A Phase 2, Randomized Placebo-Controlled, Double-Masked Study to Assess Safety and Efficacy of Multiple doses of IONIS-FB-LRX, an Antisense Inhibitor of Complement Factor B, in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration (AMD)

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To evaluate the effect of ISIS 696844 on the rate of change of the area of GA secondary to AMD measured by fundus autofluorescence (FAF)

Ethical review	Approved WMO
Status	Will not start
Health condition type	Congenital eye disorders (excl glaucoma)
Study type	Interventional

Summary

ID

NL-OMON51185

Source
ToetsingOnline

Brief title
ISIS 696844-CS5

Condition

- Congenital eye disorders (excl glaucoma)

Synonym

Geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

Research involving
Human

Sponsors and support

Primary sponsor: Ionis Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Geographic Atrophy Secondary to Age-Related Macular Degeneration (AMD), ISIS 696844, Phase 2

Outcome measures

Primary outcome

The primary efficacy endpoint is the absolute change in the GA area at Week 49

compared to baseline, as measured by FAF in study eye.

Secondary outcome

The secondary efficacy endpoints include:

• Percent change in levels of plasma FB from Baseline

The secondary efficacy endpoints include:

• Percent change in levels of serum AH50 activity from Baseline

• Absolute change in LLVA score from Baseline at Week 49

Study description

Background summary

ISIS 696844 is in development as a potential treatment for geographic atrophy (GA) associated with age-related macular degeneration (AMD).
AMD is a progressive disease of the macula and is the leading cause of central vision impairment in persons over the age of 50 years in developed countries.

The disease is characterized by progressive loss of central vision, the distortion of images and straight lines, and the presence of blurry and dark areas in the central vision. The underlying pathophysiology drivers for AMD are complex and the symptoms manifest in multiple related, but distinct forms. In the early and intermediate stages of AMD, the disease is characterized by the deposition of drusen, protein and lipid rich extracellular deposits between the retinal pigment epithelial (RPE) cells and Bruch*s membrane. As part of the natural course of the disease, there is a development of atrophic areas, which enlarge continuously and correspond with an absolute scotoma/GA. This area of GA associated with late stage AMD, corresponds with retinal regions of impaired visual function resulting from the atrophy of photoreceptor and RPE cells.

The complement system, an important component of innate immunity, is the most widely accepted pathogenic pathway of the immune system implicated in AMD. Genetic evidence from genome wide association studies (GWAS) and rare variant analyses suggest the complement alternative pathway (AP) is overactive in AMD. Specific polymorphisms of complement factor H (CFH), which is the negative regulator of the AP, confer increased risk for AMD. In contrast, specific polymorphisms of FB, the positive regulator, confer protection against AMD. FB is synthesized primarily by the liver and at very low levels in several extrahepatic sites. Ocular FB protein is located predominately in the choroidal capillaries and Bruch*s membrane region and not evident in the neural retina. Hence, choroidal FB appears to be derived from systemic sources. Plasma concentrations of AP activation products were found to be significantly elevated in AMD patients compared to controls. This suggests an ongoing systemic activation of the alternative complement pathway in AMD pathogenesis and adds to the increasing evidence that AMD is a systemic disease with local ocular manifestation in the ageing macula.
The therapeutic objective is to delay the progression of GA associated with AMD using systemic administration of an antisense oligonucleotide (ASO) targeting FB messenger ribonucleic acid (mRNA) in the liver, which will subsequently reduce the levels of plasma and ocular FB. The reduction of plasma FB, an essential component of the AP, will diminish the hyper-activation of the AP that is contributing to AMD pathology.

Study objective

To evaluate the effect of ISIS 696844 on the rate of change of the area of GA secondary to AMD measured by fundus autofluorescence (FAF)

Study design

Randomized, placebo-controlled, double-masked study conducted at multiple centers

Intervention

Initially (Stage 1), there will be approximately 60 patients, with an N = 15 per treatment group (3 different dose levels of ISIS 696844 and placebo). Patients will be randomized equally (1:1:1) to 1 of the 3 dose cohorts and, within each dose cohort, 3:1 to receive active or matching volume of placebo. After review of safety, tolerability, pharmacokinetic and pharmacodynamic changes that occur during the first 13-week Treatment Period of approximately the first 60 patients,3 treatment groups (2 active and the placebo group) will be expanded to include a total of 105 patients per group.
The Stage 2 patients will be randomized equally (1:1) to 1 of the 2 dose cohorts and, within each dose cohort, 2:1 to receive active or matching volume of placebo. The 15 or more patients of the dose group in Stage 1 that will not be expanded will continue Treatment and Post-Treatment Periods if safety profile is acceptable.
At the discretion of the Sponsor, additional patients may be added to 1 or more of the treatment groups (total N not to exceed more than1.2 times the original sample size [i.e., 126/group]), if necessary to elucidate safety or compensate for unexpected high number of patients withdrawing from the study.

The Netherlands will not participate in Stage 1 of the study

Study burden and risks

The study contains a screening phase, treatment phase and a follow-up phase.
o 10-14 week screening period
o 45 week study treatment period
o 12 week follow-up period
Most of the visits will take about 1 to 4 hours

The subject will have to undergo several examinations, tests and/or procedures before, during and after his/her treatment. Please refer to the procedure table In the ICF and Appendix A of the protocol for more information.

In addition, questions are asked about the medical history, demographics and eligibilty questions
Subjects will also be tested for HIV and hepatitis. Female patients will be tested for pregnancy .

The anticipated total duration of the study is approximately 71 weeks (18 months)

Possible side effects that are already known are described in the Investigator's Brochure and the patient informed consent form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

A full list of the inclusion criteria can be found in section 5.1 of the protocol. Below a list of the most important criteria:
1. Females must be non-pregnant and non-lactating, and either surgically sterile or post-menopausal.
2. Vaccination against Neisseria meningitidis and Streptococcus pneumoniae received at least 2 weeks prior to first dose of investigational product
3. Well-demarcated geographic atrophy (GA) due to AMD
4. Best-corrected visual acuity (BCVA) letter score of 35 letters (approx. 20/200 Snellen equivalent) or better on the ETDRS chart
5. Must have clear ocular media and adequate pupillary dilation in the study eye to permit high-quality fundus imaging

Exclusion criteria

A full list of the exclusion criteria can be found in section 5.2 of the protocol. Below a list of the most important criteria:
1.Clinically-significant abnormalities in medical history
2. A lack of full recovery from any infection for at least 14 days prior to the Study Drug administration
3. Chronic treatment with steroids, including topically or intravitreally administered
4. History or presence of diabetic retinopathy or diabetic macular edema (DME)
5. History or presence of a disease other than AMD that could affect vision or safety assessments
6. Prior treatment with another investigational drug, biological agent, or device

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Ethics review

Approved WMO

Date:	28-06-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-12-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-08-2022
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	EUCTR2020-005174-94-NL
ClinicalTrials.gov	NCT03815825
CCMO	NL77253.000.21