



## Clinical trial results:

### A Phase II Trial of Sequential treatment with Cytoreductive therapy and Reduced Intensity Conditioning Allogeneic Stem Cell Transplantation for Relapsed/ Refractory Acute Myeloid Leukemia, High Risk Myelodysplasia, or other High Risk Myeloid Malignancies

#### Summary

EudraCT number	2007-000806-64
Trial protocol	GB
Global end of trial date	09 December 2014

#### Results information

Result version number	v1 (current)
This version publication date	08 September 2017
First version publication date	08 September 2017

#### Trial information

##### Trial identification

Sponsor protocol code	BLT004973
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##### Additional study identifiers

ISRCTN number	ISRCTN32336114
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	JRMO, 5 Walden Street, London, United Kingdom, E1 2EF
Public contact	CECM Trials Team, Queen Mary University of London, 0044 02078828197, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	CECM Trials Team, Queen Mary University of London, 0044 02078828197, bci-cecmmonitoring@qmul.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	09 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 December 2014
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine whether it is safer and more effective, in treating high risk Myeloid Malignancies, to immediately follow chemotherapy with Allogeneic Haemopoietic Stem Cell Transplantation than to treat in two distinct phases, with a break to determine remission status.

Protection of trial subjects:

Side effects were closely monitored during and after the study. The patient information sheet included details on expected adverse events for patients and clinicians to look out for and also detailed that unexpected events may occur. The independent data monitoring committee for the trial was in place throughout to closely assess the side effects of the intervention on a regular basis to make sure there were no excess risks to patients. Monitoring was performed throughout the study to provide real-time review of source data to allow for early detection of signals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2007
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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

Notes:

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**Subjects enrolled per age group**

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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)	53
From 65 to 84 years	1



## Subject disposition

### Recruitment

Recruitment details:

Between 24.7.07 and 9.12.14, 54 patients with refractory or relapsed Acute Myeloid Leukaemia, High Risk Myelodysplasia or other high risk Myeloid Malignancy were recruited within the United Kingdom.

### Pre-assignment

Screening details:

Inclusion criteria included patients with histologically documented AML (any WHO type), MDS or other high risk myeloid malignancy, with primary induction failure, or at relapse where the patient was not a candidate for a myeloablative transplant.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Study Intervention
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Arm description:

Sequential treatment with cytoreductive therapy and reduced intensity conditioning allogeneic stem cell transplantation

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

Dosage and administration details:

Low Dose Cytarabine(10mg/m<sup>2</sup> sc bd for 14 days to be repeated at 28 day intervals if necessary) can be administered at the Investigator's discretion for disease control in patients with rapidly progressive disease when conditioning has to be delayed (e.g awaiting unrelated donor clearance).

D-15: Cytarabine 1.5g/m<sup>2</sup> (1 dose-pm) IV  
D-14: Cytarabine 1.5g/m<sup>2</sup> BD IV  
D-13: Cytarabine 1.5g/m<sup>2</sup> BD IV  
D-12: Cytarabine 1.5g/m<sup>2</sup> BD IV  
D-11: Cytarabine 1.5g/m<sup>2</sup> BD IV  
D-10: Cytarabine 1.5g/m<sup>2</sup> BD IV  
D-9: Cytarabine 1.5g/m<sup>2</sup> (1 dose-am) IV

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

Dosage and administration details:

D-15: Daunorubicin 45mg/m<sup>2</sup> OD IV  
D-14: Daunorubicin 45mg/m<sup>2</sup> OD IV  
D-13: Daunorubicin 45mg/m<sup>2</sup> OD IV

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

D-3: Cyclophosphamide 1 g/m<sup>2</sup> IV in 500ml N/saline

D-2: Cyclophosphamide 1 g/m<sup>2</sup> IV in 500ml N/saline

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

D-6: Fludarabine 25 mg/m<sup>2</sup> i.v. OD

D-5: Fludarabine 25 mg/m<sup>2</sup> i.v. OD

D-4: Fludarabine 25 mg/m<sup>2</sup> i.v. OD

D-3: Fludarabine 25 mg/m<sup>2</sup> IV

D-2: Fludarabine 25 mg/m<sup>2</sup> IV

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

Dosage and administration details:

D+1                    Methotrexate 5mg/m<sup>2</sup> IV OD

D+3                    Methotrexate 5mg/m<sup>2</sup> IV OD

D+6                    Methotrexate 5mg/m<sup>2</sup> IV OD

<b>Number of subjects in period 1</b>	Study Intervention
Started	54
Completed	49
Not completed	5
Did not have surgery	5

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	54	54	
Age categorical			
Units: Subjects			
Adults (18-64 years)	53	53	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Units: years			
median	53		
full range (min-max)	23 to 68	-	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	36	36	
Disease type			
Units: Subjects			
Relapsed/refractory AML	39	39	
MDS	9	9	
High-risk myeloid malignancy	6	6	
Prior Transplant			
Units: Subjects			
No	44	44	
ASCT	9	9	
ABMT	1	1	
Donor Sex			
Units: Subjects			
Did not complete transplant	5	5	
Male	32	32	
Female	17	17	
Donor-recipient sex-matching			
Units: Subjects			
Donor (M) - Recipient (F)	8	8	
Donor (M) - Recipient (M)	24	24	
Donor (F) - Recipient (F)	7	7	
Donor (F) - Recipient (M)	10	10	
Did not receive transplant	5	5	
CMV status			
Units: Subjects			
Both negative	13	13	
Other combinations	36	36	
Did not receive transplant	5	5	

Type of donor			
Units: Subjects			
Matched sibling donor	23	23	
Matched unrelated donor	26	26	
Did not receive transplant	5	5	
Dx - RIC-Allo			
Units: months			
median	15		
full range (min-max)	15 to 21	-	

## End points

### End points reporting groups

Reporting group title	Study Intervention
Reporting group description:	
Sequential treatment with cytoreductive therapy and reduced intensity conditioning allogeneic stem cell transplantation	

### Primary: Overall Survival (OS) at 1 and 2 years

End point title	Overall Survival (OS) at 1 and 2 years <sup>[1]</sup>
End point description:	
Median OS for AML=11.64 months, median OS for MDS (not reached but lower limit of 95%CI is 3.96) >3.96 months, median OS for high-risk malignancy=3.6 months; p=0.25. Median OS for over 60=4.1 months, median OS for under 60=1 year 3.24 months; p=0.34.	
End point type	Primary
End point timeframe:	
Overall Survival (OS) at 1 and 2 years	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single arm study and hence statistical analysis is not needed except the survival rate .

End point values	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: %				
number (confidence interval 95%)				
1 year OS - Overall	49 (34 to 62)			
1 year OS - Relapsed/refractory AML patients	48 (31 to 63)			
1 year OS - MDS patients	65 (25 to 87)			
1 year OS - high-risk myeloid malignancy patients	33 (5 to 68)			
1 year OS - Under 60 years of age patients	50 (34 to 65)			
1 year OS - 60 years of age and over patients	40 (12 to 67)			
2 years OS - Overall	39 (26 to 53)			
2 years OS - Relapsed/refractory AML patients	39 (23 to 55)			
2 years OS - MDS patients	65 (25 to 87)			
2 years OS - high-risk myeloid malignancy patients	17 (1 to 52)			
2 years OS - Under 60 years of age patients	41 (26 to 57)			
2 years OS - 60 years of age and over patients	30 (7 to 58)			

<b>Attachments (see zip file)</b>	Overall survival for patients that underwent RIC-AlloHSCT.jpg
	Overall survival for patients that underwent RIC-AlloHSCT for
	Overall survival for patients below the age of 60 and for

## Statistical analyses

No statistical analyses for this end point

### Secondary: Event Free Survival (EFS) at 1 and 2 years

End point title	Event Free Survival (EFS) at 1 and 2 years
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End point description:

EFS is defined as the time between day 1 and relapse or death. Any patients to reach neither relapse nor death were censored at the last date of follow-up.

Median EFS for AML=9.4 months, median EFS for MDS (not reached but lower limit of 95%CI is 4) >4 months, median EFS for high-risk malignancy=2.3 months; p=0.25.

Median EFS for MUD=11.2 months, median EFS for MFD=8.5 months; p=0.98.

