



## 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
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##### 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
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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
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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: 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: 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: 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: Occurring during the 9 weeks following ATIMP administration	
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: 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Safety Analysis Set
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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 subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders Visual field defect subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Eye disorders Uveitis subjects affected / exposed occurrences (all)	5 / 15 (33.33%) 6		
Visual acuity reduced subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Anterior chamber inflammation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Hypotony of eye subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Vision blurred subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 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