A Phase 3 Multicenter, Randomized, Double-Masked Study Comparing the Efficacy and Safety of Emixustat Hydrochloride with Placebo for the Treatment of Macular Atrophy Secondary to Stargardt Disease

Published: 11-08-2020
Last updated: 15-02-2024

To determine if emixustat hydrochloride (emixustat) reduces the rate of progression of macular atrophy (MA) compared to placebo in subjects with Stargardt disease (STGD)1. To evaluate the safety and tolerability of emixustat compared to placebo2. To...

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

Summary

ID

NL-OMON53320

Source
ToetsingOnline

Brief title
The SeaSTAR Study

Condition

- Eye disorders congenital

Synonym
macular atrophy, Stargardt Disease

Research involving

Human

Sponsors and support

Primary sponsor: Acucela Inc.
Source(s) of monetary or material Support: Acucela Inc.

Intervention

Keyword: Emixustat hydrochloride, Macular Atrophy, SeaSTAR, Stargardt Disease

Outcome measures

Primary outcome

The primary efficacy endpoint will be the mean rate of change from baseline in the total area of the MA lesion(s) in the study eye (in mm2 per year), defined as the area of definitely decreased autofluorescence as imaged by reduced-illuminance FAFc.

Secondary outcome

Secondary efficacy endpoints will include:

1. Mean change from baseline in retinal sensitivity as assessed by photopic microperimetry

2. Mean change from baseline in contrast sensitivity.

3. Mean change from baseline in reading speed.

4. Mean change from baseline in ETDRS BCVA letter score.

5. Mean rate of change from baseline in the total area of decreased autofluorescence (definitely decreased plus questionably decreased), as imaged by reduced-illuminance FAF.

6. Mean rate of change from baseline in the total area of EZ loss, as imaged on SD-OCT

7. Mean change from baseline in mean ONL thickness, as imaged on SD-OCT

8. Mean change from baseline in QOL instruments.

Exploratory Efficacy:

1. Mean change from baseline in extent of abnormal nearinfrared FAF.

Safety endpoints will include:

1. Frequency of AEs, discontinuations due to AEs, or dose modifications due to

AEs; severity and seriousness of AEs.

2. Change from baseline in laboratory values, vital signs, physical examination

findings, ECGs, and ophthalmic assessments.

Study description

Background summary

Stargardt disease is a rare, inherited degenerative disease of the retina affecting approximately 1 in 8,000 to 10,000 individuals and is the most common type of hereditary macular dystrophy. There are no approved treatments for STGD.

Study objective

To determine if emixustat hydrochloride (emixustat) reduces the rate of progression of macular atrophy (MA) compared to placebo in subjects with Stargardt disease (STGD)

1. To evaluate the safety and tolerability of emixustat compared to placebo
2. To assess changes in retinal sensitivity as determined by photopic microperimetry with emixustat compared to placebo
3. To assess changes in contrast sensitivity with emixustat compared to placebo
4. To assess changes in reading speed with emixustat compared to placebo
5. To assess changes in best-corrected visual acuity (BCVA) letter score with emixustat compared to placebo

6. To assess changes in total area of decreased autofluorescence (definitely decreased plus questionably decreased) with emixustat
compared to placebo
7. To assess changes in total area of ellipsoid zone (EZ) loss with emixustat
compared to placebo
8. To assess changes in mean outer nuclear layer (ONL) thickness with emixustat
compared to placebo
9. To assess changes in quality-of-life instruments (QOLs) with emixustat
compared to placebo

Study design

This is a multicenter, randomized, double-masked, placebo-controlled study to evaluate the efficacy and safety of emixustat compared to
placebo in subjects who have MA secondary to STGD. Subjects will be randomly assigned to one of two treatment arms in a 2:1 ratio.
Treatment arms include:
* Emixustat 10 mg
* Placebo
Subjects will take study drug once daily (QD) in the evening for 24 continuous months.
Subjects randomly assigned to the emixustat arm will start taking a dose of 5 mg on Day 1 and step-up to 10 mg at the Month 1 visit, then maintain that dose for the remainder of the dosing period, unless a dose reduction is taken.

Intervention

Emixustat (5 mg and 10 mg) tablets will be packaged in identicalappearing, tamper proof, blister packaging to maintain masking. Study drug will be taken orally QD in the evening for 24 months.

Study burden and risks

In some cases, the side effects of emixustat may affect vision and make it hard to perform daily activities. Subjects should be careful and avoid dangerous activities (such as operating a motorized vehicle and moving in a darkened room or other environment, if it is not familiar to the subject), if vision is impaired.
If efficacious, Emixustat may improve the subjects vision, if it was compromised, and your other symptoms of Stargardt disease, but this is not certain. Currently, there are no approved treatments for STGD.

Contacts

Public
Covance

Schipholweg 111
Leiden 2316 XC
NL
Scientific
Covance

Schipholweg 111
Leiden 2316 XC
NL

Trial sites

Listed location countries

Brazil, Canada, Denmark, France, Germany, Italy, Netherlands, South Africa, Spain, United Kingdom, United States of America

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects who meet all of the following criteria at Screening and Baseline (unless otherwise indicated) may be eligible for inclusion in the study:
1. Males or females, age * 16 years.
2. Clinical diagnosis of MA secondary to STGD in one or both eyes as determined by the Investigator.
3. The subject must have 1 or more pathogenic mutation(s) of the ABCA4 (ATP binding cassette subfamily A member 4) gene. If only one ABCA4 pathogenic mutation is identified or if two ABCA4 pathogenic mutations that typically occur on the same allele (ie, *in cis*) are identified, the subject must have a

typical STGD phenotype (at least one eye has flecks at the level of the retinal pigmented epithelium [RPE] typically seen in STGD) and be approved by the Sponsor. If 2 or more pathogenic mutations that do not typically occur on the same allele are identified, a typical STGD phenotype and separate Sponsor approval are not required. Segregation analysis is not required. The pathogenicity of all mutations will be determined by the Sponsor working with experts in ophthalmic genetics.
4. The study eye must meet the following criteria as determined by the central reading center*s assessment of FAF imaging at Screening:
a. Total area of DDAF
i. If the lesion is unifocal: * 3.0 * 22.0 mm2 (~1.2 * 8.7 disc areas) in size.
ii. If the lesion is multifocal: * 1.0 * 22.0 mm2 (~0.4 * 8.7 disc areas) in size.
b. The entire lesion must be completely visualized on the macula-centered image (Field 2 * Macula Image). The DDAF lesion must be able to be imaged in its entirety, and all lesion borders must be * 300 microns from all image edges.
5. Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA letter score of * 25 letters (approximately * 20/320 Snellen) in the study eye at Screening.
6. Adequate clarity of ocular media and adequate pupillary dilation to permit good quality imaging of macular atrophy in the study eye as determined by the Investigator.
7. Able to reliably administer oral medication by self or with available assistance.
8. Able and willing to provide written informed consent/assent
a. For subjects * 18 years of age: able and willing to provide written informed consent before undergoing any study-related procedures.
b. For subjects * 16 and 18 years of age: able and willing to provide written informed assent, and has a parent or legal guardian able and willing to provide written informed consent for the minor before the subject undergoes any study-related procedures. Where required by local regulations, both parents must consent to the subject*s participation in the study, if both have legal custody.

Exclusion criteria

Subjects will be excluded from participation in the study if they meet any of the following criteria at Screening or Baseline (unless otherwise indicated):,
1. Macular atrophy associated with a condition other than STGD in either eye.,
2. DDAF with contiguous area of peripapillary atrophy in the study eye, as determined by the reading center.
3. Mutation(s) in any of the following genes * elongation of very long chain fatty acids-like 4 (ELOVL4), prominin 1 (PROM1), or peripherin 2 (PRPH2)/retinal degeneration slow (RDS) * determined by the Sponsor working with experts in ophthalmic genetics to likely be disease-causing.
4. If tested, any mutation(s):

a. In a gene(s) encoding a visual cycle protein [e.g., retinal pigment epithelium 65 (RPE65), lecithin:retinol acyltransferase (LRAT), retinol dehydrogenase 12 (RDH12), RDH5, and retinaldehyde binding protein 1 (RLBP1)], confirmed by the Sponsor working with experts in ophthalmic genetics to likely be disease-causing. Testing for these mutations is not required.,
b. Associated with a non-STGD retinal dystrophy/degeneration, confirmed by the Sponsor working with experts in ophthalmic genetics to likely be disease-causing. Testing is not required.,
5. Presence in either eye of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including, but not limited to, choroidal neovascularization, diabetic retinopathy, uveitis, other macular diseases, or uncontrolled glaucoma/ocular hypertension.,
6. History of any intraocular or ocular surface surgery in either eye * 3 months prior to Screening., 7. Current or previous participation in an interventional study to treat STGD using gene therapy or stem cell therapy.
8. Current or previous participation in a study to treat STGD using a vitamin A derivative * 6 months prior to Screening.
9. Current or previous participation in a study to treat STGD using a complement inhibitor * 6 months prior to Screening.
10. Known hypersensitivity to emixustat or any of the excipients in emixustat tablets (ie, silicified microcrystalline cellulose, pregelatinized starch, colloidal silicon dioxide, and stearic acid).,
11. Prohibited medications: Please refer to page 29 of the protocol.,
12. Any of the following laboratory abnormalities at Screening: Please refer to page 30 of the protocol,
13. Participation in any study using an investigational drug within 30 days or 5 half-lives (of the investigational drug) of Screening.
14. Participation in any study of an interventional, investigational device within 60 days of Screening.,
15. Anticipated participation during the study period in any study using an investigational drug or an interventional, investigational device.
16. Presence of other medical or ophthalmic disease, physical examination finding, or clinical laboratory finding that in the opinion of the Investigator contraindicates the use of an investigational drug, places the subject at risk by participating in the study, might interfere with the evaluation of the efficacy or safety of emixustat, negatively impacts subject compliance with the protocol, confounds the ability to interpret data from the study, or jeopardizes the subject*s ability to complete the protocol.
17. Current or history of cancer (except for adequately treated basal cell or squamous cell carcinoma of the skin) within 1 year of Screening.,
18. History of myocardial infarction, stroke, unstable ischemic heart disease, uncontrolled cardiac arrhythmia, or hospitalization for congestive heart failure within 6 months of Screening.,
19. Abnormal electrocardiogram (ECG) results that are considered by the Investigator to be clinically significant at Screening.,
20. Female subjects who are pregnant or lactating.,
21. Female subjects of childbearing potential [(ie, not postmenopausal (without

menses for 12 months without an alternative medical cause) for at least two years and not surgically sterile via hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)] who are not willing to practice a medically accepted method of birth control with their non-surgically sterile male sexual partner from Screening through 30 days following the completion of the study. Medically accepted methods of birth control include true abstinence, estrogen+progestogen hormonal hormonal contraceptives, progestogen-only hormonal contraceptives, nonhormonal or hormonal intrauterine contraceptive device with spermicide, bilateral tubal occlusion, male or female condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide, or cervical cap with spermicide. True abstinence is when abstinence from heterosexual intercourse is in line with the preferred and usual lifestyle of the subject and is not just limited to the duration of this study.,
22. Male subjects who are not surgically sterile and are not willing to practice a medically accepted method of birth control with their female partner of childbearing potential (as listed above) from Screening through 30 days after completion of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2019
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Emixustat hydrochloride

Ethics review

Approved WMO Date:	27-05-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	2018-003498-82
ClinicalTrials.gov	NCT03772665
CCMO	NL68418.091.19

Study results