An Open-Label Study to Evaluate the Effects of Repeated Treatments of Oral QLT091001 on Safety and Vision Outcome 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) (Extension of Study RET IRD 01)

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• To evaluate the safety of up to 3 additional courses of oral QLT091001 administered once daily for 7 days in subjects with LCA or RP caused by RPE65 or LRAT gene mutations who have been treated previously with a single 7-day course of QLT091001 in...

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

Summary

ID

NL-OMON39289

Source
ToetsingOnline

Brief title
RET IRD 02 - Extension of Study RET IRD 01

Condition

- Vision disorders

Synonym
Inherited ophthalmology disorder

Research involving
Human

Sponsors and support

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

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 is an extension of Study RET IRD 01. Subjects who received a single 7-day treatment course of QLT091001 in Study RET IRD 01 and meet entry criteria for treatment will be enrolled. Enrollment and follow-up in this extension study supersedes follow-up after Day 30 in Study RET IRD 01.
Study RET IRD 01, a proof-of-concept study investigating the effects of one treatment course of QLT091001, is now completed. This study is the core study to the RET IRD 02 extension study. Early results from the LCA cohort indicate that QLT091001 may have promising efficacy with improvements in vision and subjectively reported daily functioning that have lasted up to 14 months after

dosing in some subjects. The database was closed on 16 November 2012 and analysis is currently underway.
Only one treatment course of QLT091001 is allowed in Study RET IRD 01, although when the study was planned it was thought that if a beneficial effect of QLT091001 was shown and the drug was to be developed further, an intermittent, continuing dose regimen would be required to maintain beneficial effect. The current extension study (RET IRD 02) is designed to investigate the effect of additional treatment courses of QLT091001 in subjects who have already received their one course of therapy in Study RET IRD 01. In Study RET IRD 02, subjects will be evaluated after additional treatment courses to see if the beneficial effect observed after one treatment course can be reproduced or further improved with additional treatment courses while maintaining remaining tolerable and reversible safety effects.
With continued follow-up in Study RET IRD 01, the beneficial effects of one treatment course of QLT091001 are diminishing over time. Some subjects who had severely impaired vision before treatment experienced improved vision and improved daily function after their one treatment course. It is important to these subjects to retain the vision and associated expanded capabilities that additional treatment courses may provide. Additional treatments may also result in vision improvement for those who did not respond to the single treatment course and better vision improvement for those who responded to the single treatment course.
The primary purpose of this extension study is to provide treatment to subjects whose visual function improved after the previous single treatment course but whose visual function is now regressing. It is designed also to evaluate the safety and efficacy of continued treatment for these subjects. This protocol also offers additional treatment for subjects whose vision did not improve after a single treatment course. Subjects will be followed up for up to 6 months after their last treatment in this study.

Study objective

• To evaluate the safety of up to 3 additional courses of oral QLT091001 administered once daily for 7 days in subjects with LCA or RP caused by RPE65 or LRAT gene mutations who have been treated previously with a single 7-day course of QLT091001 in Study RET IRD 01
• To evaluate whether up to 3 additional courses of oral QLT091001 administered once daily for 7 days can maintain or improve visual function in subjects with LCA or RP caused by RPE65 or LRAT gene mutations who have been treated previously with a single 7-day course of QLT091001 in Study RET IRD 01

Study design

This is an open-label study for subjects with LCA or RP due to inherited deficiency of RPE65 or LRAT who previously completed follow-up through at least Day 30 in Study RET IRD 01, in which they received a single 7-day treatment

course of QLT091001 (10 or 40 mg/m2). In this treatment extension study, subjects will receive 3 courses of once-daily oral dosing of QLT091001 (40 mg/m2) for 7 days. Treatment is based on protocol-defined GVF response criteria. Each of the 3 treatment courses will be separated by a minimum period of 30 days (starting from Day 0) up to a maximum of 60 days. After receiving Treatment Course 3, subjects will be followed until Month 6.
Subjects are treated on an outpatient basis but receive study treatment in the research clinic under medical supervision for each day of treatment. During each study treatment period and for 7 days post-treatment, subjects are required to limit vigorous physical activity and instructed to follow dietary guidelines to avoid excessive vitamin A intake to reduce the influence of such factors on the assessment of safety.
Subjects will undergo visual function and ocular testing on both eyes.

Intervention

For each treatment course, subjects will receive an oral dose of 40 mg/m2 QLT091001 once daily for 7 days in the study clinic under medical supervision. Upon review of the subject's GVF and safety results, subjects may be administered 10 mg/m2 as judged by the Investigator.

Subjects may receive up to 3 courses of study treatment in Study RET IRD 02. A minimum of 3 weeks is required between the last day of the previous treatment course and the first day of the next treatment course.
Retreatment in Courses 2 and 3 will either occur after the Day 30 visit of the previous treatment course (if there are no safety concerns and the subject meets GVF retreatment criteria) or after the Month 2 visit (provided there are no safety concerns).

Second Treatment Course Treatment Criteria:
Subjects will be evaluated for their second treatment course at the Day 30 visit of the first treatment course. A subject will receive the second treatment course (once daily dose of QLT091001 for 7 days), with the dose at the discretion of the Investigator, if there are no safety concerns and:
• Follow-up GVF in at least 1 eye did not increase (i.e., increased <=20% from the RET IRD 02 study baseline), or
• Follow-up GVF in at least 1 eye decreased below the highest previous response by >20% after the first course of treatment in RET IRD 02, or
• The subject does not meet the GVF criteria but is considered by the Investigator as a reasonable candidate for treatment based on (1) regression or lack of response in other parameters of visual function (e.g., subjective reports of changes in color vision or adaptation to low light), or (2) the potential for further improvement in GVF if GVF response was sustained.
If a subject does not meet GVF treatment response criteria at Day 30 the subject will return for the Month 2 visit and start the next treatment course within 7 days contingent upon the review of safety evaluations.
Third Treatment Course Treatment Criteria:

A subject will be evaluated for their third treatment course at Day 30, if there are no safety concerns and:
• Follow-up GVF in at least 1 eye decreased below the highest previous response by >20% after the second course of treatment in RET IRD 02, or
• The subject does not meet the GVF criteria but is considered by the Investigator as a reasonable candidate for treatment based on (1) regression or lack of response in other parameters of visual function (e.g., subjective reports of changes in color vision or adaptation to low light), or (2) the potential for further improvement in GVF if GVF response was sustained .
If the subject does not meet the GVF treatment response criteria at Day 30 the subject will return for the Month 2 visit and start the next treatment course within 7 days contingent upon the review of safety evaluations. After the subject receives Treatment Course 3, subject will be followed until Month 6.

Study burden and risks

The main risks of QLT091001 and 9-cis-retinol in humans are not completely known 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. These and other risks in humans are described in more detail in the Protocol and IB for QLT091001.
Patients may experience discomfort or risks assoiciated with study procedures and blood drawing.

Preliminary results from RET IRD 01 study with QLT091001 oral treatment showed rapid and long-lasting vision improvements (visual acuity and/or visual field).
In subjects who have retained some photoreceptors and retinal architecture, the potential benefits of QLT091001 are (1) preserved visual function by preventing progressive degeneration of the retina and (2) improved vision, both due to production of isorhodopsin within the photoreceptors.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Subjects with LCA or RP due to RPE65 or LRAT deficiency who received a 7-day treatment course of QLT091001 and completed the Day 30 visit in Study RET IRD 01.
2. Subjects who meet any one of the following criteria at least 1 month after the start of the 7-day treatment course in Study RET IRD 01:
a. No increase in GVF (in at least 1 eye): i.e., follow-up GVF increased <=20% from baseline
or
b. Decrease in GVF (in at least 1 eye): i.e., follow-up GVF decreased below the highest previous response by >20%
or
c. Considered a reasonable candidate for treatment, as determined by the Investigator, based on regression or lack of response in other parameters of visual function (e.g., subjective reports of changes in color vision or adaptation to low light) but who do not meet the other (GVF) criteria for study entry
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 prior to study dosing. 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. (Women are considered postmenopausal after 1 complete year of amenorrhea).
4. Subjects who are boys or men must (1) agree to completely abstain from sexual intercourse, (2) have had a vasectomy, (3) use a barrier method (condoms) with spermicide and, if his partner is not using oral contraceptives, implantable or injectable contraceptives, or an IUD (as described in the criterion above), ensure that she is using a diaphragm with spermicidal gel during sexual intercourse, during the treatment phase of the study and for 2 months after finishing the last dose of study drug in Treatment Course 3.
5. Subjects who provide informed consent and, if applicable, assent, for the study. The parent or guardian must sign an approved informed consent form for the study for subjects younger than the age of majority.
6. 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.
7. Subjects who are willing to comply with the protocol.

Exclusion criteria

1. Subjects with any clinically important abnormal physical finding at Screening as determined by the Investigator.
2. Subjects who have taken any prescription or investigational oral retinoid medication (e.g., Accutane/Roaccutane® or Soriatane/Neotigason®) excluding study medication QLT091001 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.
3. Subjects with liver failure, cirrhosis, hepatitis, uncontrolled thyroid disease, or chronic hyperlipidemia.
4. Subjects with a hypersensitivity to retinoids or hypervitaminosis A syndrome.
5. Subjects with any of the following findings at Screening:
• Blood pressure reading upon repeated measurement (i.e., 2 measurements) taken in a sitting or supine position of the following (by age group).
5-9 years: 120/80 mmHg or higher
10-13 years: 132/83 mmHg or higher
14-17 years: 140/90 mmHg or higher
18 years and older: 150/95 mmHg or higher ;• Resting heart rate upon repeated measurement of the following (unless the subject has a known consistent lower heart rate):
5-9 years: <70 bpm or >130 bpm
10-13 years: <45 bpm or >105 bpm
14-17 years: <40 bpm or >100 bpm
18 years and older: <40 bpm or >100 bpm ;• ALT, AST, or fasting triglycerides >3 times the upper limit of the clinical laboratory value normal range (upon repeated measurement)
• Thyroid stimulating hormone (TSH) >2 times the upper limit, or 0.75 times the lower limit, of the clinical laboratory value normal range (upon repeated measurement); other thyroid function tests to be evaluated by Investigator to exclude subjects with uncontrolled thyroid disease.
• Serum retinol clinical laboratory value above 98 µg/dL.
• 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.
6. Subjects with a marked QTc prolongation (>450 milliseconds [ms]) upon repeated demonstration (e.g., 2 of 3 assessments) at screening or baseline, which is considered to be clinically significant by the Investigator.
7. Subjects with a history of 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.
8. Subjects who have taken any supplements containing >=10,000 IU vitamin A within 60 days of Screening.
9. Subjects who are actively participating in an experimental therapy study (other than RET IRD 01) or who have received another experimental therapy (in addition to QLT091001) within 60 days of Day 0.
10. Subjects with a documented and known allergy to soy.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-10-2012
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	not applicable

Ethics review

Approved WMO Date:	23-05-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2013
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	EUCTR2011-004214-42-NL
ClinicalTrials.gov	NCT01521793
CCMO	NL40193.078.12