Clinical trial results:
A Single Centre Study Investigating the Safety and Efficacy of an Immune Modulation Regimen in Mitigating the Alloimmune Response to Intravenous Laronidase in Infants With Severe Mucopolysaccharidosis type I (Hurler syndrome) Prior to Haematopoietic Stem Cell Transplantation

Summary

EudraCT number	2015-003031-35
Trial protocol	GB
Global end of trial date	31 October 2017

Results information

Result version number	v1 (current)
This version publication date	09 February 2020
First version publication date	09 February 2020

Trial information

Trial identification

Sponsor protocol code	R04049

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9WL
Public contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, 0044 01612674125, lynne.webster@mft.nhs.uk
Scientific contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, 0044 01612674125, lynne.webster@mft.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	31 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to investigate the safety and efficacy of methotrexate as an immune tolerance induction agent in mitigating the alloimmune response to enzyme replacement therapy with laronidase in severe MPS I.

Protection of trial subjects:

To minimise the inconvenience to families participating in the study, patients enrolled on the trial received their doses around the first infusion of laronidase. All other treatment was as standard of care and the protocol did not interfere with routine timescales for enzyme replacement therapy (ERT) and scheduling of haematopoietic stem cell transplantation (HSCT).

The main study procedure was urine and blood sampling. All patients received standard care for Hurler syndrome and therefore required peripheral venous cannulation for ERT infusions as well as central venous catheter insertion in preparation for HSCT. Most study related blood tests were therefore taken at the point of cannulation or from the central venous catheter, minimising the need for additional venepunctures. This study did not involve any significant invasive procedures or radiographic imaging.

Methotrexate is a drug commonly used in children with inflammatory disorders and its side effect and toxicity profile is well understood. Participants were monitored closely throughout the study and were made aware of the known risks and side effects prior to participation so that they could make an informed decision.

Background therapy:

There was no background therapy

Evidence for comparator:

There was no comparator in the study as it is a single arm study where everyone received the IMP.

Actual start date of recruitment	01 October 2015
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: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	3
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 11th Feb 2016 at Manchester Royal Infirmary. Recruitment and the trial ended on 31st Oct 2017.

Pre-assignment

Screening details:

Screening and baseline was to be completed within 7 days prior to first infusion of laronidase. A maximum of 7 days from informed consent, however due to the fact many patients travel long distances this will often take place on the same day as the first laronidase treatment.

Period 1

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

Blinding implementation details:

The trial was open label

Arms

Arm title	methotrexate

Arm description:

Participants enter a treatment phase where patients receive methotrexate for 3 weeks (three doses per week) in addition to standard care. Following this all patients continue on weekly ERT until transplantation as per standard of care, receiving a minimum of 4 weeks of ERT in total. It was anticipated that all patients would receive at least 8 weeks of ERT and therefore have study samples collected at 8 weeks for the primary endpoint. However in the unlikely event that HSCT is scheduled earlier, study samples will be collected at 4 weeks after commencing ERT and immediately prior to HSCT for secondary endpoints only.

Arm type	Experimental
Investigational medicinal product name	Methotraxate
Investigational medicinal product code	PL 00427/0233
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

0.4mg/kg per day is the maximum allowed dose. Three doses, given 1 hour prior to the infusion of laronidase and 24 hours and 48 hours after infusion. This treatment pattern will be repeated at weeks 1 and 2 meaning 9 doses in total. All other treatment will be as standard care

Number of subjects in period 1	methotrexate
Started	3
Completed	3

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	3	3	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
median	11.5		
full range (min-max)	4.5 to 13.6	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	2	2	
Genotype Units: Subjects			
c.1205G > A/c.1205 G > A [p. (Trp402Ter)/	1	1	
c.1205G > A/c.979G > C [p. (Trp402Ter)/	1	1	
c.1205G > A/c.46_57del12 [p. (Trp402Ter) /	1	1	
Iduronidase Enzyme Activity Units: Subjects			
0.02	1	1	
0.17	1	1	
undetectable	1	1	

End points

End points reporting groups

Reporting group title	methotrexate

Reporting group description:

Participants enter a treatment phase where patients receive methotrexate for 3 weeks (three doses per week) in addition to standard care. Following this all patients continue on weekly ERT until transplantation as per standard of care, receiving a minimum of 4 weeks of ERT in total. It was anticipated that all patients would receive at least 8 weeks of ERT and therefore have study samples collected at 8 weeks for the primary endpoint. However in the unlikely event that HSCT is scheduled earlier, study samples will be collected at 4 weeks after commencing ERT and immediately prior to HSCT for secondary endpoints only.

Primary: Peak anti-laronidase IgG titres of < 1:4000

End point title	Peak anti-laronidase IgG titres of < 1:4000[1]

End point description:

End point type	Primary

End point timeframe:

between 4 weeks post-ERT and pre-HSCT

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: No participants had a peak anti-laronidase IgG titre of less than 1:4000 (i.e. 0 out of 3 participants met the endpoint).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent to commencement of conditioning therapy for haematopoietic stem cell transplantation.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	3

Reporting groups

Reporting group title	Methotrexate

Reporting group description: -

Serious adverse events	Methotrexate		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Admission to commence ACE inhibitors for mitral regurgitation			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Planned hospital admission for hip arthroscopy			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Methotrexate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Investigations			

Deranged LFTs alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1		
Cardiac disorders Mitral regurgitation alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 2		
General disorders and administration site conditions Pyrexia alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 3		
Immune system disorders Allergic reaction alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 2 / 3 (66.67%) 2		
Gastrointestinal disorders Vomiting alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 3		
Respiratory, thoracic and mediastinal disorders Cough alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 2 / 3 (66.67%) 2		
Skin and subcutaneous tissue disorders hair thinning and hair loss alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1		
Musculoskeletal and connective tissue disorders			

arthrogram and removal of hip spica alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2016	The first two participants received three doses of oral methotrexate around the first laronidase infusion only. A minimum of 2 further participants will be enrolled and will receive three doses of oral methotrexate around each of the first three laronidase infusions. This was due to the fact the first 2 patients developed antibodies to the methotrexate.

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.

The study was terminated early after 3 patients. Following the development of antibodies by the first 2 subjects, the duration of the Methotrexate regimen was increased. The 3rd participant on this extended dose also developed antibodies.

Notes: