EXPLORE: a phase 2, outcomes assessor-masked, multicentre, randomised study to evaluate the safety and efficacy of two doses of GT005 administered as a single subretinal injection in subjects with geographic atrophy secondary to age-related macular degeneration

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The overall objectives of the study are to evaluate the safety and efficacy (anatomical and functional visual outcomes) of two doses of GT005 in genetically defined subjects with GA due to AMD.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vision disorders
Study type	Interventional

Summary

ID

NL-OMON52776

Source
ToetsingOnline

Brief title
EXPLORE GT005-02

Condition

- Vision disorders

Synonym
Age-Related Macular Degeneration, Geographic Atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Gyroscope Therapeutics
Source(s) of monetary or material Support: Gyroscope Therapeutics Limited

Intervention

Keyword: Age-related Macular Degeneration (AMD), Gentherapy, Geographic Atrophy (GA)

Outcome measures

Primary outcome

Primary endpoint:

• The change in GA area from baseline to Week 48 measured by fundus

autofluorescence (FAF)

Secondary outcome

Secondary endpoints:

• The change from baseline to Week 72 and Week 96 in GA areas as measured

by fundus Autofluorescence (FAF)

• Frequency of Treatment Emergent Adverse Events (AEs)

• Change on ophthalmic examination.

• Change in other parameters of safety, including imaging modalities, Best

Corrected Visual Acuity (BCVA), vital signs, and laboratory assessments

• Change in retinal microstructures on optical coherence tomography (OCT)

• Change in presence of area of nascent GA on OCT

• Change in GA morphology on multimodal imaging

• Macular Sensitivity as assessed by Mesopic Microperimetry

• Change in BCVA Score via the early treatment for diabetic retinopathy (ETDRS)

chart

• Change in Low Luminance Difference (LLD) via the ETDRS chart

• Change in reading performance as assessed by Minnesota Low-Vision Reading Test (MNRead) Chart

• Change in Functional Reading Independence (FRI Index)

• Change in quality of life measured on the Visual Functioning Questionnaire-25 (VFQ-25)

Exploratory endpoints:

• Change in local and systemic levels of proteins including complement proteins and protein biomarkers associated with AMD

• Antibody titre to AAV2 and CFI, and T-cell response to AAV2 in GT005 treated subjects

Study description

Background summary

Dry AMD is a disease of the retina that results in loss of vision in the macula (center of the eye). When Dry AMD progresses, this can lead to a condition called Geographic Atrophy (GA) causing further loss of vision due to degeneration of the cells in the retina. Eventually, this may lead to blurred or loss of bision that affects one or both eyes.

There is currently no treatment available for Dry AMD.

A family history of Dry AMD increases the risk of developing the disease, which suggests there is a genetic link. It has also been shown that over-activation of a part of the immune system called the complement system further contributes to the disease.

A recent study has shown that subjects with a known family history risk who

have an over-active complement system are at an even higher risk of developing severe Dry AMD disease than subjects that do not have these two risk factors.

AAV2 vector-based CFI gene transfer (GT005) is expected to provide a sustained expression of human CFI in AMD patients* eyes, which would result in down-regulation of the alternative complement pathway.

Study objective

The overall objectives of the study are to evaluate the safety and efficacy (anatomical and functional visual outcomes) of two doses of GT005 in genetically defined subjects with GA due to AMD.

Study design

This is a Phase 2, outcomes assessor-masked, multicentre, randomised , controlled study to evaluate the safety and efficacy of two doses of GT005 administered as a single subretinal injection in subjects with GA secondary to AMD. Approximately 75 subjects are planned to be randomised to GT005 or the untreated control group.

Intervention

The study will test two doses of GT005; low dose (2E10 vg) and high dose (2E11 vg). These doses are selected to optimise the ability to demonstrate a therapeutic effect and identify minimal effective dose.

Subjects allocated to treatment are injected with GT005 in a three-step procedure. First a pars plana vitrectomy is performed and then the retina is partially detached through a cannula using balanced salt solution in order to form a bleb. Once the bleb is formed, a fixed volume (100 µL) of the allocated dose of GT005 is injected into the subretinal space that has been created.

Study burden and risks

Potential Benefit:
AMD is a progressive degenerative disease and is the most common cause of blindness among the elderly in the western world. Supplementing AMD subjects with human CFI (a down regulator of the complement system) has the potential to dampen an over-activated complement system associated with AMD and slow down disease progression. Using AAV2 vector based CFI gene transfer (GT005) is a way to ensure sustained expression of human CFI in subjects* eyes with one single injection. The true impact of GT005 can only be hypothesised as participants may not receive any clinical benefit. Given the degenerative nature of AMD, it is not expected to see any gain in visual acuity as once RPE and photoreceptors have degenerated, the function is definitively lost in the atrophic area. The

potential benefit would be to slow down macular atrophy extension and ultimately prevent future visual loss.

Risk/Benefit:
GT005 is currently being evaluated in an ongoing Phase 1/2 clinical study and therefore the potential risks are based on clinical data from an ongoing dose escalation safety study, preclinical data, and available scientific knowledge of AAV2 vectors carrying different transgenes for the treatment of various retinal conditions without significant AEs related to these Drug Products.

The main product-related risks are the generation of cellular and/or humoral immune responses to the AAV capsid. ATA immune responses seen in toxicology studies are considered to be species-specific and are therefore not expected in subjects with lifelong CFI exposure.

The surgical technique for the subretinal delivery of gene therapy builds upon established subretinal procedures such as subretinal tissue plasminogen activator injection and has been further developed and successfully used for the Choroidemia gene therapy clinical studies.

The risk to subjects exposed to GT005 is therefore considered to be low and upon careful evaluation of the potential benefits afforded by such a treatment, the risk/benefit ratio of GT005 in the study population is favourable.

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

1. Able and willing to give written informed consent
2. Age >=55 years
3. Have a clinical diagnosis of GA secondary to AMD in the study eye, as determined by the Investigator, and a diagnosis of AMD in the contralateral eye (except if the subject is monocular)
4. Have GA lesion(s) total size between or equal to 1.25mm2 to 17.5mm2 in the study eye
5. The GA lesion in the study eye must reside completely within the FAF image
6. Up to 25% of the enrolled study population are permitted to have CNV in the fellow eye, defined as either:
a. Non-exudative/sub-clinical fellow eye CNV identified at Screening, or
b. Known history of fellow eye CNV with either >=2 years since diagnosis or with no active treatment required in 6 months prior to Screening
7. Have a BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent) or better, using ETDRS charts, in the study eye
8. Subjects carrying a CFI rare variant genotype (minor allele frequency of <= 1%) previously associated with low serum CFI or subjects carrying an unreported CFI rare variant genotype that have tested to have a low serum CFI
9. Able to attend all study visits and complete the study procedures
10. Women of child-bearing potential must have a negative pregnancy test within 2 weeks prior to randomisation. A pregnancy test is not required for postmenopausal women (defined as being at least 12 consecutive months without menses) or those surgically sterilised (those having a bilateral tubal ligation/bilateral salpingectomy, bilateral tubal occlusive procedure, hysterectomy, or bilateral oophorectomy)

Exclusion criteria

1. Have a history, or evidence, of CNV in study eye

2. Presence of moderate/severe or worse non-proliferative diabetic retinopathy in the study eye
3. Have history of vitrectomy, sub-macular surgery, or macular photocoagulation in the study eye
4. History of intraocular surgery in the study eye within 12 weeks prior to Screening (Visit 1). Yttrium aluminium garnet capsulotomy is permitted if performed >10 weeks prior to Visit 1.
5. Have clinically significant cataract that may require surgery during the study period in the study eye
6. Presence of moderate to severe glaucomatous optic neuropathy in the study eye, uncontrolled intraocular pressure (IOP), despite the use of more than two topical agents, a history of glaucoma-filtering or valve surgery
7. Axial myopia of greater than -8 dioptres in the study eye
8. Have any other significant ocular or non-ocular medical or psychiatric condition which, in the opinion of the Investigator, may either put the subject at risk or may influence the results of the study
9. Have a contraindication to the specified protocol corticosteroid regimen
10. Have received any investigational product for the treatment of GA within the past 6 months, or 5 half-lives (whichever is longer) other than nutritional supplements such as the age-related eye disease study (AREDS) formula
11. Have received a gene or cell therapy at any time
12. Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant
13. Active malignancy within the past 12 months, except for: appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a stable prostate-specific antigen (PSA) >=12 months

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-01-2020
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GT005
Generic name:	a recombinant, non-replicating adenoassociated viral vector serotype 2 (AAV2) expressing human Compl

Ethics review

Approved WMO Date:	14-01-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-06-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	05-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2023
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	EUCTR2019-003421-22-NL
CCMO	NL71665.000.19