

**Clinical trial results:****Evaluation of Treosulfan pharmacokinetics (PK) in children undergoing allogeneic haematopoietic stem cell transplantation (HSCT)****Summary**

EudraCT number	2013-003257-20
Trial protocol	GB
Global end of trial date	15 December 2017

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information**Trial identification**

Sponsor protocol code	10MI28
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02048800
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Great Ormond Street Hospital for Children
Sponsor organisation address	Great Ormond Street , London, United Kingdom, WC1 3JH
Public contact	research.governance@gosh.nhs.uk, Great Ormond Street Hospital for Children NHS Foundation Trust Bone Marrow Transplant Unit , 0044 02074059200 , research.governance@gosh.nhs.uk
Scientific contact	Dr. Robert Chiesa, Great Ormond Street Hospital for Children NHS Foundation Trust Bone Marrow Transplant Unit , 0044 02074059200 , robert.chiesa@gosh.nhs.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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 May 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to describe Treosulfan PK in children and infants undergoing allogeneic stem cell transplantation and to determine if this is a significant variable in determining transplant outcome.

The primary objective of the study is to assess PK parameters after Treosulfan infusion in children prior to allogeneic haematopoietic stem cell transplantation.

Protection of trial subjects:

In conducting the trial, the Sponsor and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- the Human Rights Act 1998
- the Data Protection Act 1998
- the Freedom of Information Act 2000
- the Human Tissue Act 2004
- the Medicines Act 1968
- the Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version), ICH Good Clinical Practice Guidelines and in accordance with the terms and conditions of the ethical approval given to the trial. The trial has received a favourable opinion from the Research Ethics Committee. CI has submitted Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

All subjects/guardians were provided informed consent prior to entering the study. The investigator was responsible for explaining the benefits and risk of the participation in the study to each subject's legal representative for obtaining informed consent.

Background therapy:

Treosulfan is a busulfan analogue with a different mechanism of action and is widely used in the allo-HSCT setting. Whilst busulfan is a direct DNA alkylating agent, treosulfan is a prodrug with alkylating activity mediated by its main epoxybutane derivatives requiring a pH and temperature-dependent non-enzymatic two-step process to form first the mono and then diepoxide. Since the first report of treosulfan-based conditioning in paediatric allo-HSCT in 2002, this drug has been increasingly used off-label in children, largely due to a perceived wide therapeutic index and a lower propensity to cause hepatotoxicity (in particular veno-occlusive disease) than busulfan. The aim of this study was to characterise the PKPD profile of treosulfan in children undergoing allo-HSCT in an investigator-initiated, multicentre phase II clinical trial.

Evidence for comparator:

N/A

Actual start date of recruitment	08 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	34
Children (2-11 years)	21
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 centres in the UK between September 2014 and December 2017. Children with an indication to HSCT and treatment with Treosulfan were screened for possible enrollment into this PK study.

Pre-assignment

Screening details:

There are total 60 subjects screened in this study however only 57 subjects enrolled in to this study. The total number comprise from two sites in the UK.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Infusion of Treosulfan within condition regimen
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Arm description:

Treosulfan is infused intravenously over 2 hours three days on day -7, -6 and -5 pre Hemopoietic Stem cell transplant. Also Fudarabine is administered 30mg/m²/day for 5 days on day -7 to -3 as part of conditioning regimen.

Arm type	Experimental
Investigational medicinal product name	Treosulfan
Investigational medicinal product code	I01AB02
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan given at a total dose of 30-42 gm/m² over three days. The dosage is based on age. Infants <3 months was dosed at 10 gm/m², children ag3-12 months were dosed at 12gm/m² and children over 12 months dosed at 14 gm/m².

Number of subjects in period 1	Infusion of Treosulfan within condition regimen
Started	60
Completed	57
Not completed	3
Consent withdrawn by subject	2
abnormal liver results	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	34	34	
Children (2-11 years)	21	21	
Adolescents (12-17 years)	5	5	
Gender categorical Units: Subjects			
Not relevant	60	60	

Subject analysis sets

Subject analysis set title	Overall analysis
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Subject analysis set type	Full analysis
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Subject analysis set description:

The primary end point was to measure Treosulfan PK and the secondary endpoint was to assess its short term toxicity, graft failure and mortality.

Furthermore measures and models of efficacy (engraftment) and toxicity will be tested against PK parameters to ascertain dose/concentration-response relationships. These comparisons will be done by comparing the x2 distributed objective function value (OFV) between nested models, with the addition of one parameter giving a drop in OFV of 3.84 at a significance level of $p < 0.05$.

Reporting group values	Overall analysis		
Number of subjects	57		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	34		
Children (2-11 years)	21		
Adolescents (12-17 years)	4		
Gender categorical Units: Subjects			
Not relevant	57		

End points

End points reporting groups

Reporting group title	Infusion of Treosulfan within condition regimen
Reporting group description: Treosulfan is infused intravenously over 2 hours three days on day -7, -6 and -5 pre Hemopoietic Stem cell transplant. Also Fudarabine is administered 30mg/m ² /day for 5 days on day -7 to -3 as part of conditioning regimen.	
Subject analysis set title	Overall analysis
Subject analysis set type	Full analysis
Subject analysis set description: The primary end point was to measure Treosulfan PK and the secondary endpoint was to assess its short term toxicity, graft failure and mortality. Furthermore measures and models of efficacy (engraftment) and toxicity will be tested against PK parameters to ascertain dose/concentration-response relationships. These comparisons will be done by comparing the x2 distributed objective function value (OFV) between nested models, with the addition of one parameter giving a drop in OFV of 3.84 at a significance level of p <0.05.	

Primary: Assess the Area Under the Curve (AUC) 0-∞, steady-state volume of distribution and clearance of Treosulfan

End point title	Assess the Area Under the Curve (AUC) 0-∞, steady-state volume of distribution and clearance of Treosulfan ^[1]
End point description:	
End point type	Primary
End point timeframe: Assess the Area Under the Curve (AUC) 0-∞, steady-state volume of distribution and clearance of Treosulfan	
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: Statistical analysis of of end point is not mandatory field. This is a single arm study and no comparison group available.	

End point values	Infusion of Treosulfan within condition regimen			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: number				
Steady-state volume of distribution (L/70Kg)	45			
Clearance of Treosulfan (L/h/70 kg)	17			
Cumulative Treosulfan AUC (dose 30 g - mg.h/L)	4521			
Cumulative Treosulfan AUC (dose 36 g - mg.h/L)	5204			
Cumulative Treosulfan AUC (dose 42 g - mg.h/L)	4590			

Statistical analyses

No statistical analyses for this end point

Secondary: Assess the incidence of grade III-IV adverse events (NCI common toxicity criteria, version 4.0) within the first 30 days after transplant;

End point title | Assess the incidence of grade III-IV adverse events (NCI common toxicity criteria, version 4.0) within the first 30 days after transplant;

End point description:

Safety endpoints - Assess the incidence of grade III-IV adverse events (NCI common toxicity criteria, version 4.0) within the first 30 days after transplant;

End point type | Secondary

End point timeframe:

30 days

End point values	Infusion of Treosulfan within condition regimen	Overall analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: subjects affected				
Infection grade III-IV	29	29		
Liver grade III-IV	18	18		
Mucositis grade III-IV	17	17		
Diarrhoea grade III-IV	10	10		
Nausea/Vomiting grade III-IV	13	13		
Neurology grade III-IV	2	2		
Pulmonary grade III-IV	8	8		
Dermatology grade III-IV	6	6		
Renal grade III-IV	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Assess transplant related mortality at 100 days after transplant

End point title | Assess transplant related mortality at 100 days after transplant

End point description:

Safety endpoint - assess transplant related mortality at 100 days after transplant;

End point type | Secondary

End point timeframe:

100 days after transplant

End point values	Infusion of Treosulfan within condition regimen			
Subject group type	Reporting group			
Number of subjects analysed	57 ^[2]			
Units: number				
number (not applicable)				
Number deaths	4			

Notes:

[2] - One patient died after the conditioning regimen, but prior to the transplant.

Statistical analyses

No statistical analyses for this end point

Secondary: Assess cumulative incidence and severity of acute GvHD.

End point title	Assess cumulative incidence and severity of acute GvHD.
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End point description:

End point type	Secondary
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End point timeframe:

End of study assessment of acute and chronic GVHD

End point values	Infusion of Treosulfan within condition regimen			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: subjects affected				
Acute grade I GVHD	12			
Acute grade 2 GVHD	12			
Acute grade 3 GVHD	0			
Acute grade 4 GVHD	1			
Chronic GVHD	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Assess the timing of neutrophil and platelet recovery;

End point title	Assess the timing of neutrophil and platelet recovery;
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End point description:

End point type	Secondary
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End point timeframe:
First month post-BMT

End point values	Infusion of Treosulfan within condition regimen			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: days to recovery				
Median time for neutrophil recovery (days)	16			
Median time for platelet recovery (days)	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Assess donor engraftment after transplant

End point title Assess donor engraftment after transplant

End point description:

End point type Secondary

End point timeframe:

Assess myeloid and T-cell engraftment after transplant.

End point values	Infusion of Treosulfan within condition regimen			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: number				
Full donor engraftment at last follow-up (myeloid)	26			
Full donor engraftment at last follow-up (T-cell)	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Assess overall survival and disease-free survival at 1 year post transplant.

End point title	Assess overall survival and disease-free survival at 1 year post transplant.
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End point description:

End point type	Secondary
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End point timeframe:
1 year post transplant

End point values	Infusion of Treosulfan within condition regimen			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: number				
Patients alive 1 year post-BMT	53			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall

End point title	Overall
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End point description:

End point type	Other pre-specified
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End point timeframe:
30 days

End point values	Infusion of Treosulfan within condition regimen	Overall analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: 57	57	57		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were recorded after Treosulfan administration (day - 7). Documentation started at the time of first Treosulfan administration and up to 100 days after last Treosulfan administration.

Adverse event reporting additional description:

After the end of this documentation period, patients safety was monitored by the respective transplant treatment protocol. AEs are to be documented after each sampling period giving the highest CTCAE grade within the reporting period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	overall trial
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Reporting group description:

Single cohort of children and infants aged 28 days-16 years old receiving Treosulfan as part of their conditioning regimen prior to HSCT.

Serious adverse events	overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 57 (7.02%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Sepsis due to staphylococcus	Additional description: Child died of multi-organ failure.		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Encephalopathy and lymphoproliferative disease due to EBV infection	Additional description: Patient died due to infection in an immunocompromised host.		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
RSV pneumonitis	Additional description: The patient developed RSV pneumonitis associated with engraftment.		

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
History of diarrhoea and vomiting pre BMT and norovirus in stools			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)		
General disorders and administration site conditions			
Liver toxicity	Additional description: IMP Toxicity		
subjects affected / exposed	46 / 57 (80.70%)		
occurrences (all)	46		
Mucosal toxicity			
Additional description: IMP Toxicity			
subjects affected / exposed	35 / 57 (61.40%)		
occurrences (all)	35		
Diarrhoea			
Additional description: IMP Toxicity			
subjects affected / exposed	32 / 57 (56.14%)		
occurrences (all)	32		
Nausea/Vomiting			
Additional description: IMP Toxicity			
subjects affected / exposed	42 / 57 (73.68%)		
occurrences (all)	42		
Neurological toxicity			
Additional description: IMP toxicity			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Pulmonary toxicity			
Additional description: IMP Toxicity			
subjects affected / exposed	20 / 57 (35.09%)		
occurrences (all)	20		
Renal toxicity			
Additional description: IMP toxicity			

subjects affected / exposed occurrences (all)	41 / 57 (71.93%) 41		
Gastrointestinal disorders			
Dermatological toxicity	Additional description: IMP toxicity		
subjects affected / exposed occurrences (all)	37 / 57 (64.91%) 37		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported