission or plateau and response to PAD re-induction therapy) and whether or not mobilisation therapy was received.	
Comparison groups	High dose melphalan and ASCT v C-weekly

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0435
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.99

## Secondary: Progression-Free Survival

End point title	Progression-Free Survival
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### End point description:

Disease progression will be determined according to the international uniform response criteria for multiple myeloma. Progression-free survival is defined as the time from randomisation to first documented evidence of disease progression or death from any cause. Patients who do not progress will be censored at the last date they were known to be alive and progression free.

The analysis of this end point is based off data from the final download on 20/1/2017.

End point type	Secondary
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### End point timeframe:

Progression-free survival is defined as the time from randomisation to first documented evidence of disease progression or death from any cause.

End point values	C-weekly	High dose melphalan and ASCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	89		
Units: Months				
median (confidence interval 95%)	11 (9 to 12)	19 (16 to 25)		

## Statistical analyses

Statistical analysis title	Progression-Free Survival
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### Statistical analysis description:

Cox regression analysis will be used to analyse progression-free survival accounting for the stratification factors (length of first remission or plateau and response to PAD re-induction therapy) and whether or not mobilisation therapy was received.

Comparison groups	High dose melphalan and ASCT v C-weekly
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Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.58

## Secondary: Feasibility of stem cell collection

End point title	Feasibility of stem cell collection
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End point description:

The feasibility of stem cell collection will be determined by the satisfactory mobilisation of an adequate number of peripheral blood stem cells ( $\geq 10$  CD34+ cells/ $\mu$ l blood) and the subsequent harvest of sufficient numbers of stem cells to support high-dose chemotherapy ( $\geq 2.0 \times 10^6$  CD34+ cells/kg or  $\geq 2.0 \times 10^8$  PBMC/kg).

Note that any results relating to this endpoint are based on data downloaded following the original data lock on 9/7/2013.

End point type	Secondary
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End point timeframe:

This is measured following PAD re-induction therapy only in patients who had PBSC mobilisation and harvest as part of the trial.

End point values	Re-induction PAD and PBSC Harvest			
Subject group type	Reporting group			
Number of subjects analysed	100 <sup>[1]</sup>			
Units: Participants				
Not adequate	30			
Adequate	70			

Notes:

[1] - Only 100 participants completed PBSC mobilisation and harvest on the trial.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Effect of type of PBSC mobilisation and harvest on time to disease progression

End point title	Effect of type of PBSC mobilisation and harvest on time to disease progression <sup>[2]</sup>
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End point description:

Type of PBSC mobilisation and harvest is categorised as: pre-relapse harvest with no mobilisation

therapy received post-relapse; pre-relapse harvest with mobilisation therapy received post-relapse; post-relapse harvest; or mixed harvest. Mobilisation therapy includes re-mobilisation therapy.

The results relating to this endpoint are based off data from the first follow-up analysis download, dated 14/7/15.

The upper 95% confidence interval limit was not reached for the median survival time in the mixed harvest group, this has been indicated by 999.

End point type	Secondary
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End point timeframe:

Time to disease progression is measured from randomisation to the first documented evidence of disease progression.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to those who underwent an ASCT following randomisation and therefore values are only given for one arm.

<b>End point values</b>	High dose melphalan and ASCT			
Subject group type	Reporting group			
Number of subjects analysed	82 <sup>[3]</sup>			
Units: Months				
median (confidence interval 95%)				
All stem cells harvested prior to first ASCT	16 (13 to 20)			
All stem cells harvested post PAD	25 (19 to 32)			
Mixed harvest	43 (12 to 999)			

Notes:

[3] - Information on this endpoint was not available for 7 participants.

## Statistical analyses

No statistical analyses for this end point



## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

Adverse reactions were collected from the time of registration until 100 days post-ASCT or 30 days post cyclophosphamide.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	3

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

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#### Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Leeds Institute of Clinical Trials Research is an academic trials unit where full MedDRA coding is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories cannot be completed.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2007	Protocol version 2 and PIS version 2, with updates to clarify exclusion criteria and correct mistakes. Addition of sites.
02 November 2007	Protocol version 3 and PIS version 3
01 April 2008	Protocol version 4
07 November 2008	Protocol version 5
20 October 2010	Protocol version 6
10 October 2011	Protocol version 7

Notes:

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### 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.

On the grounds of efficacy data reviewed by the DMEC, the trial was closed to recruitment on 21 November 2012.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24033132>

<http://www.ncbi.nlm.nih.gov/pubmed/24948586>

<http://www.ncbi.nlm.nih.gov/pubmed/27374467>

<http://www.ncbi.nlm.nih.gov/pubmed/26827659>