A multi-national, multi-centre, double-masked, placebo-controlled proof of concept trial to evaluate the safety and efficacy of oral soraprazan in Stargardt disease

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Primary objective:To evaluate the efficacy of soraprazan in reducing the amount of lipofuscin inRPE cells of subjects with Stargardt disease by assessing the change inquantitative auto-fluorescence (qAF8) from baseline to after treatment...

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

Summary

ID

NL-OMON48130

Source
ToetsingOnline

Brief title
A phase II study of soraprazan in patients with Stargardt disease

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
juvenile macular degeneration, or fundus flavimaculatus, Stargardt disease, Stargardt macular dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Katairo GmbH
Source(s) of monetary or material Support: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779317.

Intervention

Keyword: Patients with Stargardt disease, Remofuscine, Soraprazan

Outcome measures

Primary outcome

Change in qAF8 score from baseline to end of treatment (EoT) for soraprazan

compared to placebo treated subjects. Evaluation of qAF8 score for all subjects

will be done at a central reading centre.

Secondary outcome

Functional

1. Best-corrected visual acuity (BCVA) as measured by Early

Treatment Diabetic Retinopathy Study (ETDRS) charts

2. BCVA as measured by ETDRS chart under low luminance

conditions (LLVA)

3. Low Luminance Deficit (LLD) calculated as the difference between

BCVA and LLVA

4. Change from baseline in binocular and monocular maximum

reading speed as assessed by Radner Charts

5. Change from baseline in binocular and monocular critical print size

as assessed by Radner charts.

6. Macular functional response as assessed by mesopic

microperimetry

7. Subject-reported visual function as assessed by the National Eye

Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) and

Functional Reading Independence (FRI) Index

Structural

8. Changes in central subfield retinal thickness (CSRT) as assessed

by spectral-domain optical coherence tomography (SD-OCT)

9. Changes in macular volume as assessed by SD-OCT

10. Changes in outer nuclear layer (ONL) thickness as assessed by

SD-OCT

11. Changes in Ellipsoid Zones (EZ) as assessed by SD-OCT

12. Presence and changes of macular atrophy by fundus

autofluorescence

13. Lesion progression

Study description

Background summary

Stargardt disease (STGD) is an orphan indication and genetic eye disorder that causes progressive vision loss. Individuals with the condition have abnormal accumulation of fatty yellow pigment (lipofuscin) in the cells of the retinal pigment epithelium (RPE) underlying the macula. Lipofuscin is auto-fluorescent and readily discernible with non-destructive/non-invasive, ophthalmic imaging methods.

To date there are no treatments available for STGD disease. The only recommendation for such patients is eye protection from bright light (e.g. by using sun glasses) and to avoid exposure to substances that might cause eye irritations, like tobacco smoke. These measures cannot prevent but may possibly slow down disease progression. Existing approaches targeting lipofuscin are

restricted to limiting further accumulation of lipofuscin in the RPE cells to avoid worsening of the disease progression. However, no treatment is currently available to remove the already accumulated lipofuscin and to allow RPE cell regeneration.

This study investigates the drug calles Soraprazan. This drug was initially developed to stop acid production in the stomach to treat gastroesophageal reflux disease (GERD). Soraprazan has been tested in several hundred patients with GERD and caused no serious side effects. However, development was stopped because there were many other products for use in GERD on the market. A study in monkeys showed that soraprazan removed pigments from the retina. The main pigment removed from the retina by soraprazan was lipofuscin. Since soraprazan removes lipofuscin from the retina, it could be the first product that may help in Stargardt Disease.

Study objective

Primary objective:
To evaluate the efficacy of soraprazan in reducing the amount of lipofuscin in RPE cells of subjects with Stargardt disease by assessing the change in quantitative auto-fluorescence (qAF8) from baseline to after treatment with soraprazan compared to placebo for up to 12 months.

Secondary objective:
To assess the safety and efficacy of soraprazan based on safety parameters and secondary efficacy parameters such as change in visual function and structural changes after treatment with soraprazan compared to placebo for up to 12 months.

Study design

The investigational drug soraprazan has demonstrated (in pre-clinical studies) the ability to remove lipofuscin from RPE cells. The amount of lipofuscin in RPE cells can be shown by its level of auto-fluorescence. A reduction of the amount of lipofuscin in the RPE cells will result in reduced auto-fluorescence signal. Quantitative Autofluorescence (qAF) is a technique to measure fundus autofluorescence changes as a marker of lipofuscin levels in the retina.

This is a randomized proof of concept, double-masked, placebo-controlled, two arm, multicenter trial to evaluate the efficacy and safety of soraprazan (20 mg orally once a day) in subjects with Stargardt disease by measuring the reduction of the amount of lipofuscin in the RPE cells subjets with qAF. Retinal sensitivity will be measured by microperimetry.

90 subjects are planned to be randomized in 5 European sites in Germany, the Netherlands, United Kingdom and Italy. Subjects with Stargardt disease will be

randomized to the trial treatment in a 2:1 ratio (soraprazan:placebo). Subjects will be treated for up to 12 months.

Intervention

Soraprazan or placebo, 20mg orally once a day.

Study burden and risks

Previous GERD studies done by Altana Pharma with soraprazan have demonstrated a good safety profile. Observed adverse events were mainly related to gastrointestinal symptoms (such as flatulence, nausea, abnormal stools and abdominal pain), dizziness, and headaches. Soraprazan 20 mg daily dose was well tolerated by the majority of the subjects in these studies and was used for up to 8 weeks.

In the present study, the same oral dose will be used as in the GERD studies. All subjects will be closely monitored for safety parameters throughout the study. In addition, all subjects will have the possibility to withdraw their consent at any time, without giving any explanation. Subjects with already known APA intolerance or reduced liver function will not be enrolled. Subject safety will be observed and evaluated by a Data Safety and Monitoring Board (DSMB) during the course of the study. Thus, the safety risk for subjects participating in this clinical trial is considered to be low.

There is currently no cure or standard treatment available for STGD. Other development projects for the treatment of STGD can only prevent further accumulation of lipofuscin in the RPE. Thus there is no possibility for RPE cell regeneration with these research approaches, and most STGD patients will eventually lose visual function. Therefore, soraprazan aims to address this medical need for lipofuscin removal in STGD.

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

• Elevated qAF in at least one eye at screening (value >=300 Units).;• Male or female of any ethnicity and >= 18 years old.;• Onset of STGD disease before the age of 45 years;• Visual acuity of the study eye: BCVA 0.2-0.8 (decimal unit).;• Clinical diagnosis of typical autosomal recessive Stargardt*s macular dystrophy (STGD1).;• Genetic report indicating at least two ABCA4 mutations (one with confirmed pathogenesis by a certified lab, one reported previously).;• Study eye must have clear ocular media and adequate pupillary dilation, including no allergy to dilating eye drops and with sufficient fixation to permit good quality retinal imaging.;• Able and willing to comply with study requirements, restrictions and instructions and is likely to complete the 12-months study.;• Signed and dated informed consent form.;• Female subjects of childbearing potential and male subjects participating in the study who are sexually active must use acceptable contraception. Male and female subjects documented as being of non-child bearing potential (e.g. infertile, surgically sterile, postmenopausal) are exempt from the contraceptive requirements.

Exclusion criteria

• Intolerance to acid pump antagonists (APAs).;• Intake of prohibited medications/supplements (supplements containing vitamin A or beta-carotene, medications to treat any liver disease, or oral retinoid medications) within 28 days prior to screening and throughout the study.;• Intake of other drugs with a pH dependent absorption, e.g. ketoconazole.;• Breastfeeding, pregnant, or positive urine pregnancy test at screening or visit 2 (first intake of Investigational Medicinal Product (IMP)).;• At screening, clinically significant abnormal haematology or biochemistry findings.;• Acute or unstable severe disease or history of disease which in the opinion of the investigator would preclude

participation in the study.;• Active or history of an additional ocular disorder in the primary study eye that, in the opinion of the investigator, may confound the study results. These include, but are not limited to, any reason that might interfere with the imaging techniques used in the study (such as optic media opacity or poor pupil dilatation), inflammatory eye disease, other retinal disorders besides STGD, confirmed glaucoma or baseline intraocular pressure of >=25mmHg, optic neuritis, high myopia (>8D spherical equivalent), amblyopia.;• Intraocular surgery or injections in the primary study eye within 180 days of the screening visit.;• Clinically significant abnormal electrocardiogram (ECG), or a corrected QT interval (QTc) of >=450 ms in males or >=470 ms in females.;• Participation in any other investigational clinical trials within 28 days of the screening visit.

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:	Recruiting
Start date (anticipated):	05-06-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Soraprazan
Generic name:	Not applicable

Ethics review

Approved WMO Date:	09-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-04-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2020
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	EUCTR2018-001496-20-NL
CCMO	NL68179.091.18