# Phase 3 Randomized, Controlled Study of AAV5-hRKp.RPGR for the Treatment of Xlinked Retinitis Pigmentosa Associated with Variants in the RPGR gene

Published: 18-10-2021 Last updated: 13-06-2024

Primary:To assess the effect of bilateral treatment with AAV5-hRKp.RPGR on functional vision as measured by vision-guided mobility assessment.Secondary:To assess changes after treatment administration in retinal function, functional vision, visual...

Ethical review	Approved WMO
Status	Pending
Health condition type	Congenital eye disorders (excl glaucoma)
Study type	Interventional

# Summary

### ID

NL-OMON52296

**Source** ToetsingOnline

**Brief title** MGT-RPGR-021 gene therapy study in patients with XLRP

### Condition

• Congenital eye disorders (excl glaucoma)

Synonym genetic eye disease, XLRP

**Research involving** Human

### **Sponsors and support**

Primary sponsor: Janssen-Cilag Internation NV

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#### Source(s) of monetary or material Support: pharmaceutical industry

### Intervention

Keyword: AAV5-hRKp.RPGR, Phase III, XLRP

### **Outcome measures**

#### **Primary outcome**

Change from baseline to week 52 in binocular VMA

#### Secondary outcome

Retinal Function assessed by

- Changes from baseline in mean retinal sensitivity within the central 10

degrees excluding scotoma (MRS10) in static perimetry at Week 52

- Changes from baseline in mean retinal sensitivity of worse-seeing eye within

the central 10 degrees excluding scotoma in static perimetry (MRS10) at Week 52

- Pointwise response in full visual field at Week 52
- Pointwise response in worse-seeing eye in full visual field at Week 52
- Pointwise response in the central 30 degrees visual field at Week 52
- Pointwise response in worse-seeing eye in the central 30 degrees visual field

at Week 52

- Change from baseline in mean retinal sensitivity within the full visual field

excluding scotoma

Functional Vision assessed by

- Vision-guided mobility assessment response in the "worse-seeing eye" as

assessed by VMA at Week 52

- Change from baseline in the modified Low Luminance Questionnaire (mLLQ)

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Visual Function assessed by

- Change from baseline in low luminance visual acuity by Early Treatment

Diabetic Retinopathy Study (ETDRS) chart letter score in monocular assessment

at Week 52

- Change from baseline in best corrected visual acuity (BCVA) by ETDRS chart

letter score in monocular assessment at Week 52

- Change from baseline in low luminance visual acuity by ETDRS chart letter

score in worseseeing eye at Week 52

Adverse Events

Laboratory assessments

Please refer to the clinical trial protocol for the full list of secondary end

points.

# **Study description**

#### **Background summary**

Retinitis pigmentosa (RP) constitutes a group of inherited diseases of the retina characterized by a progressive reduction in vision, initially manifest as nyctalopia (night blindness) that usually becomes apparent in childhood or early adulthood and is progressive throughout the individual\*s lifetime (Tee 2016).

Currently, there is no approved treatment for XLRP, and the condition is serious and progressive. There is a real possibility that gene therapy could

offer a significant benefit in terms of markedly slowing or halting progressive retinal loss thereby preserving central vision and improving sight and quality of life (QoL). The approval of Voretigene Neparvovec (Luxturna, Spark Therapeutics) for biallelic RPE65 disease (Russell 2017) provides convincing proof of concept. This is reinforced by our own experience from the first gene therapy study for IRD (Bainbridge 2008) and preclinical data demonstrating improved outcome in animal models of RPGR-XLRP. Preliminary data from the ongoing Phase 1/2 Study MGT009 has also demonstrated significant improvement in both visual function (as determined by assessment of visual fields by static perimetry), and functional

vision (as determined by a visual mobility assessment in low illumination levels) (see Section 2.2, Background).

Taking into account the measures taken to minimize risk to participants of this study and the preliminary efficacy results of the MGT009 study, the potential risks identified in association with AAV5-hRKp.RPGR are justified by the anticipated benefits that may be afforded to participants with RPGR-XLRP

#### **Study objective**

Primary:

To assess the effect of bilateral treatment with AAV5-hRKp.RPGR on functional vision as measured by vision-guided mobility assessment.

Secondary:

To assess changes after treatment administration in retinal function, functional vision, visual function and to assess the safety and tolerability of bilateral subretinal delivery of AAV5-hRKp.RPGR

### Study design

This is a randomized, controlled, multicenter, interventional study of bilateral subretinal treatment with AAV5-hRKp.RPGR gene therapy in individuals with RPGR-XLRP.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to provide expert input on safety of the investigational product, surgical procedure, and related issues.

Participants will be male and female, ages 3 years and older meeting all eligibility criteria and with a confirmed genetic variant in RPGR. AAV5-hRKp.RPGR gene therapy will be administered by subretinal injection using a standardized surgical procedure; all participants will be offered bilateral treatment, with the second eye treated 7 to 21 days after the first. The study will be conducted in 3 phases:

1. Screening and Baseline Phase: The screening phase (up to 6 months) is the period during which the eligibility of potential participants is assessed and all baseline procedures/tests are performed prior to study treatment.

2. Core Phase: The core phase of the study is a 52-week period to assess immediate treatment compared with deferred treatment.

- Immediate treatment group: The 52-week period for the immediate treatment group begins on the day of treatment administration in the first eye (Day 1) through the completion of the Week 52 visit. All study visits starting from Week 4 will be dated from the day of the first treatment (Day 1, Visit 3) in order to ensure a consistent duration of follow-up.

- Deferred treatment group: The 52-week period for the deferred treatment group begins on the day of the final Baseline Visit (Day 1) through the completion of the Week 52 visit.

The primary efficacy and safety outcome assessments will be performed at the completion of the core phase of the study. The total duration of individual participation in this protocol will be up to 18 months.

After the IDMC makes a recommendation to continue the study, pediatric participants can be enrolled. The first pediatric participant randomized to immediate treatment will be gated similar to the adult safety Cohort 1 adult participants. This pediatric participant will complete the Week 10 safety assessments, then the IDMC will be convened to review the relevant pediatric safety data prior to further enrolment of pediatric aged study participants. Additional pediatric participants will be enrolled only after the IDMC completes their review of safety data and makes a recommendation to the sponsor to continue to enroll further pediatric participants.

3. Long-term Follow-up: Following completion of this study, all participants will be enrolled in a follow-up study, MGT-RPGR-022; participants must consent to participate in the follow-up study in order to participate in Study MGT-RPGR-021.Participants who were randomly assigned to receive immediate treatment in Study MGT- RPGR-021 will continue directly into the long-term follow-up phase of Study MGT- RPGR-022 for an additional 48 months of follow-up with no additional treatment. Participants who were randomly assigned to deferred treatment in Study MGT-RPGR-021 will be offered bilateral treatment in MGT-RPGR-022 with 52 weeks of assessment identical to the MGT- RPGR-021 study, and then transition to the long-term follow-up phase of the MGT- RPGR- 022 study.

Participants will be enrolled and randomized 1:1:1 to immediate bilateral treatment with the RPGR2e11 dose (in up to 800  $\mu$ L in each eye), immediate bilateral treatment with the RPGR4e11 dose (330 $\mu$ L to 800  $\mu$ L in each eye), or

deferred bilateral treatment (in Study MGT-RPGR-022) given approximately 1 year after completion of baseline examinations. Participants randomized to deferred treatment will be re- randomized at Week 52 in a 1:1 ratio to receive the RPGR2e11 dose or RPGR4e11 dose for their subsequent treatment in Study MGT-RPGR-022.

All participants will receive bilateral treatment, with surgical delivery to the 2 eyes performed 7 to 21 days apart. The first eye treated will be the worse-seeing eye as determined by visual acuity, and the second eye will receive identical treatment unless there is a contraindication. If visual acuity is identical in both eyes, static perimetry MRS will be used to determine the worse-seeing eye. If both visual acuity and MRS are equal in both eyes, the right eye will be the first eye receiving treatment.

#### Intervention

AAV5-hRKp.RPGR gene therapy is injected in the subretinal space of the treatment eye in the operating room by a retinal surgeon who is trained and qualified to deliver the investigational product. Delivery of vector liquid to the subretinal space will be performed following standard surgical vitrectomy. This will involve a 3-port pars plana vitrectomy followed by injection of vector liquid using a fine cannula through a retinotomy into the subretinal space, resulting in a transient retinal detachment. One or more retinotomies may be used. A pre-bleb (with, eg, balanced salt solution) is not allowed.

Eligible participants will be randomly assigned to immediate bilateral treatment with the RPGR2e11 dose ( $300\mu$ L to  $800\mu$ L in each eye), immediate bilateral treatment the RPGR4e11 dose ( $300\mu$ L to  $800\mu$ L in each eye), or deferred bilateral treatment given approximately 1 year after completion of all baseline examinations (in Study MGTR-PGR-022). The total volume of injection should not exceed 0.8 mL. Previous gene therapy clinical studies have shown that the bleb of subretinal vector liquid is expected to resolve spontaneously over the course of approximately the first 24 to 48 hours postoperatively as the fluid is resorbed by the underlying retinal pigment epithelium.

All participants will receive bilateral treatment, with surgical delivery to the 2 eyes performed 7 to 21 days apart. The first eye treated will be the worse-seeing eye as determined by visual acuity, and the second eye will receive identical treatment. In the event of a significant ocular adverse event in the first eye, or any other intercurrent issue that persists through Day 21 post first surgery, the investigator will consult with the sponsor\*s Medical Monitor about the risks, benefits, and timing of treatment to the second eye. If visual acuity is identical in both eyes, static perimetry MRS will be used to determine the worse-seeing eye. If both visual acuity and MRS are equal in both eyes, the right eye will be the first eye receiving treatment.

The first 3 participants randomly assigned to immediate therapy, regardless of

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dose assignment, will be gated to allow assessment of safety of the second eye treatment. These first 3 participants will be males aged 18 years or older. These participants will be followed through the Week 10 visit and safety will be reviewed with the SAC before additional participants are randomized.

To minimize the occurrence and severity of immune response to the investigational product, all participants will receive a defined regimen of local and systemic immune suppression initiated prior to and continued following the completion of surgery.

### Study burden and risks

For full details see table 1.3 in the protocol (schedule of activities) table 1 and table 2 on page 24-30

The patient participation in this study will last approximately 18 months. During this time the patient will visit the hospital approximately 16 times in group 1 (immediate treatment) and 6 times in group 2 ( deferred treatment until 022 study). The visits will take about 2-9 hours.

During these visits the following tests and procedures will take place:

- Physical exam, vital signs, demographic and medical history
- Questionnaires
- Blood and urine tests
- Pregnancy tests in women of childbearing potential
- tears sample and saliva samples
- several eye tests, and images of the eye
- visual mobility assessments
- patients will take part in interviews

- Patients in group 1 will receive the study drug through retinal injection via Surgical vitrectomy. The second eye will be treated 7-21 days after the first eye

- Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study and for 40 weeks (0 months) following the last does of the

the entire study and for 40 weeks (9 months) following the last dose of the study drug.

- Male patients: due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and continuing for at least 40 weeks (9 months) following the last dose of study drug

Possible side effects that are already known are described in the IB and patient information letter.

# Contacts

Public Janssen-Cilag Internation NV

Turnhoutseweg 30 Beerse 2340 BE **Scientific** Janssen-Cilag Internation NV

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# **Trial sites**

### **Listed location countries**

Netherlands

# **Eligibility criteria**

#### Age

Adolescents (12-15 years) Adolescents (16-17 years) Adults (18-64 years) Children (2-11 years)

### **Inclusion criteria**

 Male or female.
3 years of age or older.
Has X-linked retinitis pigmentosa (generalized rod-cone dystrophy) confirmed by a retinal specialist AND has a predicted disease-causing sequence variant in RPGR confirmed by a sponsor-approved laboratory.

Please refer to the protocol for additional inclusion criteria

### **Exclusion criteria**

1.Has had ocular surgery within 3 months prior to screening or is anticipated to require ocular surgery within 6 months after the study intervention administration.

2.Any investigational ocular treatment or any other ocular treatment that could confound the interpretation of the efficacy results or affect participant compliance with the visit schedule.

3.Has undergone prior retinal surgery involving the macula, macular laser photocoagulation, external-beam radiation therapy, transpupillary thermotherapy, glaucoma filtration surgery or corneal surgery (except cataract surgery or YAG capsulotomy).

4. History of an ocular implant, with the exception of an intraocular lens.

'Please refer to the protocol for additional exclusion criteria'

# **Study design**

### Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

### Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-07-2022
Enrollment:	3
Туре:	Anticipated

# Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Botaretigene Sparoparvovec
Generic name:	AAV5-hRKp.RPGR

# **Ethics review**

Approved WMO	
Date:	18-10-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	14-03-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	27-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	11-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	09-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	09-12-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	21-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	26-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	20-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	03-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	27.11.2022
Date:	27-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	22-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	23-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	05-06-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

# **Study registrations**

## Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

Register	ID
Other	04671433
EudraCT	EUCTR2020-002873-88-NL
ССМО	NL75521.000.21