



## 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

|                                       |              |
|---------------------------------------|--------------|
| <b>Number of subjects in period 1</b> | 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<br>(gestational age < 37 wks) | 0           | 0     |  |
| Newborns (0-27 days)                                  | 0           | 0     |  |
| Infants and toddlers (28 days-23<br>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.<br>(Trp402Ter)]          | 1           | 1     |  |
| c.1205G > A/c.979G > C [p.<br>(Trp402Ter)]            | 1           | 1     |  |
| c.1205G > A/c.46_57del12 [p.<br>(Trp402Ter) /         | 1           | 1     |  |
| Iduronidase Enzyme Activity                           |             |       |  |
| Units: Subjects                                       |             |       |  |
| 0.02  | 1           | 1     |  |
| 0.17  | 1           | 1     |  |
| undetectable  | 1           | 1     |  |

## End points

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### 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. |              |

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

|   |  |
|---|--|
| End point title   | Peak anti-laronidase IgG titres of < 1:4000 <sup>[1]</sup> |
| 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).                            |  |

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

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

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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.

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: