



## Clinical trial results:

### A RANDOMISED, CROSS-OVER, PHASE II STUDY, TO INVESTIGATE THE EFFICACY AND SAFETY OF GLUCARPIDASE FOR ROUTINE USE AFTER HIGH DOSE METHOTREXATE IN PATIENTS WITH BONE SARCOMA

#### Summary

EudraCT number	2006-003203-40
Trial protocol	GB
Global end of trial date	13 April 2015

#### Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

#### Trial information

##### Trial identification

Sponsor protocol code	06/085
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	University College London Joint Research Office
Sponsor organisation address	1st Floor Maple House, Suite A 149 Tottenham Court Rd , London, United Kingdom, W1T 7DN
Public contact	Prof Jeremy Whelan, University College London Joint research Office, 44 0203447 9346, jeremy.whelan@nhs.net
Scientific contact	Prof Jeremy Whelan, University College London Joint Research Office, 44 0203447 9346, jeremy.whelan@nhs.net

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	14 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 April 2015
Global end of trial reached?	Yes
Global end of trial date	13 April 2015
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 investigate whether glucarpidase rescue after high-dose methotrexate reduces delay to subsequent cycle of chemotherapy due to methotrexate toxicity

Protection of trial subjects:

Written informed consent taken

Safety measures to enable appropriate patient assessment pre-chemotherapy and timely reporting of treatment related adverse reactions/events.

Background therapy:

MAP chemotherapy (methotrexate, doxorubicin, cisplatin) for high-grade bone osteosarcoma

Evidence for comparator: -

Actual start date of recruitment	13 June 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: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	14
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients with osteosarcoma undergoing standard first line chemotherapy

-> Enter recruitment dates etc, hover over 'i' on the right to get the info

### Pre-assignment

Screening details:

Written informed consent from patient or parent/guardian

Diagnosis of high grade osteosarcoma, localised or metastatic  
or high grade osteosarcoma as a second malignancy

or spindle cell sarcoma of bone

or relapsed high grade osteosarcoma

Age: 5-50 years at registration

Ability to comply with study and follow up procedures (WHO performance 0-2)

### Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	A (M-GluM)

Arm description:

Cycle 1 methotrexate alone Day 1 and Day 8. Cycle 2 Methotrexate plus glucarpidase Day 1 and Day 8

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	B (GluM-M)

Arm description:

Cycle 1 Methotrexate plus glucarpidase Day 1 and Day 8. Cycle 2 methotrexate alone Day 1 and Day 8.

Arm type	Experimental
Investigational medicinal product name	Glucarpidase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

50u/kg by slow iv injection

<b>Number of subjects in period 1<sup>[1]</sup></b>	A (M-GluM)	B (GluM-M)
Started	16	16
Completed	14	16
Not completed	2	0
Adverse event, non-fatal	2	-

Notes:

[1] - 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: 2 patients were not randomised

## Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	A (M-GluM)

Arm description:

Glucarpidase plus Methotrexate

Arm type	Experimental
Investigational medicinal product name	Glucarpidase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

50u/kg by slow iv injection

<b>Arm title</b>	B (GluM-M)
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Arm description:

Methotrexate only

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	GluM

Arm description:

Outcomes for patients when on Glucarpidase (aggregated over both periods)

Arm type	Experimental
Investigational medicinal product name	Glucarpidase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

50u/kg by slow iv injection

<b>Arm title</b>	No Glu
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Arm description:

Outcomes for patients when not on Glucarpidase (aggregated over both periods)

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	A (M-GluM)	B (GluM-M)	GluM
Started	14	16	29
Completed	12	11	29
Not completed	2	5	0
MTX Toxicity	1	5	-
Progressive Disease	1	-	-

<b>Number of subjects in period 2</b>	No Glu
Started	29
Completed	29
Not completed	0
MTX Toxicity	-
Progressive Disease	-

## Baseline characteristics

### Reporting groups

Reporting group title	A (M-GluM)
Reporting group description:	
Cycle 1 methotrexate alone Day 1 and Day 8. Cycle 2 Methotrexate plus glucarpidase Day 1 and Day 8	
Reporting group title	B (GluM-M)
Reporting group description:	
Cycle 1 Methotrexate plus glucarpidase Day 1 and Day 8. Cycle 2 methotrexate alone Day 1 and Day 8.	

Reporting group values	A (M-GluM)	B (GluM-M)	Total
Number of subjects	16	16	32
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	1	1
Adolescents (12-17 years)	11	9	20
Adults (18-64 years)	5	6	11
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	18.7	5.2	
standard deviation	± 22.9	± 11.8	-
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	13	12	25
Metastases			
Units: Subjects			
Yes	4	1	5
No	12	15	27
Site			
Units: Subjects			
Extremity	15	11	26
Other	1	5	6
Histology			
Units: Subjects			
Osteosarcoma	14	15	29
Other	2	1	3

## End points

### End points reporting groups

Reporting group title	A (M-GluM)
Reporting group description:	
Cycle 1 methotrexate alone Day 1 and Day 8. Cycle 2 Methotrexate plus glucarpidase Day 1 and Day 8	
Reporting group title	B (GluM-M)
Reporting group description:	
Cycle 1 Methotrexate plus glucarpidase Day 1 and Day 8. Cycle 2 methotrexate alone Day 1 and Day 8.	
Reporting group title	A (M-GluM)
Reporting group description:	
Glucarpidase plus Methotrexate	
Reporting group title	B (GluM-M)
Reporting group description:	
Methotrexate only	
Reporting group title	GluM
Reporting group description:	
Outcomes for patients when on Glucarpidase (aggregated over both periods)	
Reporting group title	No Glu
Reporting group description:	
Outcomes for patients when not on Glucarpidase (aggregated over both periods)	
Subject analysis set title	Fitness for chemotherapy at day 15
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The McNemar's test considers the null hypothesis that the proportions of patients fit for chemotherapy after Glu and no Glu are equal.	

### Primary: Fitness for chemotherapy at Day 15 following Glu or no Glu

End point title	Fitness for chemotherapy at Day 15 following Glu or no Glu
End point description:	
End point type	Primary
End point timeframe:	
Day 15 fitness post chemotherapy	

End point values	A (M-GluM)	B (GluM-M)	A (M-GluM)	B (GluM-M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	16	13	16
Units: Yes or No				
Fitness at Day 15	5	5	8	5

End point values	GluM	No Glu		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		

Units: Yes or No				
Fitness at Day 15	13	10		

## Statistical analyses

<b>Statistical analysis title</b>	Fitness for chemotherapy at Day 15
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Statistical analysis description:

The McNemar's test considers the null hypothesis that the proportions of patients fit for chemotherapy after Glu and no Glu are equal.

Comparison groups	A (M-GluM) v B (GluM-M)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
P-value	< 0.05
Method	McNemar

Notes:

[1] - The sample size calculation is based on a McNemar's test with an assumption that the responses to glucarpidase and folinic acid rescue are independent. With anticipated proportions of responses to standard rescue and glucarpidase+folinic acid of 55% and 90% respectively, the study will require 38 patients to give 80% power at a significance level of 5% and to allow for up to 30% drop-out during the study. The O'Brien and Fleming boundary method will be used for testing significance of effect.

## Secondary: Mucositis assessment

End point title	Mucositis assessment
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End point description:

End point type	Secondary
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End point timeframe:

Assessment at Day 15

End point values	GluM	No Glu		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: CTCAE grade				
number (not applicable)				
Mucositis	4	9		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Renal toxicity

End point title	Renal toxicity
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End point description:

End point type	Secondary
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End point timeframe:

Day 15

End point values	GluM	No Glu		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: CTCAE grade				
number (not applicable)				
Renal toxicity	5	6		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Neutropenia

End point title	Neutropenia
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End point description:

End point type	Secondary
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End point timeframe:

Day 15

End point values	GluM	No Glu		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: CTCAE grade				
number (not applicable)				
Neutropenia	1	1		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Liver toxicity

End point title	Liver toxicity
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End point description:

End point type	Secondary
End point timeframe:	
Day 15	

End point values	GluM	No Glu		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: CTCAE grade				
number (not applicable)				
Liver toxicity	13	14		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Thrombocytopenia

End point title	Thrombocytopenia
End point description:	
End point type	Secondary
End point timeframe:	
Day 15	

End point values	GluM	No Glu		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: CTCAE grade				
number (not applicable)				
Thrombocytopenia	2	1		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE related to IMP followed up until resolution. AE not related to IMP followed up until the end of the study (Day 21 of cycle 2)

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	3

### Reporting groups

Reporting group title	Data analysis
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Reporting group description: -

Serious adverse events	Data analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Data analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2006	Inclusion of new study site and clarifications on administration of care
17 April 2007	Manufacturer's data amending timing of folinic acid administration post glucarpidase to minimise competition
08 September 2009	To provide real-time stability data for IMP To provide new safety data for IMP Change of study design to double blind, randomised to unblind, randomised Revision of sample size to allow drop-out rate of 30% Administrative changes to contact details Study solely sponsored by UCL
03 November 2010	Notification of additional laboratory conducting anti-glucarpidase antibody analysis Change in co-investigator Updated hydration details of methotrexate addition of safety reporting procedures to protocol
02 February 2011	IMP updated to new batch Updated methotrexate hydration details
24 May 2012	ALT and albumin measurement ranges removed from inclusion criteria Platelet count reduced to 75 for inclusion IMP shelf life changed to 4 hours ASR replaced with DSUR Clarifications to reporting of SAEs
23 August 2013	Change of Chief Investigator title Notification of new Co-investigator New contact details Updated protocol and appendices

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.

Results are preliminary and unpublished

Notes: