Thyroid Eye Disease Clinical Trials

AT STANFORD UNIVERSITY SCHOOL OF MEDICINE

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 or 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 enrolled in clinical trials who meet criteria.

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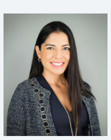
Websites

- 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

BEFORE & AFTER OF STANFORD TED PATIENTS


Patient and Dr. Kossler after TED treatment completion

OUR TEAM



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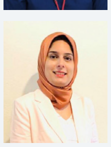

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Horizon Therapeutics, Inc.
Clinical Study Protocol: HZNP-TEP-402

Sponsor / Study Title: A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab

Primary Objective: To evaluate the safety, efficacy and tolerability of 3 treatment durations (4, 8 and 16 infusions) and the need for re-treatment.

Other Objectives:

1. Change in proptosis measurement in the study eye.

2. Proptosis responder rate (i.e., the percentage of patients with a ≥2-mm reduction from Baseline in the study eye.

3. Binocular diplopia responder rate (i.e., the percentage of patients with baseline binocular diplopia >0 who have a reduction of ≥1 grade and/or complete resolution.

4. Change from Baseline in the Quality of Life (GO-QoL) questionnaire.

5. Durability of complete response at the end of the Initial Follow-up Period.

6. CAS:•percentage of patients with a CAS of 0 or 1 who had active disease (CAS ≥3) at Baseline

7. Percentage of patients with Common Terminology Criteria for Adverse Events (CTCAE)version 5.0 Grade 3 or higher AEs.

8. Effect of teprotumumab on the mean change from Baseline over time in serum biomarkers for patients with a Baseline CAS ≥3.

Inclusion Criteria:

Eligible patients must meet all of the following criteria

1. Written informed consent

2. Age between 18 and 80 years

3. Initial diagnosis of TED within 7 years prior to screening.

4. Proptosis >3 mm above normal for race and gender.

5. Euthyroid or mild hypo-or hyperthyroidism (defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits) at screening.

6. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the trial.

7. Diabetic patients must have HbA1c ≤8.0% at Screening.

8. Patients with a history of IBD (ulcerative colitis or Crohn's disease) must be in clinical remission for at least 3 months, with no history of bowel surgery within 6 months prior to Screening.

9. Women of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy tests at all protocol-specified timepoints.

10. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

Exclusion Criteria:

1. Decreased best-corrected visual acuity due to optic neuropathy within the last 6months.

2. Corneal decompensation unresponsive to medical management.

3. Prior orbital irradiation, orbital decompression or strabismus surgery.

4. Use of any steroid (intravenous [IV], oral, steroid eye drops) for the treatment of TED or other conditions within 3 weeks prior to Screening.

5. Any treatment with rituximab (Rituxan® or MabThera®) within 12months prior to the first infusion of teprotumumab or tocilizumab (Actemra® or Roactemra®) within 6months prior to the first infusion of teprotumumab. Use of any other non-steroid immunosuppressive agent within 3months prior to the first infusion of teprotumumab.

6. Any previous treatment with teprotumumab.

7. Treatment with any mAb within 3months prior to Screening.

8. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).

9. Pregnant or lactating women.

10. Human immunodeficiency virus, untreated or positive viral load for hepatitis C or hepatitis B infections.

THE HEARING IMPAIRMENT SUB- STUDY Phase 3b/4 TEP-402

THE HEARING IMPAIRMENT SUB- STUDY Phase 3b/4 TEP-402

Purpose: To investigate the hearing impairment among thyroid eye disease (TED) patients treated with teprotumumab by assessing the incidence rate of hearing impairment, identifying risk factors and evaluating the reversibility if patients experience hearing impairment.

OBJECTIVES

1. To assess the incidence of hearing impairment among TED patients treated with teprotumumab.

2. To assess the reversibility of hearing impairment at 3 or 6 months post teprotumumab treatment.

3. To explore potential risk factors associated with ototoxicity among TED patients treated with teprotumumab.

For all patients in the hearing impairment sub-study, an audiogram will be conducted at Screening and Weeks 12 and 24; at Weeks 39 and 54 (for proptosis responders or patients who choose not to receive a second course); and at Weeks 36, 48 and 60 (for proptosis non-responders). In addition, any patient experiencing hearing impairment should contact the investigational site for evaluation and assessments.

VasaraGen Therapeutics, Inc.

Clinical Study Protocol Study Number: Vgn-Ted-301

Title: A APhase 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.

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 overall score.

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.

Viridian Therapeutics, Inc.

Clinical Study Protocol: VRDN-001-101

Title: A Phase 1/2, multiple ascending dose (MAD) safety, tolerability and efficacy study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in subjects with 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 6 weeks in the MAD study, and 24 weeks in the extension cohorts.

