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Drug Class Update with New Drug Evaluation: Thyroid Eye Disease, Monoclonal Antibodies

Date of Review: October 2026

Generic Name: Veligrotug-vvze

Date of Last Review: April 2024
Dates of Literature Search: 01/16/2024 - 08/05/2026
Brand Name (Manufacturer): Lumvoa (Viridian Therapeutics)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of medications for thyroid eye disease (TED).
- Analyze the data supporting the efficacy and safety of veligrotug, a new therapy for TED, and determine its appropriate place in therapy.

Plain Language Summary:

- Thyroid eye disease, sometimes also called Graves' Orbitopathy, is a disease that can result in sore, gritty, or red eyes, double vision, reduced sight, and blindness. Thyroid eye disease can range from mild, moderate, severe, or sight threatening. Thyroid eye disease is also either "active" where symptoms usually get worse, or "inactive", where symptoms stay stable but may still be severe.
- Veligrotug is a new medication for thyroid eye disease that can reduce eye bulging more than placebo (a look-alike that has no active medicine). Treating two patients with veligrotug could reduce eye bulging for one patient.
- Veligrotug and teprotumumab are both medicines for thyroid eye disease, and they work in the same way. There is no evidence that one is better than the other or that using one when the other has not reduced eye bulging in a particular person will help.
- Drug Use Research and Management recommends that Oregon Health Plan (OHP) pay for veligrotug for people with thyroid eye disease with prior authorization. Prior authorization is when a prescriber must explain to OHP why a medicine is needed and ensure certain safety assessments are made before use.

Research Questions:

1. What is the efficacy and safety of veligrotug for the treatment of TED?
2. Is there comparative evidence for treatments of TED?
3. Are there sub-populations (based on age, gender, ethnicity, comorbidities, disease duration, or severity) of patients with TED for which insulin-like growth factor-1 receptor (IGF-1R) inhibitors is more effective or associated with fewer adverse events?

Conclusions:

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- Two clinical trials[1-3] (one unpublished) of veligrotug and one Food and Drug Administration (FDA) safety labeling edit[4] were found since previous review of TED.
- There is no head-to-head data for insulin-like growth factor-1 receptor (IGF-1R) inhibitors.
- Evidence from a single randomized controlled trial (RCT) in patients with acute TED found veligrotug had improved proptosis response rate (PRR) versus placebo measured by Hertel exophthalmometry (70% vs. 5%; difference 65%, 95% confidence interval [CI] 52-78; P < 0.001; number needed to treat [NNT] 2; low quality evidence) and when assessed by magnetic resonance imaging (MRI) or computed topography (CT) (71% vs. 9%; difference 61%, 95% CI 40-83; P < 0.001; NNT 2; low-quality evidence) at week 15.[3] Selection, detection, reporting, and other bias were unclear based on published information.
- Evidence from a single RCT in patients with chronic TED found a statistically significant improvement in PRR compared to placebo (57% veligrotug vs. 8% placebo; 49% difference, 95% CI 38 to 60%; NNT 2; risk of bias unable to be assessed).[1,5]
- There is no evidence showing different response to treatment or safety to TED therapies based on subgroup demographics.
- There is insufficient evidence for retreatment with the same or a different IGF-1R monoclonal antibody after inadequate response to initial therapy.

Recommendations:
- Change class name to Insulin-like Growth Factor-1 Receptor Inhibitors.
- Make veligrotug non-preferred on the PDL and modify PA to accommodate both agents in IGF-1R inhibitor class.
- After evaluation of costs in executive session, no additional changes were made.