Median EFS for over 60=4.1 months, median EFS for under 60=9.4 months; p=0.67.

End point type	Secondary
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End point timeframe:

Event Free Survival (EFS) at 1 and 2 years

End point values	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: %				
number (confidence interval 95%)				
1 year EFS - Overall	43 (29 to 56)			
1 year EFS - relapsed/refractory AML patients	40 (24 to 56)			
1 year EFS - MDS patients	65 (25 to 87)			
1 year EFS - high-risk myeloid malignancy patients	33 (5 to 68)			
1 year EFS - matched unrelated donor patients	37 (17 to 57)			
1 year EFS - matched family donor patients	48 (27 to 66)			
1 year EFS - under 60 years of age patients	43 (28 to 58)			
1 year EFS - 60 years of age and over patients	40 (12 to 67)			
2 years EFS - Overall	31 (18 to 44)			
2 years EFS - relapsed/refractory AML patients	28 (14 to 43)			
2 years EFS - MDS patients	65 (25 to 87)			
2 years EFS - high-risk myeloid malignancy patient	17 (1 to 52)			
2 years EFS - matched unrelated donor patients	37 (17 to 57)			
2 years EFS - matched family donor patients	29 (12 to 48)			

2 years EFS - under 60 years of age patients	31 (17 to 46)			
2 years EFS - 60 years of age and over patients	30 (7 to 58)			

<b>Attachments (see zip file)</b>	EFS of patients that underwent RIC-alloHSCT.jpg
	EFS of patients that underwent RIC-alloHSCT for high-risk
	EFS of patients that underwent RIC-alloHSCT with matched
	EFS of patients below the age of 60 and for patients 60 and

## Statistical analyses

No statistical analyses for this end point

### Secondary: Engraftment and Chimerism Analysis (Full Split Chimerism at Days 30, 60, 100 and 1 year following RIC Allo-HSCT)

End point title	Engraftment and Chimerism Analysis (Full Split Chimerism at Days 30, 60, 100 and 1 year following RIC Allo-HSCT)
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End point description:

Neutrophil Engraftment and Platelet Engraftment are calculated as time between day 1 to first of two consecutive days with a neutrophil count exceeding 500/ $\mu$  and to the first day of three consecutive days with an unsupported platelet count exceeding 20 x 10<sup>9</sup> / L respectively.

37 patients experienced complete haematologic recovery after RIC-allogeneic SCT. The median time to achieve more than 0.5x10<sup>9</sup>/L neutrophils in the peripheral blood was 18.5 days (range, 10–30) after transplantation; a sustained platelet count greater than 20x10<sup>9</sup>/L was achieved at 14.5 days (range, 6–39), 12 patients did not reach this count by the time of death or censoring) after transplantation.

Chimerism studies demonstrate that by one year median engraftment was 97%. Full split chimerism studies confirmed over 98% donor engraftment in both CD3 and CD15 at 1 year.

End point type	Secondary
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End point timeframe:

Time to Engraftment is categorised as Neutrophil Engraftment and Platelet Engraftment. Full Split Chimerism at Days 30, 60, 100 and 1 year following RIC Allo-HSCT.

End point values	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: %				
median (inter-quartile range (Q1-Q3))				
Day 30: Whole Blood	96 (50 to 98)			
Day 30: CD3	95 (87 to 98)			
Day 30: CD15	95 (25.5 to 98)			
Day 60: Whole Blood	92 (35 to 98)			
Day 60: CD3	92 (83 to 97)			
Day 60: CD15	93.5 (11 to 98)			
Day 100: Whole Blood	77.5 (20 to 96)			
Day 100: CD3	94 (82 to 97)			

Day 100: CD15	73 (13 to 98)			
1 year: Whole Blood	97 (94 to 100)			
1 year: CD3	98 (96 to 100)			
1 year: CD15	99 (94 to 100)			

<b>Attachments (see zip file)</b>	Neutrophil engraftment following transplantation.jpg
	Platelet engraftment following transplantation.jpg

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence and Grade of Acute Graft versus Host Disease (GVHD)

End point title	Incidence and Grade of Acute Graft versus Host Disease (GVHD)
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End point description:

Grades were only recorded for acute GVHD where available.