SECONDARY EFFICACY ENDPOINTS

Proptosis Responder Rate (i.e., reduction of proptosis of ≥ 2 mm from baseline) at 12 weeks in the MAD study. Change from Baseline at 6 and 12 weeks in the MAD study, and 24 and 52 weeks in the extension cohorts in the following:

- Change in measurement of proptosis by MRI
- volume of orbital fat by MRI
- volume of extraocular muscles by MRI
- facial fat volume by MRI
- Change in measurement of proptosis by exophthalmometer
- Change in digital measurement of eye color
- Change in digital and manual measurement of lid retraction
- Change in clinical activity score (CAS)
- Change in subjective diplopia score
- Change in Graves' Orbitopathy-Quality of Life (GO-QoL) combined score
- Change in Snellen best corrected visual acuity (BCVA)

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. Provide written informed consent

2. Age 18 years of age or older

3. Have had a clinical diagnosis of Graves' disease associated with TED with a CAS of ≥4 on the 7-item scale for the study eye

4. Have moderate to severe (an appreciable impact on daily living) active TED

5. Have documented evidence of ocular symptoms or signs associated with TED that began within 1 year prior to study screening

6. Be euthyroid, or with only mild hyper- or hypothyroidism defined as free thyroxine (FT4) and free triiodothyronine (FT3) levels <50% above or below the normal limits at screening. Thyroidectomy is NOT an exclusion

7. Not require immediate surgical ophthalmological intervention in the study eye for any reason.

8. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels <3 in times the upper limit of normal (ULN) or serum creatinine <1.5 times the ULN for their age

9. Diabetic subjects must have a HbA1c of <8.5% with no new diabetic medication started within 12 weeks, or have had more than a 10% change in the dose of a currently prescribed diabetic medication within the previous 12 weeks

10. Have a negative serum pregnancy test at screening and further negative urine tests immediately before

each dose of study medication and other applicable visits. as described in Appendices 1B and 1C if the subject is a woman of childbearing potential (including those with <2 years since the onset of menopause, amenorrhea for <1 year, or not surgically sterile); such subjects must agree to use an acceptable method of contraception such as a condom and a second highly effective contraception as described in from Screening up to and including 100 days after the last dose of study medication.

11. 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 contraception as described in from Screening up to and including 100 days after the last dose of study medication

12. 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 mAb or previously participated in this study

2. Have decreased best corrected visual acuity (BCVA) in the study eye, defined as ≥2 Snellen lines, due to optic neuropathy, new visual field defect, or color defect secondary to optic nerve involvement within previous 6 months

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

4. Have a decrease in CAS of ≥2 points between screening assessment and Day 1

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

6. Have had previous orbital irradiation or surgery in the study eye for TED

7. Have known history of clinically significant ear pathology, ear surgery or hearing impairment

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

9. Have used oral corticosteroids for any condition, including TED, within 4 weeks prior to the first dose of study medication (topical is permitted)

10. Have received rituximab, or tocilizumab, or other immunosuppressive agent within 90 days prior to the first dose of study medication

11. Have received an investigational agent for any condition within 60 days

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

13. Be a pregnant or lactating woman

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

15. Have a known hypersensitivity to any of the components of VRDN-001 or placebo formulations, or prior hypersensitivity to monoclonal antibodies (mAbs)

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

17. Have a positive test to human immunodeficiency virus (HIV-1 and HIV-2) or active hepatitis B or hepatitis C infection

Colorado Multiple Institutional Review Board
(COMIRB Protocol)

Title: Outcomes of clinical interventions for diplopia and/or compressive optic neuropathy in patients with Thyroid Eye Disease

Objective: The purpose of this study is to evaluate the efficacy of various treatments (surveillance, teprotumumab, orbital radiation and/or surgery) for patients with diplopia and/or compressive optic neuropathy due to thyroid eye disease (TED).

Inclusion Criteria:
- 18 years of age or older and provide informed consent
- Clinical diagnosis of TED with either of the following:
o Diplopia group: baseline Diplopia Questionnaire (DQ) Score of ≥40 with quantifiable strabismus using alternate cover testing
o CON group: compressive optic neuropathy as evidenced by Humphrey visual field mean deviation (MD) worse than -3 dB with radiographic (CT or MRI) confirmation of orbital apex crowding in one or both eyes.
- Patients who have already decided to proceed with any management option (surveillance, teprotumumab, corticosteroids, orbital radiation, and/or surgery)

Exclusion Criteria:
- Prior orbital decompression or strabismus surgery, scheduled elective orbital decompression and/or strabismus surgery within 6 months of anticipated baseline study visit,
- Other causes of binocular diplopia and/or strabismus (childhood or latent strabismus, cranial nerve palsy, myasthenia gravis), and monocular diplopia that accounts for patient symptomatology,
- history of amblyopia in either eye,
- optic neuropathy not related to TED,
- retinal disease leading to decreased MD on Humphrey visual fields.

Primary outcome measures:
Diplopia: Improvement of ≥30 points on the DQ at the 6-month visit.
CON : Improvement of ≥3 dB on Humphrey visual field mean deviation in the worse-seeing (study) eye at the 6-month visit.

Secondary outcomes:
Diplopia: Improvement in EOM function (increased range of motion), reduction of the magnitude of deviation in worst position of gaze by ≥15 prism diopters, decreased EOM volume on MRI, stereopsis, and reduced discomfort with eye movement.

CON: Improvement in low-contrast visual acuity, improved color vision by pseudo-isochromatic plate assessment, decreased EOM volume at the orbital apex, preservation of OCT findings including macular ganglion cell complex and retinal nerve fiber layers (RNFL), and improved high-contrast visual acuity.

Follow up: 6, 12, 18, 24, 36, 52, 78, and 104 weeks following the initiation of teprotumumab therapy. Patients on traditional therapy may be seen less frequently at the treating physicians' discretion but typically at a minimum of 24, 52, 78, and 104 weeks from the initiation of therapy/surgery. Timepoints for data extraction and questionnaire completion will follow this schedule for each of the indicated interventions (teprotumumab vs other treatment).