Summary of Prior Reviews and Current Policy
- Monoclonal antibodies used for TED were first evaluated in 2020 with the initial approval of teprotumumab where it was made non-preferred and clinical prior authorization criteria were implemented. Evidence for teprotumumab approval was based on a phase 2 and a phase 3 trial of patients with acute TED which showed moderate quality evidence that:
    a. Teprotumumab showed a greater response rate compared to placebo using a composite endpoint of proptosis reduction of at least 2 mm [69% vs. 20%; odds ratio (OR) 8.86, 95% confidence interval (CI) 3.29 to 23.8; P<0.001); absolute risk reduction (ARR) 49%, NNT 3][6] and clinical activity score (CAS) reduction of at least 2 points [78% vs 7%; difference 72.46%, 95% CI 57.57% to 87.35%; P<0.001; ARR 71%, NNT 2] over a period of 24 weeks.[7]
    b. Teprotumumab showed a reduction of proptosis of at least 2 mm compared to placebo over a period of 24 weeks (Change from baseline -2.46±0.2mm vs -0.15±0.19mm, P<0.001)[6] (83% vs. 10%; difference 73%, 95% CI 59% to 88%, p<0.001; ARR 73%, NNT 2).[7]
- A PA update was completed in 2024 to review updated guidelines, an expanded indication for teprotumumab for treatment of TED regardless of activity or duration, and review updated warnings and precautions in the prescribing information. Updated warnings included: screening for hyperglycemia prior to use and monitoring during use, while ensuring those with hyperglycemia or pre-existing diabetes are under appropriate control during therapy, in addition to warnings about risk of hearing loss, which can sometimes be permanent. The PA criteria were modified to accommodate the new indication and guideline recommendations.
    a. The indication expansion was based on a single, double blind, RCT in patients with inactive TED. Teprotumumab reduced proptosis more than placebo from baseline to week 24 (teprotumumab -2.41 mm vs. placebo -0.92; difference -1.48 mm; 95% CI -2.28 to -0.69; P=0.0004; low quality evidence).[8] Proptosis response (≥2 mm reduction from baseline) was achieved in 61.9% of teprotumumab patients compared to 25.0% of placebo patients (absolute risk reduction [ARR] 36.9%; 95% CI 5.4 to 59.2%; P=0.0134; NNT 3; low quality evidence).[8]
    b. Data on retreatment with teprotumumab in patients who have not had an adequate response after initial therapy, or have a disease flare after treatment, is insufficient.

Background:

Hyperthyroidism, caused by an inappropriately high synthesis and secretion of thyroid hormones, is a relatively common condition in the United States (US).[9] Overt hyperthyroidism affects an estimated 0.5% of adults, while subclinical hyperthyroidism has a prevalence of 0.7%.[9] Graves' disease (GD) is the most common cause of hyperthyroidism and accounts for 50-80% of the cases.[10] The female to male prevalence of GD is 5:1.[10]

Thyroid eye disease is an orbital inflammatory disease that develops in conjunction with autoimmune thyroid disorders. It is also known in the medical literature as dysthyroid eye disease, thyroid orbitopathy, thyroid-associated ophthalmopathy, and thyroid-associated orbitopathy. When associated specifically with GD, additional names include Graves' eye disease, Graves' orbitopathy, Graves' ophthalmopathy, and Graves' dysthyroid opthalmopathy.[11,12] TED is the result of inflammation in both the orbital connective tissue and extraocular muscles, with eventual fibrosis of the extraocular muscles and adipogenesis within the orbits.[13] Patient symptoms may include sore, gritty, or red eyes, double vision, reduction of vision, and loss of vision.[14] Clinical signs include periorbital edema, lid lag, lid retraction, chemosis, exophthalmos, and dysmotility. More severe forms may result in exposure keratopathy, diplopia, and compressive optic neuropathy. Vision loss can occur about 3-7% of those with TED due to corneal exposure (exposure keratopathy) or compressive optic neuropathy (dysthyroid optic neuropathy).[14,15] Mild cases may still result in significant quality of life (QoL) reductions in affected patients.[13,14] TED generally follows a biphasic course and is usually self-limiting.[16,17] There is an 18-36 month active phase with ongoing inflammation accompanied by rapid deterioration, followed by a stable or inactive phase that often results in regression of many signs and symptoms toward baseline, though vision loss may be permanent.[9,16,17] A group of 59 patients with TED who had never received medical or surgical treatment for eye disease at presentation to a specialty thyroid-eye clinic were then followed for a median of 12 months to study the natural disease course; 22.0% improved substantially, 42.4% showed minor improvement, 22% were unchanged, and 13.5% continued to deteriorate necessitating immunosuppressant treatment.[18]

