Thyroid Eye Disease Clinical Trials

AT STANFORD UNIVERSITY SCHOOL OF MEDICINE

Byers Eye Institute at Stanford
2452 Watson Court
Palo Alto, CA 94303
650.723.6995

For more information on TED clinical trials contact us:
650.497.8328
amritats@stanford.edu

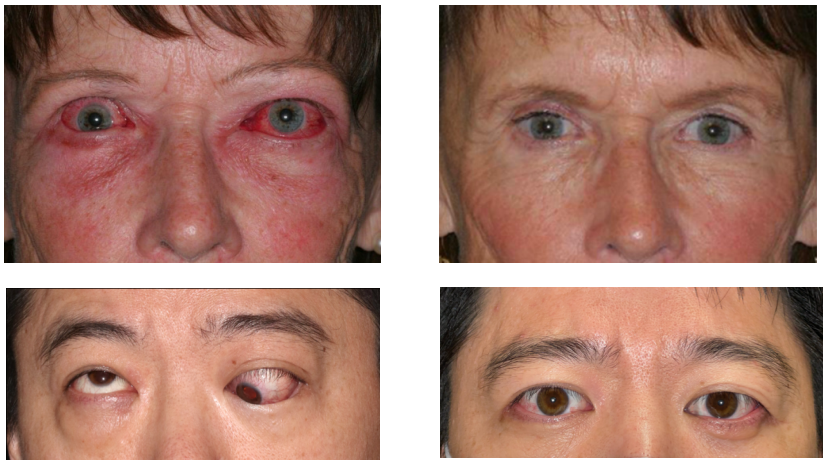
Websites

- https://stanfordhealthcare.org/medical-conditions/eyes-and-vision/thyroid-eye-disease.html
- med.stanford.edu/drkossler
- ophthalmology.stanford.edu
- med.stanford.edu/ophthalmology/research/clinical_trials
- https://stanfordhealthcare.org/trials/a/NCT05176639.html
- https://stanfordhealthcare.org/trials/a/NCT05276063.html

WHAT IS THYROID EYE DISEASE (TED)? Thyroid eye disease, also known as Graves Orbitopathy, is an autoimmune inflammatory disorder that can be vision-threatening and disfiguring. New medical therapies are emerging to prevent and treat the disabling consequences of the disease, such as bulging eyes, double vision, eyelid changes, inability to close the eyes, and loss of vision. The Byers Eye Institute at Stanford has multiple clinical trials aimed at providing targeted therapy for TED.

Treatment costs are covered for patients who meet criteria for enrollment in clinical trials.

BEFORE & AFTER OF STANFORD TED PATIENTS



OUR TEAM

Andrea Kossler, MD
Co-Director, Thyroid Eye Clinic
Director, Oculoplastic Surgery & Orbital Oncology
Associate Professor of Ophthalmology

Chrysoula Dosiou, MD, MS
Co-Director, Thyroid Eye Clinic
Program Director, Endocrinology Fellowship
Clinical Professor of Medicine - Endocrinology

Mariana Nunez
Clinical Research Manager at the Mary M. and Sash A. Spencer Center for Vision Research at the Byers Eye Institute at Stanford

Amrita Srinivasan, B.A.
Clinical Research Coordinator Associate at the Mary M. and Sash A. Spencer Center for Vision Research at the Byers Eye Institute at Stanford

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Viridian Therapeutics, Inc.
Clinical Study Protocol: VRDN-001-301

Title: A randomized, double-masked, placebo-controlled safety, tolerability, and efficacy study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants with **chronic** thyroid eye disease (TED).

OBJECTIVE

The objectives of the study are safety, tolerability, preliminary efficacy and dose-finding pharmacokinetics.

SAFETY ENDPOINTS

Adverse Events (AEs), Serious Adverse Events (SAEs) and Laboratory Assessments will be monitored and recorded throughout the duration of the study.

PRIMARY EFFICACY ENDPOINT

Proptosis Responder Rate (i.e., reduction of proptosis of ≥ 2 mm from baseline) at 3 weeks post the fifth infusion (Week 15).

SECONDARY EFFICACY ENDPOINTS

- Change from Baseline in Proptosis for the study eye as measured by exophthalmometer at Week 15
- Clinical Activity Responder Rate in the study eye at Week 15
- Change from baseline in CAS in the study eye at Week 15
- Overall Response Rate in the study eye at Week 15
- Diplopia Resolution Rate (i.e., reduction in Diplopia Score to 0 from baseline for participants with baseline Diplopia Score >0) at Week 15

OTHER ENDPOINTS

VRDN-001, IGF-1 and ADA blood levels at various timepoints pre- and post-infusions

Inclusion Criteria:
Eligible patients must meet all of the following criteria

1. Be able to understand the study procedures and the risks involved and be willing to provide written informed consent before the first study-related activity

2. Be an adult male or female participant, at least 18 years of age or older

3. Have had a clinical diagnosis of TED, with any CAS (0-7)

4. Have moderate to severe (i.e., has an appreciable impact on daily living) chronic TED associated with proptosis of ≥3 mm above normal values for race and gender in the opinion of the investigator

5. Have documented evidence of ocular symptoms or signs associated with chronic TED that began >15 months prior to study screening

6. VRDN-001 can be started concomitantly with attempts to achieve euthyroid status. Underlying thyroid status is not an inclusion criterion.

7. Not require immediate surgical ophthalmological or orbital surgery in the study eye for any reason

8. VRDN-001 can be used with caution in patients with diabetes mellitus. Diabetic participants should be monitored by their general practitioners or other appropriately trained personnel and have at study entry a glycated hemoglobin (HbA1c) of <8.5%

9. If female, have a negative serum pregnancy test at screening and further negative urine pregnancy tests immediately before each dose of study medication and following the last dose

10. Be surgically sterile males for at least 6 weeks, or agree to use an acceptable method of contraception such as a condom and a second highly effective method of contraception

11. Be willing and able to comply with all the requirements of the protocol for the entire duration of the study

Exclusion Criteria:

1. Have received prior treatment with another anti-IGF-1R therapy or any investigational agent for TED

2. Have used systemic corticosteroids for any condition, including TED, within 2 weeks prior to the first dose of study medication (topical is permitted)

3. Have received other immunosuppressive agents, including rituximab, or tocilizumab, for any condition, including TED, within 8 weeks prior to the first dose of study medication

4. Have received any other therapy for TED within 8 weeks prior to the first dose of study medication (artificial tears are permitted)

5. Have received an investigational agent for any condition within 8 weeks prior to the first dose of study medication

6. Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future

7. Have corneal decompensation in the study eye unresponsive to medical management

8. Have a decrease in CAS of ≥2 points in the study eye between screening assessment and Day -1 for participants with a screening CAS >2

9. Have a decrease in proptosis of ≥2 mm in the study eye between screening assessment and Day -1

10. Have had previous orbital irradiation for TED to the study eye's orbit

11. Have a pre-existing ophthalmic condition in the study eye which in the opinion of the Investigator, would confound interpretation of the study results

12. Have history of or screening audiometry assessment of significant (as determined by the Investigator) ear pathology, relevant ear surgery or hearing loss

13. Have inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease)

14. Be a pregnant or lactating woman

15. Be an active alcoholic or illicit drug user or considered at high risk of relapse by the Investigator

16. Have a known hypersensitivity to any of the components of VRDN-001 or placebo formulations, or prior hypersensitivity to mAbs

17. Have any condition, which in the opinion of the Investigator, would preclude inclusion in the study

18. Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2)

19. Have a positive test for active hepatitis B or hepatitis C infection

20. Have previously participated in this study or any study of VRDN-001

VasaraGen Therapeutics, Inc.
Clinical Study Protocol Study Number: VGN-TED-301

Title: A Phase 2b, Randomized, Double-Mask, Placebo-Controlled, Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Oral Linsitinib in Subjects with Active, Moderate to Severe Thyroid Eye Disease (TED) Administering linsitinib early in active TED is designed to decrease the duration and intensity of disease, to prevent the progression to inactive TED and avoid the need for surgical intervention. (ACTIVELY ENROLLING)

Primary Objective: To study the effect of linsitinib versus placebo on the proptosis responder rate (>2 mm reduction) at Week 24.

Secondary Objectives (analyzed hierarchically):

1. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 in proptosis measurement in the primary study eye.

2. Evaluate the effect of linsitinib versus placebo on the diplopia responder rate (i.e., the percentage of subjects with baseline diplopia > 0 in the primary study eye who have a reduction of ≥1 grade) at Week 24.

3. Evaluate the effect of linsitinib versus placebo on the percentage of subjects with a CAS value of 0 or 1 at Week 24 in the primary study eye.

4. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire

Inclusion criteria:

Eligible patients must meet all of the following criteria

1. Subjects must be ≥18 years of age at Screening.

2. Clinical diagnosis of Graves' Disease and/or autoimmune Hashimoto's thyroiditis associated with active moderate to severe TED with a CAS ≥ 4 (on the 7- item scale) for the most severely affected eye (primary study eye) at Screening and Baseline.

3. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life, with onset within 12 months prior to the Baseline visit

4. Subjects must be euthyroid (defined as normal TSH) or have subclinical hyperthyroidism (defined as normal FT4 and FT3 with TSH below the normal range).

5. Does not require immediate surgery, radiotherapy or other ophthalmological intervention at the time of Screening and is not planning for any such treatment during the course of the study.

6. Diabetic subjects must have HbA1c < 9.0%. Type 2 diabetic subjects who are not on insulin, must not be prescribed insulin within 60 days prior to screening. If Type 1 or Type 2 diabetic subjects are on insulin, the prescribed total daily insulin dose must not have changed by more than 20% or more than 10 units (whichever is greater) in the 60 days prior to Screening. Subjects must not have severe hypoglycemic events (requiring medical care by health care professional) in

the 60 days before screening.

7. Women of childbearing potential are required to have a negative serum pregnancy test at time of Screening and a negative urine pregnancy test at each treatment timepoint.

Exclusion criteria:

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months.

2. Corneal decompensation unresponsive to medical management.

3. Decrease in CAS of ≥ 2 points in the primary study eye between Screening and Baseline.

4. Decrease in proptosis of ≥ 2 mm in the primary study eye between Screening and Baseline.

5. Previous orbital irradiation or surgery.

6. Prior IGF-1R inhibitor therapy for any condition.

7. Any steroid use (intravenous [IV] or oral) with a cumulative dose equivalent to > 1g of methylprednisolone for the treatment of TED within 3 months of screening.

8. Corticosteroid use (including topical) for conditions other than TED within 4 weeks prior to Screening (inhaled steroids are allowed). Use of any other non-steroid immunosuppressive agent within 4 weeks prior to Screening.

9. Any previous treatment with anti-IL6 receptor, anti- CD20, (MS4A1) antibodies or monoclonal antibody within 9 months prior to Screening.

10. Selenium and/or biotin use as a treatment for TED within 3 weeks prior to screening is disqualifying and must not be restarted during the clinical trial or Follow-up period. In addition, a multivitamin containing selenium and/or biotin must be discontinued at screening and not restarted during the trial.

11. Use of an investigational agent for any condition within 30 days prior to Screening or anticipated use during the course of the trial.

12. Subjects are not permitted to be re-randomized. Note: Prior to enrollment subjects who have failed screening may be allowed to rescreen after consultation with the Medial Monitor.

13. Identified pre-existing ophthalmic or other disease that in the judgement of the Investigator, would preclude study participation or complicate interpretation of study results.

14. Ocular surgery (routine cataract surgery or subsequent YAG laser capsulotomy are allowed if performed more than 3 months prior to randomization).

15. Biopsy-proven or clinically suspected inflammatory bowel disease

16. History of QTcF prolongation; or QTcF prolongation at Screening; mean QTcF interval > 450 msec (males); and > 470 msec (females).

17. Use of drugs causing QT interval prolongation within 14 days prior to Day 1 dosing

18. Bleeding diathesis that in the judgment of the Investigator would preclude inclusion in the clinical trial.

19. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) according to age at Screening. Serum creatinine > 2 x ULN for the reference range laboratory according to age at Screening.

20. Malignant conditions being actively treated or treated in the past 12 months (with the exception of successfully

treated basal cell of the skin). Recent (within 3 months of screening) basal cell of the eyelid skin is excluded.

21. Pregnant or lactating women.

22. Current drug, marijuana or alcohol abuse, or history of either within the past 1 year, in the opinion of the Investigator, or as reported by the subject.

23. In the opinion of the Investigator, any conditions which may pose increased risk of participation for the subject or may interfere with interpretation of study results.

24. Positive Human immunodeficiency virus (HIV), hepatitis C, or hepatitis B.

Treatment Period Study Visits (Weeks 3, 6, 9, 12, 15, 18, 21 and 24)
Follow-up Period Study Visits (Weeks 28, 36, 48, 60 and 72)
A 48-week Follow-up period will occur immediately after the treatment period, with visits at Weeks 28, 36, 48, and 60 and 72. No study drug will be administered during this period. If subjects meet the response criteria at Week 24 but subsequently experience a disease relapse during the 48-week Follow-Up Period, they will have the option to enter the VGN-TED-302 Extension Study.

Extended Follow-up Period (Weeks 96 and 120)
Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff (Week 96 and Week 120, respectively).

Study Duration
The planned study duration per subject is from 2-4 weeks screening, plus an additional 120 weeks.

Lassen Therapeutics
Clinical Study Protocol: LASN01

Title: A Phase 2, Proof-of-Concept, Randomized, Double-Masked, Placebo-Controlled Study to Determine the Efficacy and Safety of LASN01 in Patients with Thyroid Eye Disease

OBJECTIVE The randomized treatment arms will evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD of 2 dose levels of LASN01 administered IV Q4W ×4 doses in anti-IGF-1R-naïve patients with TED. The open-label post-teprotumumab treatment arm will evaluate the same parameters with the high dose of LASN01.

SAFETY ENDPOINTS

Adverse Events (AEs), Serious Adverse Events (SAEs) and Laboratory Assessments will be monitored and recorded throughout the duration of the study.

PRIMARY EFFICACY ENDPOINT To assess changes in proptosis following IV administration of 2 dose levels of LASN01in patients with TED

SECONDARY EFFICACY ENDPOINTS

- To assess changes in TED-related clinical parameters following IV administration of LASN01 in patients with TED
- To assess the safety and tolerability of IV administration of LASN01 compared with placebo in patients with TED
- To characterize the pharmacokinetic profile of IV administration of LASN01 in patients with TED
- Characterize the immunogenicity of IV administration of LASN01 in patients with TED
- To assess orbital, muscle, and fat compartment volumes and confirm change in proptosis
- To explore the potential pharmacodynamic profile of IV administration of LASN01 in patients with TED

Inclusion Criteria:
Eligible patients must meet all of the following criteria

1. Male or female patients ≥18 years of age at the time of Screening

2. Clinical diagnosis of Graves' disease associated with active TED and a CAS of ≥3 on the CAS 7-point scale and proptosis ≥3 mm above normal for race and gender in the more affected eye (study eye) as determined by the PI or designee.

3. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life) determined by the PI (or designee), usually associated with ≥1 of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, proptosis ≥3 mm above normal for race and gender, and/or inconstant or constant diplopia

4. For anti-IGF-1R-naïve patients: less than 15 months from onset of TED symptoms in the study eye as determined by the PI or designee. For post-teprotumumab patients who did not respond to teprotumumab treatment for any reason, less than 24 months from initial onset of TED symptoms in the study eye, as determined by the PI or designee. For postteprotumumab patients who have reactivation of disease after responding to treatment, less than 15 months from the renewed onset of TED symptoms in the study eye, as determined by the PI or designee.

5. No previous:
- Medical treatment for TED, with the exception of:
    - o Local supportive measures
    - o Mycophenolate, and oral or injectable steroids if the maximum cumulative dose is ≤4.5 g methylprednisolone or equivalent with ≥6 weeks between last administration of oral steroids and/or mycophenolate and Screening
    - o Previous use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation, more than 9 months before randomization
    - o Previous use of any other immunomodulating therapy more than 3 months before randomization unless approved by the Medical Monitor

• **For the post-teprotumumab treatment arm only:** Previous treatment with teprotumumab is required provided the last dose was administered more than 100 days (5 half-lives) prior to Screening. A history of other anti-IGF-1R treatments for TED is not permitted.
• Surgical treatment in the study eye with the exception of routine or minor procedures at least 3 months before Screening as determined by the PI or designee
• Orbital irradiation/radiotherapy

6. Euthyroid or with mild hypo- or hyper-thyroidism defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits (every effort should be made to correct the mild hypo- or hyper-thyroidism promptly). Patients should otherwise be on stable medical regimen and unlikely to require adjustment of thyroid medications during the 12-week treatment period as determined by the PI or appropriate designee.

7. Does not require immediate surgical intervention or procedure and is not planning radioactive iodine treatment during the course of the study

8. WOCBP patients with male partners and WOCBP partners of male patients must be nonpregnant, nonlactating, use a highly effective method of contraception, unless considered permanently surgically sterile for >6 months (ie, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), from the start of the study and for ≥90 days following the last dose of study drug or until the EOS visit, whichever is later. Males must use a highly effective method of contraception unless considered permanently surgically sterile following a bilateral orchidectomy

9. Able to comprehend and willing to sign an ICF and understand and comply with the requirements of the study

Exclusion Criteria

1. Patients with 2 mm proptosis decrease between Screening and Baseline, or a 1-point decrease on the CAS 7-point scale in any 2 weeks during the Screening period and patients that no longer meet the eligibility criteria at the Baseline ophthalmology assessment.

2. Patients with a known decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 3 lines on the ETDRS chart (or equivalent), new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months before Screening; or any known optic neuropathy or compression or any neurologic or neuroophthalmologic condition that may result in visual field loss.

3. Previous or any planned orbital irradiation/ radiotherapy or planned surgery for TED during the study period (ie, treatment and FU)

4. Any planned procedures or hospitalizations during the study. EXCEPTION: minor or routine procedures that do not interfere with the conduct of the study may be approved by the PI or designee

5. Poor peripheral venous access that would preclude study assessments

6. Use of oral and/or IV corticosteroid for conditions other than TED in the 6 weeks before Screening (topical steroids for conditions other than TED are allowed)

7. Active autoimmune disorder(s) requiring or likely to require treatment (other than Grave's disease and TED) that would interfere with study assessments, as determined by the PI or designee

8. Any liver function test result (including aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, or total bilirubin) ≥1.5× the upper limit of normal; levels may be repeated once at the discretion of the PI or designee during the Screening period or before dosing, and the lower of the 2 readings may be used (note that subjects with Gilbert's Syndrome will not be excluded)

9. Previous use of an anti-IGF-1R targeted treatment at any time.
a. For the post-teprotumumab treatment arm only: treatment with teprotumumab is required with the last dose administered at least 100 days (5 half-lives) prior to Screening

10. Use of selenium within 3 weeks before randomization or expected use during the clinical trial (multivitamins that include selenium are allowed in usual doses)

11. Use or expected use of biotin (including multivitamins that include biotin) within 2 days before any laboratory collection

12. Receipt of blood products within 2 months before Day 1

13. Donation of blood >400 mL within 30 days before Day 1 or planned through EOS visit, inclusive, or plasma >400 mL within 7 days before Day1 through EOS visit, inclusive

14. Current or history of drug or alcohol abuse within the previous 2 years in the opinion of the PI or as reported by the patient

15. Known hypersensitivity to any of the components of LASN01 or placebo formulations or previous hypersensitivity to monoclonal antibodies

16. Previous participation in a study investigating LASN01

17. Currently receiving or have received within 4 weeks or 5 half-lives (whichever was greater) before Screening or any other therapy that, in the opinion of the PI, may compromise the objectives of the study

18. Any acute or chronic condition or any other reason that, in the opinion of the PI, would limit the patient's ability to participate in and complete this clinical study