



## Clinical trial results:

**An open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV5-hRKp.RPGR) for gene therapy of adults and children with X-linked Retinitis Pigmentosa owing to defects in Retinitis Pigmentosa GTPase Regulator (RPGR)**

### Summary

EudraCT number	2016-003967-21
Trial protocol	GB Outside EU/EEA
Global end of trial date	18 November 2021

### Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

### Trial information

#### Trial identification

Sponsor protocol code	MGT009
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03252847
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	MeiraGTx UK II Ltd
Sponsor organisation address	92 Britannia Walk, London, United Kingdom, N1 7NQ
Public contact	Gwen Vanneste, MeiraGTx UK II Ltd, Gwen.Vanneste@meiragtx.com
Scientific contact	Robert Zeldin, MeiraGTx UK II Ltd, Robert.Zeldin@meiragtx.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002827-PIP01-20
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	18 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2021
Global end of trial reached?	Yes
Global end of trial date	18 November 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary research objective is to assess the safety of AAV5-hRKp.RPGR for RGPR-ORF15 gene replacement in the retina of patients with RPGR X-linked Retinitis Pigmentosa (XLRP). Safety is defined as the absence of an Advanced Therapy Investigational Medicinal Product (ATIMP)-related reduction in visual acuity by 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more, severe unresponsive inflammation, infective endophthalmitis, ocular malignancy and grade III or above non-ocular Suspected Unexpected Serious Adverse Reaction (SUSAR).

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), clinical laboratory assessments, vital sign measurements, and physical examinations for the 12-month duration of the study. In addition, participants in Study MGT009 were encouraged to join the long-term follow-up safety study MGT010 (up to 5 years after the intervention).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	45
EEA total number of subjects	0

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)	0
Children (2-11 years)	1
Adolescents (12-17 years)	2
Adults (18-64 years)	42
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from a total of 5 sites, 2 sites in the United Kingdom (UK) and 3 sites in the United States (US).

### Pre-assignment

Screening details:

n/a

### Period 1

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

Blinding implementation details:

Participants were enrolled in the dose escalation phase, the dose confirmation phase (paediatric participants), or the randomized expansion phase of this open-label study. Participants in the dose escalation phase and the dose confirmation phase were not randomized. Participants enrolled in the expansion phase were randomized to immediate treatment or deferred treatment. Treatment assignment was not blinded.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	immediate low dose group

Arm description:

Participants in this group received the low dose of AAV5-hRKp.RPGR in one eye in either the dose escalation phase or the expansion phase of the study

Arm type	Experimental
Investigational medicinal product name	AAV5-hRKp.RPGR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

AAV5-hRKp.RPGR solution is administered by intraocular injection into the subretinal space. In the dose escalation and dose confirmation phases, AAV5-hRKp.RPGR was administered to the worse-seeing eye as identified by the participant and investigator, taking into consideration ocular dominance and visual acuity. In the expansion phase of the study, AAV5-hRKp.RPGR was administered to 1 randomized eye.

<b>Arm title</b>	immediate intermediate dose group
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Arm description:

Participants in this group received the intermediate dose of AAV5-hRKp.RPGR in one eye in either the dose escalation phase, dose confirmation phase or expansion phase of the study

Arm type	Experimental
Investigational medicinal product name	AAV5-hRKp.RPGR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

AAV5-hRKp.RPGR solution is administered by intraocular injection into the subretinal space. In the dose escalation and dose confirmation phases, AAV5-hRKp.RPGR was administered to the worse-seeing eye as identified by the participant and investigator, taking into consideration ocular dominance and visual acuity. In the expansion phase of the study, AAV5-hRKp.RPGR was administered to 1

randomized eye.

<b>Arm title</b>	immediate high dose group
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Arm description:

Participants in this group received the high dose of AAV5-hRKp.RPGR in one eye in the dose escalation phase.

Arm type	Experimental
Investigational medicinal product name	AAV5-hRKp.RPGR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

AAV5-hRKp.RPGR solution is administered by intraocular injection into the subretinal space.

In the dose escalation and dose confirmation phases, AAV5-hRKp.RPGR was administered to the worse-seeing eye as identified by the participant and investigator, taking into consideration ocular dominance and visual acuity. In the expansion phase of the study, AAV5-hRKp.RPGR was administered to 1 randomized eye.

<b>Arm title</b>	deferred group (prior to treatment)
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Arm description:

Treatment of participants in this group was deferred for 6 months

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

Number of subjects in period 1	immediate low dose group	immediate intermediate dose group	immediate high dose group
Started	11	17	4
Completed	11	16	3
Not completed	0	1	1
Consent withdrawn by subject	-	-	1
patient decision	-	1	-

Number of subjects in period 1	deferred group (prior to treatment)
Started	13
Completed	13
Not completed	0
Consent withdrawn by subject	-
patient decision	-

## Baseline characteristics

### Reporting groups

Reporting group title	immediate low dose group
Reporting group description:	
Participants in this group received the low dose of AAV5-hRKp.RPGR in one eye in either the dose escalation phase or the expansion phase of the study	
Reporting group title	immediate intermediate dose group
Reporting group description:	
Participants in this group received the intermediate dose of AAV5-hRKp.RPGR in one eye in either the dose escalation phase, dose confirmation phase or expansion phase of the study	
Reporting group title	immediate high dose group
Reporting group description:	
Participants in this group received the high dose of AAV5-hRKp.RPGR in one eye in the dose escalation phase.	
Reporting group title	deferred group (prior to treatment)
Reporting group description:	
Treatment of participants in this group was deferred for 6 months	

Reporting group values	immediate low dose group	immediate intermediate dose group	immediate high dose group
Number of subjects	11	17	4
Age categorical			
Units: Subjects			
Children (2-11 years)	0	1	0
Adolescents (12-17 years)	0	2	0
Adults (18-64 years)	11	14	4
Age continuous			
Units: years			
median	27.0	27.0	20.5
full range (min-max)	18 to 60	11 to 47	18 to 24
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	11	17	4

Reporting group values	deferred group (prior to treatment)	Total	
Number of subjects	13	45	
Age categorical			
Units: Subjects			
Children (2-11 years)	0	1	
Adolescents (12-17 years)	0	2	
Adults (18-64 years)	13	42	
Age continuous			
Units: years			
median	28.0	-	
full range (min-max)	19 to 61	-	

Gender categorical Units: Subjects			
Female	0	0	
Male	13	45	

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### Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes all participants who enrolled and received treatment in the study (as treated).

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Reporting group values	Safety Analysis Set		
Number of subjects	45		
Age categorical Units: Subjects			
Children (2-11 years)	1		
Adolescents (12-17 years)	2		
Adults (18-64 years)	42		
Age continuous Units: years			
median	26.0		
full range (min-max)	11 to 61		
Gender categorical Units: Subjects			
Female	0		
Male	45		

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## End points

### End points reporting groups

Reporting group title	immediate low dose group
Reporting group description: Participants in this group received the low dose of AAV5-hRKp.RPGR in one eye in either the dose escalation phase or the expansion phase of the study	
Reporting group title	immediate intermediate dose group
Reporting group description: Participants in this group received the intermediate dose of AAV5-hRKp.RPGR in one eye in either the dose escalation phase, dose confirmation phase or expansion phase of the study	
Reporting group title	immediate high dose group
Reporting group description: Participants in this group received the high dose of AAV5-hRKp.RPGR in one eye in the dose escalation phase.	
Reporting group title	deferred group (prior to treatment)
Reporting group description: Treatment of participants in this group was deferred for 6 months	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: Includes all participants who enrolled and received treatment in the study (as treated).	

**Primary: The primary safety outcome was defined as absence of any of the below occurring during the 9 weeks following administration, at least possibly related to AAV5-hRKp.RPGR, not surgery alone**

End point title	The primary safety outcome was defined as absence of any of the below occurring during the 9 weeks following administration, at least possibly related to AAV5-hRKp.RPGR, not surgery alone <sup>[1]</sup>
End point description: The primary safety outcome was defined as absence of any of the below occurring during the 9 weeks following administration, at least possibly related to AAV5-hRKp.RPGR, not surgery alone: <ul style="list-style-type: none"><li>• Reduction in visual acuity by 15 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>	
End point type	Primary
End point timeframe: Within 9 weeks following administration of AAV5-hRKp.RPGR	
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 statistical analysis was performed on the primary endpoint. The analysis was descriptive.	

End point values	immediate low dose group	immediate intermediate dose group	immediate high dose group	deferred group (prior to treatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	0 <sup>[2]</sup>
Units: participants meeting criteria	0	0	0	



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Notes:

[2] - The primary endpoint was analyzed for participants in the dose escalation phase only.

<b>End point values</b>	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: participants meeting criteria	0			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Data from Immediate-treatment participants are included from signing of ICF until their 12-month visit. Data of deferred-treatment participants are included from signing of ICF until the time of surgery (i.e., control group).

Adverse event reporting additional description:

There were 3 SAEs (all non-fatal) reported during the study, 2 in the immediate treatment group (preferred terms retinal detachment and uveitis), and 1 in the deferred treatment group (preferred term intraocular pressure increased).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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### Reporting groups

Reporting group title	Total
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Reporting group description:

Data from Immediate-treatment participants are included from signing of ICF until their 12-month visit. Data of deferred-treatment participants are included from signing of ICF until the time of surgery.

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	1 / 45 (2.22%)		
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 %

<b>Non-serious adverse events</b>	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 45 (82.22%)		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	16 / 45 (35.56%)		
occurrences (all)	18		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Intraocular pressure decreased			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Conjunctival abrasion			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	9		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	23 / 45 (51.11%)		
occurrences (all)	23		
Anterior chamber cell			
subjects affected / exposed	16 / 45 (35.56%)		
occurrences (all)	16		
Visual acuity reduced			
subjects affected / exposed	16 / 45 (35.56%)		
occurrences (all)	19		
Eye inflammation			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	11		
Foreign body sensation in eyes			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	8		

Ocular discomfort subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 8		
Cystoid macular oedema subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 9		
Eye pain subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5		
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Posterior capsule opacification subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Retinal haemorrhage subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Uveitis subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Cataract subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Retinal cyst subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Vitreous floaters subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5		
Rash subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Infections and infestations			
Rhinitis subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 7		
Metabolism and nutrition disorders			
Increased appetite subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2017	To incorporate the flow chart for the dose escalation, dose of drugs used at the time of administration of AAV5-hRKp.RPGR and reconsenting the children as they progress through the age brackets.
12 April 2017	To extend the course of post-surgery prophylactic steroids from 4 weeks to 8 weeks. Consequently, the duration for considering dose-limiting events was extended from 6 weeks to 9 weeks to cover the period of steroid administration and one additional week and other minor clarifications.
25 May 2017	To add 2 additional exclusion criteria, and to refer to a barrier and spermicide form of contraception, rather than double barrier method and also to clarify that only males should have been included in the study.
13 November 2017	To update the medium and high dose, to reduce the gap between participant 1 and 2/3 in a cohort from 9 weeks to 4 weeks, to update the prophylactic post-administrative steroid regimen in children, and to clarify safety reporting and confirmatory safety dose for children.
27 February 2018	To clarify the allowance of data obtained from the natural history study be used for screening and or baseline assessments (with consent from participants) in order to avoid unnecessary testing of participants and to clarify that more than 1 surgeon at a site may inject vector.
11 February 2019	To include a randomized component to the expansion phase of the study, to include further QOL measurement tool, to reduce the follow-up from 18 to 12 months and to include an Interim Analysis at 3- and 6-months post-treatment for patients in the low/intermediate dose treatment arms of the randomized component of the study.
09 August 2019	To amend and clarify the inclusion and exclusion criteria for the study. To remove FST at all assessments and to remove ERG at screening to reduce the assessment burden on patients. To add Low Luminance Visual Acuity testing and include additional Patient-Reported Outcome measures, to add a Clinician-Reported Outcome measure and include Treatment Experience interviews. To correct minor errors in the Patient Visit Schedule.
22 June 2020	To include guidance on the management of patients during COVID 19 pandemic, to update wording on steroid risks and local steroid use and to correct minor errors.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported