A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial Of Retinal Gene Therapy For Choroideremia Using An Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)

Published: 07-04-2016
Last updated: 17-04-2024

The objective of the study is to evaluate the efficacy and safety of a single sub-retinal injection of AAV2-REP1 in subjects with choroideremia (CHM).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Retina, choroid and vitreous haemorrhages and vascular disorders
Study type	Interventional

Summary

ID

NL-OMON47482

Source
ToetsingOnline

Brief title
STAR study

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
choroideremia, retinal degeneration

Research involving
Human

Sponsors and support

Primary sponsor: NightstaRx Ltd.
Source(s) of monetary or material Support: Sponsor of the study: NightstaRx a member of the Biogen group of companies

Intervention

Keyword: adeno-associated viral vector (AAV2), Choroideremia, retinal gene therapy, timrepigene emparvovec

Outcome measures

Primary outcome

Primary Endpoint: The primary efficacy endpoint is the proportion of subjects

with a *15-letter improvement from Baseline in best corrected visual acuity

(BCVA) at Month 12 as measured by the Early Treatment of Diabetic Retinopathy

Study (ETDRS) chart.

Secondary outcome

Key Secondary Efficacy Endpoints:

There are 3 key secondary efficacy endpoints:

1. Change from Baseline in BCVA at Month 12 measured by the ETDRS chart

2. Proportion of subjects with a *10-letter improvement from Baseline in BCVA

at Month 12 measured by the ETDRS chart

3. Proportion of subjects with no decrease from Baseline in BCVA or a decrease

from Baseline in BCVA of <5 ETDRS letters at Month 12 in BCVA measured by the

ETDRS chart

Other Secondary Endpoints:

* Change from Baseline in BCVA at Months 4 and 8

* Change from Baseline in total area of preserved autofluorescence (AF) at Month 12

* Change from Baseline in the area of preserved ellipsoid zone (spectral domain optical coherence tomography [SD-OCT]) at Month 12

* Change from Baseline in microperimetry at Month 12

* Change from Baseline in contrast sensitivity score at Month 12

* Change from Baseline in colour vision at Month 12

* Change from Baseline in reading speed test at Month 12

* Change from Baseline in the 25-item Visual Function Questionnaire (VFQ-25) at Month 12

Exploratory Efficacy Endpoint:

* Evaluation of other anatomical and functional outcome measures

Safety Endpoint:

* Evaluation of safety assessments, including adverse events (AEs), clinical laboratory assessments, vital signs

Study description

Background summary

CHM is currently defined as an incurable genetic orphan disease that causes blindness. The disease is caused by a defect in a certain gene located on the X-chromosome, and this is why the disease affects men and women differently. In CHM, this faulty gene results in a progressive degeneration of the retina

(the light sensitive part of the eye responsible for vision, which is like a camera film that lines the back of the eye). Sight loss in CHM begins with *night blindness* (i.e. loss of night vision) in adolescence, followed by a gradual loss of peripheral vision which results in progressively worsening *tunnel vision*. Ultimately, central vision is lost by the fourth or fifth decade.
There are currently no effective treatments available for CHM. This clinical trial will investigate whether a gene therapy, (a technique that involves putting normal copies of the faulty gene back into the cells of the retina) may help the cells in the retina affected by this disease, to function normally.
The gene therapy consists of a virus which has been disabled so that it cannot cause infection. This virus has been specially altered to carry the normal genes into the cells in the retina. The altered virus is delivered to the retina during an operation where it will produce multiple copies of the normal gene.

Study objective

The objective of the study is to evaluate the efficacy and safety of a single sub-retinal injection of AAV2-REP1 in subjects with choroideremia (CHM).

Study design

Study Design: This is an outcomes-assessor-masked, prospective, randomised, parallel-controlled group, multi-centre, global, interventional study. The study consists of 8 visits with a 12-month evaluation period. During the Screening/Baseline period, each subject will be assessed for eligibility. For eligible subjects, a study eye will be assigned, and the subjects will be randomised in a 2:1:2 ratio to receive either AAV2-REP1 high dose (1.0×10^11 genome particles [gp]), AAV2-REP1 low dose (1.0×10^10 gp) or to enter the untreated Control group.
On the Injection Day Visit (Visit 2, Day 0), subjects in the AAV2-REP1 high- and low-dose treatment arms will undergo vitrectomy and receive a sub-retinal injection of the assigned treatment dose of AAV2-REP1 in their study eye; these subjects will then return to the surgical site for 2 post-operative follow up visits on Day 1 (Visit 3) and, possibly for Day 7 (Visit 4; Day 7 can occur at either the surgical site or the home site depending on the clinical status of the subject). Subjects in the Control group will not undergo surgery, receive any study drug in their study eye (i.e., Control-study eye) or attend the 2 on-site post-operative visits. Instead, a telephone contact from the site will occur for the Control group on Day 0 (Visit 2), Day 1 (Visit 3) and Day 7 (± 3 days; Visit 4).
Day 0 (Visit 2) will be defined as the projected surgical day, whether the subject is randomised to treated or control groups.
All subjects will be followed for 12 months from Visit 2 (Day 0).
Study data will be collected for both eyes of each subject. Since AAV2-REP1

treatment requires an invasive surgical procedure under general anaesthesia, the sponsor, investigator and the subject will be unmasked to the study procedure (i.e., vitrectomy and sub-retinal injection), however within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^11 gp or 1.0×10^10 gp). To further minimise the potential bias of the treated and untreated eye evaluations, all subjective ophthalmic assessments from the Screening/Baseline Period (Visit 1) and from Month 1 (Visit 5) onwards (including the Month 12 Primary Endpoint evaluation) will be conducted by a masked assessor.
Subjects will be assessed for efficacy and safety throughout the study as indicated in the Schedule of Study Procedures. Subjects who develop cataracts may undergo cataract surgery if deemed clinically necessary; if surgery is performed, it should be carried out at least 4 weeks before the Month 12 Visit/End of Study (EOS) Visit.

Intervention

Test product, dosage, and mode of administration:
All subjects receiving active treatment will undergo vitrectomy and receive a 0.1 mL sub-retinal injection of study drug containing 1 × 10e 11 AAV2-REP1 (high dose) or 1 x 10e 10 AAV2-REP1 (low dose) genome particles.

Study burden and risks

A total of 8 visits is anticipated in one year. Visits may take up to half a day or more depending on the assessments that are done. The subjects will be hospitilised for one night after the surgery.

The subject randomized in the AAV2-REP1 group should take oral corticosteroid medication starting 2 days prior to surgery and 19 days after (a total of 21 days).

The subject will get surgery in the UK and will stay overnight before and after the surgery (one-two nights). A travel agency will organize the travel and stay for the subject and a accompanying person. If needed a translator can be arranged.

The subject will be asked to complete the VFQ- 25 questionnaire (4- times). Most of the procedures are part of the routine care of the patient with their treating physician. During the study BCVA, full ophthalmic examination (IOP, lens opacities, split lamp, dilated ophthalmoscopy, SD-OCT, microperimetry, contrast sensitivity, colour vision test, 7 field colour fundus photos and reading speed test performed.

Possible risks and discomforts associated with study procedures:
Risk Associated with the Surgery (Vitrectomy and Subretinal Injection):

All surgical procedures carry a risk of side effects. Your cornea (transparent front part of the eye) could be scratched during the surgery. Scratches on the cornea usually get better without treatment but may require patching or a bandage contact lens. Some potential complications of the new intervention include vision problems that may be caused by bleeding into the eye, tears/holes or detachment of the retina: vitreous bleeding, low and elevated intraocular pressure, choroidal detachment, swelling of the central part of the retina (macular oedema), thinning of the retina and infection. One occurrence of retinal artery occlusion (a blockage of one of the blood vessels supplying the retina) has been observed so far in a subject with advanced stage choroideremia. A potential long-term complication of the surgical procedure is formation or worsening of cataracts (lens clouding). Symptoms experienced by patients with these complications include blurred vision with or without decreased visual acuity, wavy or distorted vision (metamorphopsia), flashes of light (photopsias), floaters, pain, tearing, photophobia, glare, and double vision. Vitrectomy itself is often associated with transient visual impairment. These complications can be treated effectively by medications or further surgery but rare instances result in a permanent vision loss, including complete loss of vision.
The surgery is performed under general anaesthesia, there can arise common and less serious side effects from it, for example, nausea or vomiting, shivering, temporary throat pain and hoarse voice. More pronounced, but also more seldom side effects include sensitivity to the medication used as an anesthetic.
Teeth, vocal cords and soft parts in the mouth can be injured during the use of instruments in the airways. Stomach contents can, in very rare cases enter the lungs and cause lung inflammation. These and other side effects of anaesthesia will be explained further by the anaesthesiologist.

Risks Associated with AAV2-REP1:
The virus carrying the CHM gene is developed from a virus known as adeno-associated virus (AAV) that does not cause any known diseases in humans, and which has also been disabled such that it is not expected to cause illness. There is a possibility however that the virus may cause some inflammation inside the eye. We intend to minimize any risk of inflammation by asking the subject to take oral corticosteroid tablets for 2 days prior to the operation and for a total of 21 days. The possible risks from taking the corticosteroid medicine is outlined below.

One possible serious side effect, seen in about 5% of patients treated with AAV2-REP1, was visual acuity reduced (inability to see clearly/read eye chart).

There is a theoretical possibility that the new gene might interfere with the activity of other genes, posing a potential risk of tumor formation. However, this effect has not been observed in other trials in subjects treated using this virus. Routine monitoring procedures are expected to identify this remote possibility at an early stage to enable prompt and effective treatment.
Tiny amounts of the virus injected may spread along the optic nerve towards the

brain. The intervention has been designed to limit the effect of the new gene to the retina and any risk of damage to the brain is very small.
Gene therapy can in theory affect the next generation. It is possible that the gene could be transmitted via semen, however, the risk of the new gene will be transferred from this study to future children is considered minimal, as only small amounts of virus are introduced into the eye. Nevertheless, all participants will be asked to use acceptable prevention in the form of a barrier method, or abstain from sexual intercourse for the first 3 months following treatment in order to reduce the potential risk of passing the gene therapy product on to a partner or unborn child.
Even if gene therapy in the eye is successful, it will not prevent the subjects daughters from being bearers of the disease (fathers cannot give the disease further to their sons), and the subjects grandchildren can still be affected by CHM.

Risks of Corticosteroids:
The use of corticosteroids for prevention or treatment of inflammation can cause side effects, including raised blood pressure and blood sugar, stomach ulcers, trouble sleeping and behavioral change like mood swings, irritability, and depression. These are generally reversible once medication is stopped; however, the subject will be monitored for these during the surgical period. There is also a chance that with the use of corticosteroids can suppress the natural production of hormones made by the adrenal gland. This can cause severe fatigue, loss of appetite, weight loss, nausea, or muscle weakness.

Risks related to examinations
During ophthalmic examination, SD-OCT, 7-field colour fundus photography, fundus autofluorescence, fluorescein and indocyanine angiography the subjects pupils will be dilated using eye drops which will keep the pupils dilated for 4 to 6 hours. This may result in glare in daylight.
In rare cases, the use of numbing eye drops or dilating drops may cause redness, discomfort or allergic reactions. If the subject has high blood pressure, an irregular heartbeat or glaucoma, these conditions may get worse when using the eye drops, however this can be managed. Blood will be drawn from your arm by using a needle for the immunogenicity (your body*s immune response) sampling. Risks associated with drawing blood from your arm may include pain and/or bruising, infection, excess bleeding, clotting or fainting. The subject should also not donate blood during the 24 month period after the study.
In the case that air is put into the eye during the surgery, because the surgeon considered that it is necessary, the subject should avoid air travel, travelling to high elevations or scuba diving until the air bubble has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. The disappearance of the air bubble should be verified through very careful ophthalmic examination by the study doctor. The doctor will inform the subject

if this restriction applies to them.

The gene therapy (surgery) will take place in Oxford in UK or in Tübingen, Germany. The subject must travel to UK or Germany 1-2 days before the surgery and stay there for 1-2 days after the surgery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Are willing and able to give informed consent for participation in the study
* Are male and *18 years of age
* Have a genetically-confirmed diagnosis of CHM
* Have active disease clinically visible within the macular region in the study eye

* Have reduced visual acuity in the study eye.

Exclusion criteria

1. Have a history of amblyopia in the eligible eye
2. Are unwilling to use barrier contraception methods, or abstain from sexual intercourse, for a period of 3 months, if treated with AAV2-REP1
3. Have had previous intraocular surgery performed in the study eye within 3 months of Visit 1
4. Have any significant ocular or non-ocular disease/disorder which, in the opinion of the investigator, may either put the subjects at risk because of participation in the study, or may influence the results of the study, or the subject*s ability to participate in the study. This includes but is not limited to, a subject:
a. with a contraindication to oral corticosteroid (e.g. prednisolone/prednisone)
b. with a clinically significant cataract
c. who, in the clinical opinion of the Investigator, is not an appropriate candidate for sub-retinal surgery
5. Have participated in another research study involving an investigational product in the past 12 weeks or received a gene/cell-based therapy at any time previously.

Study design

Design

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

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-12-2018
Enrollment:	5

Type:	Actual

Ethics review

Approved WMO Date:	07-04-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-10-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-12-2017
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-10-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	05-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-04-2020
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
EudraCT	EUCTR2015-003958-41-NL
ClinicalTrials.gov	NCT03496012
CCMO	NL55771.000.16

Study results

Results posted: 10-12-2021

First publication
24-11-2021