End point type	Secondary
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End point timeframe:

GVHD in patients following RIC Allo-HSCT.

End point values	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Subjects				
Acute: Yes	10			
Acute: No	44			
Chronic: Yes	10			
Chronic: No	44			
Acute: Grade: N/A	36			
Acute: Grade: 1	4			
Acute: Grade: 2	3			
Acute: Grade: 3	1			
Acute: Grade: 4	1			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Treatment Related Mortality (TRM) at d100, 1 and 2 years and cause of mortality

End point title	Treatment Related Mortality (TRM) at d100, 1 and 2 years and cause of mortality
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End point description:

Treatment Related Mortality Rate is calculated for deaths when there is no evidence of leukaemia within 100 days of treatment and then within 1 and 2 year.

Median TRM rates for MFD > 8.63 months.

Median TRM rates for MUD > 1 year 5.8 months.

Cause of mortality was mainly categorised as AML, GVHD or infection related.

End point type	Secondary
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End point timeframe:

Cumulative incidence of TRM at 100 days, 1 year and 2 years.

End point values	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: %				
number (confidence interval 95%)				
Cumulative incidence of TRM: 100 days	16 (8 to 29)			
Cumulative incidence of TRM: 1 year	32 (21 to 48)			
Cumulative incidence of TRM: 2 years	36 (23 to 53)			
Cumulative incidence of TRM: MUD: 100 days	19 (8 to 40)			
Cumulative incidence of TRM: MFD: 100 days	14 (5 to 37)			

<b>Attachments (see zip file)</b>	Treatment related mortality following RIC Allo-HSCT.jpg TRM following RIC-alloHSCT with matched family donor and Cause of mortality.jpg
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Opportunistic Infections

End point title	Opportunistic Infections
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End point description:

End point type	Secondary
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End point timeframe:

Incidence of opportunistic infections.

<b>End point values</b>	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Subjects				
Patients who gained an opportunistic infection	9			
Patients unaffected	45			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Hospitalisation

End point title	Duration of Hospitalisation
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End point description:

End point type	Secondary
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End point timeframe:

Median hospital stay.

<b>End point values</b>	Study Intervention			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Days				
median (inter-quartile range (Q1-Q3))				
Median hospital stay	36 (34 to 41)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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

Timeframe for reporting adverse events:

All serious adverse events recorded during the study are recorded. Non-serious adverse events are not recorded in this trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	4

### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

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: No Non-serious adverse events are recorded in this trial.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 49 (34.69%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events	0		
Vascular disorders			
Bilateral Subdurals			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Refractory AML			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Graft versus host disease			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			

subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
<b>Infections and infestations</b>			
<b>E. Coli septicaemia</b>			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
<b>Cardiac Failure / Sepsis</b>			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Neutropenic infection</b>			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	1 / 5		
<b>Infection, multi-organ failure</b>			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Meningioma</b>			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2008	Alterations to chemotherapy schedule and supportive medications to ensure consistency with site standard practice. Redefined early closing rule of 'unacceptable toxicity'. Expanded AE reporting requirements.
09 July 2011	Implementation of temporary halt while DSMB reviewed data to confirm if stopping rule had been met.
20 September 2011	Re-open to recruitment following confirmation from DSMB. Exclusion criteria amended to prevent entry of patients >60 years. Introduction of regular DSMB monitoring. Re-classification of MENSA, cyclosporine, and allogeneic blood stem cells as non-IMPs.
15 May 2012	Change of sponsor from Barts and the London NHS Trust to Barts Health NHS Trust following institutional mergers.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 July 2011	The study was halted to recruitment as it had potentially reached its stopping rule (see section 11.2 of the protocol -'The mortality rate will be monitored by calculating 95% Confidence Intervals for survival at 100 days. If the CIs show that there is a significant probability that the survival rate is less than 75% at day 100, then the study will be stopped.'). The DSMB met and confirmed that although the stopping rule had not been met, patients over 60 years should be excluded from entry to the trial going forwards.	07 September 2011

Notes:

### Limitations and caveats

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

A sample of 93 patients was aimed to establish a 95% CI of 0.1 but only 54 patients were accrued for the trial, with 49 undergoing transplant.

Notes: