Phase 3, Multicenter, Randomized, Double-Masked, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Tinlarebant in the Treatment ofStargardt Disease in Adolescent Subjects

Published: 09-01-2023
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2024-513483-26-00 check the CTIS register for the current data. To assesses the efficacy of Tinlarebant in slowing the rate of growth of atrophic lesion(s) in adolescent subjects with STGD1.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ocular structural change, deposit and degeneration NEC
Study type	Interventional

Summary

ID

NL-OMON53574

Source
ToetsingOnline

Brief title
LBS-008-CT03

Condition

- Ocular structural change, deposit and degeneration NEC

Synonym
Juvenile macular degeneration, Stargardt disease

Research involving

Human

Sponsors and support

Primary sponsor: Belite Bio, Inc.
Source(s) of monetary or material Support: Belite Bio;Inc.

Intervention

Keyword: juvenile macular degeneration, Stargardt Disease, STGD1

Outcome measures

Primary outcome

The primary efficacy endpoint is the rate of change from baseline in aggregate area of atrophy (definitely decreased autofluorescence [DDAF] as assessed by FAF photography. The primary estimand for the difference in the rate of change between the Tinlarebant and placebo groups will be the difference in slopes from a mixed model including terms for treatment, time (where time is considered a continuous variable assuming linearity) and treatment-by-time interaction. The intercept and slope of time are assumed to be random effects with a bivariate normal distribution and an unstructured covariance matrix while the treatment and treatment-by-time interaction are assumed to be fixed effects. Within the framework of this model, a point estimate of the treatment group difference in the regression slope between the Tinlarebant and placebo groups will be provided. The corresponding two-sided 95% confidence intervals (CIs) and p-value for the point estimate will also be presented. The primary assessment of efficacy will be performed at Month 24.

Secondary outcome

Secondary objectives:

- To assesses the efficacy of Tinlarebant in adolescent subjects with STGD1 for secondary endpoints (Secondary efficacy endpoints will be assessed at Month 24.)

- To evaluate the pharmacodynamics (PD) of Tinlarebant in adolescent subjects with STGD1

- To assess systemic and ocular safety and tolerability of Tinlarebant

Secondary outcomes:

- Change in retinal thickness and morphology by SD-OCT from baseline

- Change in BCVA measured by the ETDRS method from baseline

- Change in RBP4 levels from baseline

- Correlation between the change in RBP4 level and the rate of lesion size growth from baseline

- Physical examination, vital signs measurement, ECG, ophthalmic examination, clinical laboratory tests (including serum chemistry and hematology panels, urinalysis, and pregnancy tests on all female subjects), retinol chemistries (plasma retinol, plasma RBP4), visual function questionnaire, measurement of intraocular pressure (IOP), dark adaptation test, dilated funduscopy, contrast sensitivity, assessment of adverse events (AEs), and monitoring of concomitant medications.

Study description

Background summary

Autosomal recessive Stargardt disease (STGD1) is the most prevalent form of juvenile macular degeneration. It is a rare, inherited autosomal recessive disease that causes severe and irreversible blindness by the first or second decade of life. There is no approved treatment for this condition and remains an area of unmet need. During STGD1 onset, the retinal pigment epithelium (RPE) undergoes profound structural changes caused by the excessive accumulation of toxic vitamin by-products (bisretinoids) and cellular debris (lipofuscin) within the RPE. These changes are a direct result of the pathogenic mutations in the ABCA4 gene. The ABCA4 gene encodes a retina-specific AT P-dependent transporter (known as ABCA4, or Rim Protein) which removes reactive retinaldehydes from the retina for recycling within the RPE.
In the absence of a functional ABCA4 protein, retinaldehydes accumulate within photoreceptor outer segments of the retina where they generate membrane-damaging reactive oxygen species, and also spontaneously react with cellular lipids. These oxidized membranes and lipid-retinal species are taken into the RPE through normal diurnal phagocytic processing where they gradually accumulate. It is theorized that these compounds reach a critical mass within RPE phagolysosomes and cause dysfunction of the metabolic activities of the RPE leading to accelerated bisretinoid biosynthesis and accumulation of lipofuscin which severely compromises the ability of the RPE to provide metabolic and trophic support to the retina.
An optimal point of intervention in STGD1 is before the accumulation of cytotoxic bisretinoids and lipofuscin has led to significant structural damage to the photoreceptors and the RPE. As bisretinoids are products of retinol derivatives, the rate of bisretinoid formation depends on the availability of retinol in the retina and the uptake of serum retinol from the bloodstream to the RPE. Serum retinol is maintained in the bloodstream and is delivered to the RPE as a ternary complex comprised of retinol binding protein 4 (RBP4) and the large accessory protein, transthyretin (TTR). The binding of TTR to the RBP4-retinol complex is required to maintain a high steady-state level of retinol in the circulation. In the absence of TTR binding to the RBP4-retinol complex, RBP4-retinol would be released from the liver, but it would be rapidly eliminated through glomerular filtration in the kidney due to its small size. Because the eye has a unique preference for uptake of retinol bound to RBP4, reduction of RBP4-retinol in the circulation will lead to a reduced influx of retinol to the RPE and the inhibition of bisretinoid formation, which may be beneficial in the treatment of STGD1.
Tinlarebant (previously known as LBS-008 or BPN-14967) is an RBP4 antagonist developed as a treatment to slow or halt the progression of STGD1. The ability of Tinlarebant to bind RBP4 and reduce circulating levels of RBP4-retinol in a dose-dependent manner has been demonstrated in mice as well as non-human primates. In STGD1 animal models, Tinlarebant-mediated reduction of RBP4-retinol was effective to produce a statistically significant reduction in bisretinoid formation and lipofuscin accumulation, and also prevent photoreceptor degeneration. The safety and tolerability of Tinlarebant has been established in Phase 1 clinical studies.
Disease progression in STGD1 is assessed through the measurement of the growth

of atrophic lesions within the retina and RPE as demonstrated in the ProgStar study. The recommended imaging modalities for evaluating lesion growth rate are fundus autofluorescence (FAF) photography and spectral domain optical coherence tomography (SD-OCT) imaging. Other functional tests, such as microperimetry (optional) and best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) test are also important assessments.

Study objective

This study has been transitioned to CTIS with ID 2024-513483-26-00 check the CTIS register for the current data.

To assesses the efficacy of Tinlarebant in slowing the rate of growth of atrophic lesion(s) in adolescent subjects with STGD1.

Study design

This is a Phase 3 randomized, double-masked, parallel group, multicenter study to evaluate the efficacy and safety of Tinlarebant 5 mg in the treatment of adolescent subjects with STGD1.

Approximately 60 subjects with STGD1 will be enrolled in this study across multiple sites in Australia, Asia, Europe, and North America. Upon entry into the study, subjects will be assigned a screening number. Following screening, eligible subjects will be randomly assigned to begin treatment on Day 1 (Month 1) in 2:1 ratio to receive the study drug (either Tinlarebant 5 mg or matching placebo). Interactive response technology will be used to administer the randomization schedule. This study has a screening period of up to 28 days, treatment period of up to 24 months, and follow-up period of 28 days; thus, the total duration of study participation is approximately up to 26 months. Screening assessments will take place within 28 days before the first study visit (V1) to confirm eligibility for participation in the study and/or for baseline measurements. After beginning treatment on Day 1, subjects will return to the study site once every month for the first 4 months, and then every 3 months per the Schedule of Assessments for a total of 13 study visits (including the Screening visit). Subjects will continue treatment with the study drug orally once daily for 24 months and will be followed up for safety, efficacy, and PD assessments.

Intervention

Subjects will be treated for 24 months with Tinlarebant or placebo. The study drug is a tablet that should be taken orally every day.

For this study, we will have 2 groups:
• Group 1. The people in this group will get Tinlarebant.

• Group 2. The people in this group will get a placebo.

A draw will decide which treatment is given. The chances of receiving Tinlarebant is 66% and the probability to receive placebo is 33% (2 is to 1 chance).

Study burden and risks

The following side effects of Tinlarabant are common:
- Delayed dark adaptation (slowing in the recovery of light sensitivity by photoreceptors)
- Xanthopsia (colour vision deficiency)
- Night vision impairment

Discomforts patients can experience from the tests during the study:
• Blood collection: Collection of blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.
• Blood pressure: The blood pressure cuff used to take blood pressure may cause discomfort or bruising to the upper arm.
• Heart ultrasound (ECG): The ECG involves sticking patches on the skin. The skin may become a little red or irritated if a response to the glue used occurs.
• Eye-related assessments and pupil enlargement: There will several kinds of eye examinations during this study. The subject may feel temporary discomfort during the eye examinations due to the bright lights. When the investigator is examining the inside of the eye, sometimes there is a need to put mild pressure on the eye. This causes mild to moderate discomfort that goes away quickly. The subject may possibly experience eye swelling from the mild pressure on the eye from these examinations. For some examinations eye drops may be used to dilate the pupils of the eyes. The subject may feel side effects and discomforts, including stinging, sensitivity to lights, and blurring of vision. These effects of pupil dilation may last for 4 to 6 hours depending on the strength of the drop used.
• Tonometry: A tonometry test measures the pressure inside the eye, which is called intraocular pressure (IOP). Eyedrops to numb the surface of the eye may be used and the eyes will be numb for anywhere from 10 to 30 minutes.

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)

Inclusion criteria

1.Male or female subjects 12 to 20 years old, inclusive.
2.Subject must have clinically diagnosed STGD1 with at least 1 mutation identified in the ABCA4 gene.
3.Ability to adequately examine the fundus of the study eye at enrollment.
a.The study eye will be the eye that meets all inclusion and exclusion criteria.
b.If both eyes meet all inclusion and exclusion criteria, the eye with the smaller lesion will be selected to be the study eye.
c.If both eyes meet all inclusion and exclusion criteria and have lesions of equal size, then the eye with the better BCVA will be selected to be the study eye.
d.If both eyes meet all inclusion and exclusion criteria, have lesions of equal size, and have equal BCVA, the default will be the right eye.
4.Subject must have a defined aggregate atrophic lesion size within 3 disc areas (7.62 mm2) as imaged by FAF (DDAF) in the study eye and confirmed by the central reading center. The lesion, or at least 1 focal lesion if multiple lesions exist (multifocal atrophic lesions), must be in the macular region and greater than 0.02 disc areas (0.05 mm2).
5. Subjects must present with BCVA of 20/200 or better for the study eye based on ETDRS letter score. No minimum VA is required in the fellow eye.

6. Subject and their parent(s) or legal guardian are willing to provide their consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC)-approved informed consent form (ICF) prior to participating in any study-related procedures.
7. Subject agrees to comply with all protocol requirements.

Exclusion criteria

1. Any ocular disease other than STGD1 at screening that, in the opinion of the investigator, would complicate assessment of a treatment effect.
2. History of ocular surgery in the study eye in the last 3 months.
3. Investigational drug use of any kind in the last 3 months or within 5 half-lives of the investigational drug, whichever is shorter.
4. Any prior gene therapy.
5. Vitamin A deficiency as defined based upon plasma values less than 20 µg/dL (=0.7 µmol/L).
6. Use of medications such as isotretinoin (13-cis-retinoic acid) or other retinol modulators or derivatives that may impact the effect of the study drug in the last 2 weeks or within the washout period of the medication, whichever is longer, before beginning study treatment administration.
7. Unwilling to discontinue vitamin A or beta-carotene supplement use.
8. Use of any known drugs or supplements that are moderate or strong inhibitors/inducers of cytochrome P450 (CYP) enzymes (e.g., rifampin, barbiturates, phenothiazines, cimetidine, carbamazepine, St. John*s wort) within 30 days of study drug administration or consumption of foods that are moderate or strong inhibitors/inducers of CYP enzymes (e.g., grapefruit, pomegranate, star fruit, bitter orange [Seville orange]) within 48 hours of study drug administration, and that, in the investigator*s judgement, may impact subject safety or the validity of the study results.
9. Presence of any life-threatening disease(s), including current treatment for malignancies.
10. Alanine transaminase/aspartate aminotransferase >2.5 × the upper limit of normal at screening.
11. Renal insufficiency, as defined by an estimated glomerular filtration rate (Bedside Schwartz) <30 mL/min/1.73 m2 at screening.
12. Pregnant or nursing (breastfeeding) females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception (or abstinence). Females of childbearing age must have a negative pregnancy test prior to randomization.
13. Male subjects who do not agree that female spouses/partners will use adequate contraception (e.g., condoms) or be of nonchildbearing potential (ie, surgically sterile).
14. Unwilling or unable to provide signed informed consent/assent.
15. In the opinion of the investigator, the subject is not suitable for entry

into 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:	Recruiting
Start date (anticipated):	05-07-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tinlarebant
Generic name:	Tinlarebant

Ethics review

Approved WMO Date:	09-01-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-05-2023

Application type:	First submission
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
EU-CTR	CTIS2024-513483-26-00
EudraCT	EUCTR2021-003253-36-NL
ClinicalTrials.gov	NCT05244304
CCMO	NL83045.091.22