



## Clinical trial results:

### An Open-label, Multi-centre, Phase I/II Dose Escalation Trial of an Adeno-Associated Virus Vector (AAV2/5-OPTIRPE65) for Gene Therapy of Adults and Children with Retinal Dystrophy associated with Defects in RPE65 (LCA2)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-003418-25   |
| Trial protocol           | GB               |
| Global end of trial date | 07 December 2018 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 20 June 2021 |
| First version publication date | 20 June 2021 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CTU/2014/120 |
|-----------------------|--------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | MeiraGTx  |
| Sponsor organisation address | 34-38 Provost Street, London, United Kingdom, N1 7NH        |
| Public contact               | Julie Bakobaki, MeiraGTx UK II Ltd, ocularinfo@meiragtx.com |
| Scientific contact           | Julie Bakobaki, MeiraGTx UK II Ltd, ocularinfo@meiragtx.com |

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                       | 27 February 2020 |
| Is this the analysis of the primary completion data? | No               |

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|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 07 December 2018 |
| Was the trial ended prematurely? | No               |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary research objective is to assess the safety of a new optimised virus vector for RPE gene replacement in the retina. Safety is defined as an ATIMP related:

- Reduction in visual acuity by 15 ETDRS letters or more
- Severe unresponsive inflammation
- Infective endophthalmitis
- Ocular malignancy
- Grade III or above non-ocular SUSAR

Classification of severe unresponsive inflammation will be according to the SUN (standardisation of uveitis nomenclature) Working Group grading system (Am J Ophthalmol. 2005 Sep;140(3):50916.) i.e.

- anterior chamber cells 3+ (26-50 cells in a field size of 1mm x 1-mm slit-beam), or
- anterior chamber flare 3+ (marked, iris and lens details hazy) or
- vitreous haze 3+ (Ophthalmology 1985; 92:467-71)

that fail to improve by 2 steps (or to grade 0) during a 6 week period.

Protection of trial subjects:

Only participants who met the study entry criteria were enrolled in the study. All participants were free to withdraw from the study at any time for any reason. All participants were closely monitored throughout the study. Safety was evaluated based on adverse events (including dose-limiting events), ocular examination, retinal imaging, clinical laboratory assessments, vital sign measurements, and physical examinations.

Background therapy:

None

Evidence for comparator:

NA

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 March 2016 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | United States: 2   |
| Worldwide total number of subjects   | 15                 |
| EEA total number of subjects         | 0                  |

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Notes:

| <b>Subjects enrolled per age group</b>    |   |
|---|---|
| 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)                     | 5 |
| Adolescents (12-17 years)                 | 2 |
| Adults (18-64 years)                      | 8 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

15 patients were screened, 0 failed to meet eligibility criteria.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Dose Escalation Phase / Expansion Phase (overall period) |
| Is this the baseline period? | Yes  |
| Allocation method            | Not applicable   |
| Blinding used                | Not blinded  |

Blinding implementation details:

NA

### Arms

|                  |  |
|------------------|--|
| <b>Arm title</b> | Intervention - AAV2/5-OPTIRPE65 Gene Therapy |
|------------------|--|

Arm description:

All study participants were administered with a single dose of the gene therapy treatment in most severely affected eye at one of the following three doses:

- Low dose (1 x 10<sup>11</sup> vg/mL)
- Intermediate dose (3 x 10<sup>11</sup> vg/mL)
- High dose (1 x 10<sup>12</sup> vg/mL)

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | AAV2/5-OPTIRPE65                    |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Solution for solution for injection |
| Routes of administration               | Subretinal use                      |

Dosage and administration details:

Participants were administered a single dose of ATIMP in a total volume of no more than 1mL

|                                       |  |
|---------------------------------------|--|
| <b>Number of subjects in period 1</b> | Intervention - AAV2/5-OPTIRPE65 Gene Therapy |
| Started                               | 15   |
| Completed                             | 15   |

## Baseline characteristics

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Dose Escalation Phase / Expansion Phase |
|-----------------------|---|

Reporting group description: -

| Reporting group values                                     | Dose Escalation Phase / Expansion Phase | Total |  |
|--|---|-------|--|
| Number of subjects   | 15                                      | 15    |  |
| Age categorical  |   |       |  |
| All enrolled participants who were administered with ATIMP |   |       |  |
| 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)                   | 0                                       | 0     |  |
| Children (2-11 years)                                      | 5                                       | 5     |  |
| Adolescents (12-17 years)                                  | 2                                       | 2     |  |
| Adults (18-64 years)                                       | 8                                       | 8     |  |
| From 65-84 years   | 0                                       | 0     |  |
| 85 years and over  | 0                                       | 0     |  |
| Age continuous   |   |       |  |
| All enrolled participants who were administered with ATIMP |   |       |  |
| Units: years   |   |       |  |
| arithmetic mean  | 15.7                                    |       |  |
| standard deviation   | ± 5.79                                  | -     |  |
| Gender categorical   |   |       |  |
| All enrolled participants who were administered with ATIMP |   |       |  |
| Units: Subjects  |   |       |  |
| Female   | 9                                       | 9     |  |
| Male   | 6                                       | 6     |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Intervention - AAV2/5-OPTIRPE65 Gene Therapy |
| Reporting group description:<br>All study participants were administered with a single dose of the gene therapy treatment in most severely affected eye at one of the following three doses: <ul style="list-style-type: none"><li>• Low dose (1 x 10<sup>11</sup> vg/mL)</li><li>• Intermediate dose (3 x 10<sup>11</sup> vg/mL)</li><li>• High dose (1 x 10<sup>12</sup> vg/mL)</li></ul> |  |
| Subject analysis set title  | Safety Analysis Set                          |
| Subject analysis set type   | Safety analysis                              |
| Subject analysis set description:<br>All enrolled participants who were administered with ATIMP   |  |

### Primary: Safety of subretinal administration of AAV2/5-OPTIRPE65 – Number of Participants with a Safety Event.

|   |  |
|---|--|
| End point title   | Safety of subretinal administration of AAV2/5-OPTIRPE65 – Number of Participants with a Safety Event. <sup>[1]</sup> |
| End point description:<br>Safety was defined as an advanced therapy investigational medicinal product (ATIMP) related: <ul style="list-style-type: none"><li>• Reduction in visual acuity by 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more</li><li>• Severe unresponsive inflammation</li><li>• Infective endophthalmitis</li><li>• Ocular malignancy</li><li>• Grade III or above non-ocular suspected unexpected serious adverse reaction (SUSAR)</li></ul> |  |
| Descriptive in nature, no formal statistical testing.   |  |
| End point type  | Primary  |
| End point timeframe:<br>Occurring during the 9 weeks following ATIMP administration   |  |
| Notes:<br>[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.<br>Justification: Descriptive in nature, no formal statistical testing.   |  |

| End point values            | Intervention - AAV2/5-OPTIRPE65 Gene Therapy | Safety Analysis Set  |  |  |
|-----------------------------|--|----------------------|--|--|
| Subject group type          | Reporting group                              | Subject analysis set |  |  |
| Number of subjects analysed | 15   | 15                   |  |  |
| Units: Number of events     | 1  | 1                    |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Within 6 months of ATIMP administration

Adverse event reporting additional description:

ATIMP related eye disorders

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Safety Analysis Set |
|-----------------------|---------------------|

Reporting group description:

All enrolled participants who were administered ATIMP. Adverse events listed are eye disorders related to ATIMP.

| Serious adverse events                            | Safety Analysis Set |  |  |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events |                     |  |  |
| subjects affected / exposed                       | 3 / 15 (20.00%)     |  |  |
| number of deaths (all causes)                     | 0                   |  |  |
| number of deaths resulting from adverse events    | 0                   |  |  |
| Eye disorders                                     |                     |  |  |
| Uveitis   |                     |  |  |
| subjects affected / exposed                       | 3 / 15 (20.00%)     |  |  |
| occurrences causally related to treatment / all   | 3 / 3               |  |  |
| deaths causally related to treatment / all        | 0 / 0               |  |  |
| Visual acuity reduced                             |                     |  |  |
| subjects affected / exposed                       | 1 / 15 (6.67%)      |  |  |
| occurrences causally related to treatment / all   | 1 / 1               |  |  |
| deaths causally related to treatment / all        | 0 / 0               |  |  |

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

| Non-serious adverse events                            | Safety Analysis Set |  |  |
|---|---------------------|--|--|
| Total subjects affected by non-serious adverse events |                     |  |  |
| subjects affected / exposed                           | 10 / 15 (66.67%)    |  |  |
| Investigations  |                     |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 15 (6.67%)<br>1  |  |  |
| Nervous system disorders<br>Visual field defect<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1  |  |  |
| Eye disorders<br>Uveitis<br>subjects affected / exposed<br>occurrences (all)                        | 5 / 15 (33.33%)<br>6 |  |  |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 15 (20.00%)<br>3 |  |  |
| Anterior chamber inflammation<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 15 (6.67%)<br>1  |  |  |
| Hypotony of eye<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 15 (6.67%)<br>1  |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 15 (6.67%)<br>1  |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 28 January 2016  | Protocol Version 1.1. Clarified safety reporting procedures as requested by MHRA.  |
| 06 June 2016     | Protocol V2. Further clarification of safety reporting procedures as requested by the MHRA. Updated inclusion/exclusion criteria as requested by the US FDA. Enhanced description of the method of measuring the primary objective and outcome. Enhanced description of the dose limiting criteria. Minor modification to wording and language to correct typographical errors and ensure consistency throughout. Change in name of funder from Athena Vision Ltd. to MeiraGTx UK Ltd. |
| 02 August 2016   | Protocol V3. Visual acuity assessments at Day 1 and Day 3 post-treatment had been erroneously omitted from V2; these were replaced. UCL CCTU Clinical Project Manager was replaced and details updated.  |
| 10 February 2017 | Protocol V4. Reflected the change in Sponsor from UCL to MeiraGTx UK II Ltd. Minor modification to wording and language to correct typographical errors and ensure consistency throughout. Clarified the DLE and safety definitions. Clarified the primary objective and outcome measures. Described the outsourcing of data management, pharmacovigilance, and clinical monitoring to CROs.   |
| 12 April 2017    | Protocol V5. Extended the course of post-surgery prophylactic steroids from 4 weeks to 8 weeks. Consequently, the duration for considering DLEs was extended from 6 weeks to 9 weeks to cover the period of steroid administration and 1 additional week and other minor clarifications.   |
| 21 August 2017   | Protocol V6. Updated the prophylactic steroid regimen in children. Clarified safety reporting and safety dose for children.  |
| 23 February 2018 | Protocol V7. Clarified the allowance of data obtained from the natural history study to be used for screening and or baseline assessments (with consent from subjects), to avoid unnecessary testing of subjects. Clarified that more than 1 surgeon at a site may inject vector. Expanded the number of categories for ATIMP administration surgery from related or unrelated to; unrelated, unlikely, possibly, probably, or definitely.   |
| 11 June 2018     | Protocol V8. Added full-field stimulus testing as an assessment for children.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported