An Open-Label, Phase 1b Safety/Proof-of-Concept Study to Evaluate the Effects of Oral QLT091001 in Subjects with Leber Congenital Amaurosis (LCA) or Retinitis Pigmentosa (RP) Due to Inherited Deficiencies of Retinal Pigment Epithelial 65 Protein (RPE65) or Lecithin:Retinol Acyltransferase (LRAT)

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• To evaluate whether 7-day treatment with oral QLT091001 can improve visual function in subjects with LCA or RP caused by RPE65 or LRAT gene mutations.• To evaluate duration of visual function improvement (if observed) in subjects with LCA or RP…

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

Summary

ID

NL-OMON38343

Source
ToetsingOnline

Brief title
RET IRD 01

Condition

- Vision disorders

Synonym
Retinitis Pigmentosa / Inherited ophthalmology disorder

Research involving
Human

Sponsors and support

Primary sponsor: QLT Inc.
Source(s) of monetary or material Support: Commercial Sponsor

Intervention

Keyword: Leber Congenital Amaurosis (LCA), Retinitis Pigmentosa (RP)

Outcome measures

Primary outcome

Assessment of Vision;

Assessment of Safety

Secondary outcome

not applicable

Study description

Background summary

This will be a phase 1b study to investigate the safety, tolerability, and proof-of-concept for oral QLT091001 as a new treatment for subjects with Leber Congenital Amaurosis (LCA) or retinitis pigmentosa (RP) due to inherited mutations in RPE65 (encoding the protein retinal pigment epithelial protein 65) or LRAT (encoding the enzyme lecithin:retinol acyltransferase). The study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines, and Part C, Division 5 of the Canadian Food and Drug Regulations.
Subjects with either LCA or RP will be enrolled in approximately 2-3 study centers in North America, and adult subjects with RP will be enrolled at approximately 3 study centers in the European Union.

Study objective

• To evaluate whether 7-day treatment with oral QLT091001 can improve visual function in subjects with LCA or RP caused by RPE65 or LRAT gene mutations.
• To evaluate duration of visual function improvement (if observed) in subjects with LCA or RP caused by RPE65 or LRAT gene mutations after 7-day treatment with oral QLT091001.
• To evaluate the safety of oral QLT091001 administered once daily for 7 days in subjects with LCA or RP caused by RPE65 or LRAT gene mutations.

Study design

This will be an open-label, proof-of-concept, Phase 1b study. The study will include up to 28 subjects with LCA or RP due to inherited deficiency of RPE65 or LRAT (up to 14 subjects for each disease cohort). Subjects in each cohort (including 2 gene mutation subgroups) will receive a once-daily oral loading dose of QLT091001 (40 mg/m2) for 7 days. This was the highest dose administered in Study RET HV 01. Subjects with either LCA or RP will be enrolled in approximately 2-3 study centers in North America, and adult subjects with RP will be enrolled at approximately 3 study centers in the European Union. Subjects will be treated on an outpatient basis but will receive study treatment in the research clinic under medical supervision for each day of treatment. During the study treatment period and for 7 days post-treatment, subjects will be required to limit vigorous physical activity and will be instructed to follow dietary guidelines to avoid excessive vitamin A intake to reduce the influence of such factors on the assessment of safety variables in this study.
Each subject will have both eyes evaluated. Follow-up visits will continue through 12 months post-treatment. Additional follow-up visits will be scheduled at quarterly intervals thereafter at the Investigator's discretion.

Intervention

Subjects will receive a 40 mg/m2 oral loading dose of QLT091001 once daily for 7 days in the research clinic under medical supervision.

Study burden and risks

The main risks of QLT091001 and 9-cis-retinol in humans are unknown but, at the dose and treatment duration planned for this study, may include adverse effects on the liver based on rat and primate toxicology studies and human experience with other oral retinoid drugs. These effects will be monitored by serum chemistry analysis and are typically reversible. The risks of daily oral dosing of QLT091001 for 7 days in humans were investigated in a phase 1a healthy volunteer study. These and other risks in humans are described further in the patient informed consent form.
The potential benefits of QLT091001 are the following:
• The ability to produce isorhodopsin within the photoreceptors should result

in improved vision in subjects who have retained some photoreceptors and retinal architecture.
• Preservation of some visual function by this method may also prevent the progressive degeneration of the retina that is observed in these subjects.

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. Subjects will have either LCA or RP, with a mutation in either RPE65 or LRAT, as follows:
a. Subjects with LCA will be 5-65 years of age diagnosed with LCA by an ocular geneticist or pediatric ophthalmologist.
b. Subjects with RP will be diagnosed with RP by an ocular geneticist or ophthalmologist and be:
For Canada, Germany, The Netherlands, and UK: 18-65 years of age (inclusive).

For US only: 8-65 years of age (inclusive). ;2. Subjects who have a best-corrected standard ETDRS visual acuity of 3 letters or better (20/800 Snellen equivalent), however; subjects with a lower ETDRS score will be eligible if spectral domain OCT and FAF reveals evidence of a viable photoreceptor layer. ;3. Subjects who are girls or women of child-bearing potential must not be pregnant or lactating, must have negative serum pregnancy tests (>=25 mIU/mL sensitivity) at Screening (i.e., >=19 days before Day -1, and on Day -1) and must have been practicing 2 adequate methods of birth control or complete abstinence for at least 2 months.
Adequate methods of birth control include (1) use of oral contraceptives (excluding low-dose oral formulation), implantable or injectable contraceptives, or an intrauterine device (IUD), with an additional barrier method (diaphragm with spermicidal gel OR condoms with spermicide); (2) a double-barrier method (diaphragm with spermicidal gel AND condoms with spermicide); (3) partner vasectomy; and (4) total abstinence. ;4. Subjects who are boys or men must (1) agree to completely abstain from sexual intercourse, (2) have had a vasectomy, or (3) use a barrier method (condoms) with spermicide during sexual intercourse, during the treatment phase of the study and for 2 months after finishing the study drug. ;5. Subjects who provide informed consent and, if applicable, assent for the study (applies to subjects 7 years and older). The parent or guardian must sign an approved informed consent form for the study for subjects younger than the age of majority.
Note that use of the term "subject" throughout this protocol may also include the parent/guardian of subjects younger than the age of majority, as appropriate. ;6. Subjects who are willing to comply with the protocol. ;In the Netherlands only adult RP patients (older then 18 years) will be included.

Exclusion criteria

1. Subjects who are actively participating in an experimental therapy study or who have received experimental therapy within 60 days of Day 0. ;2. Subjects with any clinically important abnormal physical finding at Screening. ;3. Subjects who have taken any prescription or investigational oral retinoid medication (e.g., Accutane/Roaccutane® or Soriatane/Neotigason®) within 6 months of Day 0 and subjects who did not tolerate their previous oral retinoid medication will be excluded regardless of the time of last exposure. ;4. Subjects with a history of diabetes or chronic hyperlipidemia, hepatitis, pancreatitis, or cirrhosis. ;5. Subjects with liver failure, uncontrolled thyroid disease, hypersensitivity to retinoids, or hypervitaminosis A. ;6. Subjects with any of the following findings at Screening: ;- Untreated blood pressure 150/95 mm Hg or higher upon repeated measurement ;- Resting heart rate <40 bpm or >100 bpm upon repeated measurement ;- ALT or AST >3 times the upper limit of the clinical laboratory value normal range upon repeated measurement ;- Total cholesterol, triglycerides, HDL, or LDL >2 times the upper limit of the clinical laboratory value normal range upon repeated measurement ;- Thyroid function tests outside the clinical laboratory value normal range upon repeated measurement ;- Serum retinol clinical laboratory value above 90 µg/dL upon repeated measurement ;7. Subjects with a documented and known allergy to soy. ;8. Subjects who, in the Investigator*s opinion, have any severe acute or chronic medical condition, psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or administration

of study treatment, or interfere with the interpretation of study results. ;9. Subjects with a marked baseline prolongation of QT/QTc intervals (e.g., repeated demonstration of a QTc interval >450 milliseconds [ms]). ;10. Subjects with a history of additional risk factors for torsade de pointes (TdP) (e.g., heart failure, hypokalemia, history or family history of Long QT Syndrome), and Wolff-Parkinson-White (WPW) syndrome. ;11. Subjects who have taken any supplements containing >=10,000 IU vitamin A within 60 days of Screening.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-11-2011
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	QLT091001
Generic name:	QLT091001

Ethics review

Approved WMO

Date:	10-06-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	13-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-002055-33-NL
ClinicalTrials.gov	NCT01014052
CCMO	NL36955.078.11