Roughly 90% of TED cases are in patients with current or a history of GD. Other thyroid disorders, such as Hashimoto's thyroiditis, an autoimmune condition generally resulting in hypothyroidism, also have been associated with TED. Severity is usually classified as sight-threatening, moderate to severe, and mild (**Table 1**).[16] Symptomatic TED develops in roughly 30-50% of patients with GD,[9,13,14] though MRI or CT have shown extraocular muscle enlargement in as many as 70% of patients.[13] Only 5% of patients with GD go on to develop moderate or severe TED.[9] Smoking increases the risk of developing TED by 7 to 8 fold,[15] as well as the severity of TED, particularly after radioactive iodine (RAI) therapy for hyperthyroidism.[16] There is a demonstrated dose-response relationship to number of cigarettes/day and likelihood of TED development. Continued smoking may hinder the effectiveness of historical treatments such as corticosteroids, though data are lacking for if this remains true with newer therapies.[9,16] Women are more likely to develop GD and men may be at higher risk of developing severe TED. However, the sex-related risk is unclear and may be associated with historical population tobacco-use patterns.[9] More severe cases of TED are generally seen in elderly patients.[9] Incidence peaks during the 5th and 6th decades of life with a median age at diagnosis of 43 years.[9,15] Incidence rates of 16/100,000 in women and 2.9/100,000 in men, with an overall calculated prevalence of 0.25% have been reported.[14] Additional risk factors for TED development in the setting of GD are RAI use for definitive treatment of hyperthyroidism, untreated hyperthyroidism, and post-treatment hypothyroidism.[9] Most patients with active TED at time of RAI receive prophylactic oral corticosteroids (CS) beginning 1-3 days post-RAI dosed at 0.4-0.5 mg/kg/day prednisone equivalent for one month, then tapered over 2 months, to prevent TED progression.[9] Thyroid-stimulating hormone receptor autoantibodies are also an independent risk factor for severity and progression of TED.[17] A family history of TED is present in 61% of TED patients.[15] In patients who receive surgical treatment for GD, total thyroidectomy is more effective at preventing recurrent hyperthyroidism than subtotal thyroidectomy (including both bilateral subtotal thyroidectomy and the Dunhill procedure).[10] However, surgery type does not affect regression of TED.[10] Antithyroid medications (e.g. methimazole, propylthiouracil) may be used to manage hyperthyroidism without affecting the disease course of TED.[16]

The treatment of active and inactive TED changed with the approval of the first IGF-1R inhibitor, teprotumumab, in 2020. Guidelines from the American Thyroid Association (ATA) and European Thyroid Association (ETA) published in 2022 list intravenous (IV) glucocorticoid therapy as the preferred treatment for active moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia.[19] Teprotumumab is preferred in patients with active moderate-to-severe TED with significant proptosis and/or diplopia.[19] "Significant proptosis" is usually defined in the literature as ≥3 mm above the upper limit for race and sex. The authors felt patients with moderate-to severe TED and a degree of proptosis of <3 mm above the upper limit for race and sex could also be defined as "significant proptosis" if it sufficiently impacted daily life and would justify the risks of treatment, in addition to using the standard numeric threshold.[19] Rituximab and tocilizumab are recommended in for certain patients, though neither is FDA approved for use in TED. Radiotherapy and surgery may also be options for some patients, with orbital decompression sometimes needed for dysthyroid optic neuropathy requiring urgent treatment and not responsive to glucocorticoids. [19]

The Clinical Activity Score is commonly used and it differentiates active from non-active forms of TED (**Table 2**). The 10-point (10 item) version requires 2 clinical examinations as 3 items reflect change in clinical signs. A score of 3 of 7 at first examination or 4 of 10 after repeat examination indicates active disease, though a score of at least 4 of 7 has been required in some medication trials.[14] The European Group of Graves' Orbitopathy (EUGOGO) modified this scoring to only use the 7 items that do not require repeat examination, and excludes change in visual acuity, diplopia, or proptosis.[14] CAS was originally validated based on its ability to correctly predict response to 12 weeks of tapered oral prednisone or orbital radiotherapy treatment, in 43 patients with moderate to severe Graves' ophthalmopathy.[20] These patients were 20-75 years old and had been euthyroid for at least 3 months.[20] This validation study determined that a CAS at least 4 of 7 on the initial assessment had a sensitivity of 55% and specificity of 86%. With an assumed 35% non-response rate, this led to a positive predictive value of 80% and negative predictive value of 64% of a change of at least one NO SPECS (an older classification system) class.[20] It is important to note that increased sympathetic state caused by hyperthyroidism can result in lid retraction or stare. When these are present without associated eye changes, they are not thought to be part of TED and should be scored as absent on CAS.[9]

Table 1: EUGOGO Disease Severity for Graves' Orbitopathy[21]

Severity	Specific signs/symptoms	General Management
Mild	Typically, one or more of following: minor lid retraction ≤2mm, mild soft tissue involvement, exophthalmos < 3mm above normal for race and gender, transient or no diplopia, corneal exposure responsive to lubricants.	• Minor impact on daily life • Disease not sufficient to justify immunosuppressive or surgical treatment
Moderate to Severe	Typically, one or more of following: Lid retraction ≥ 2mm, moderate-severe soft tissue involvement, exophthalmos ≥3mm above normal for race and gender, inconstant or constant diplopia	• Not sight threatening • Disease has sufficient impact on daily life to justify immunosuppression (active disease) or surgical intervention (inactive disease)
Sight threatening	Dysthyroid optic neuropathy and/or corneal breakdown	• Immediate intervention needed

Table 2: Clinical Activity Score[9,17]

Elements	**Each visit**	**Comparison with previous visit**	**Score**
Painful feeling behind the globe over last 4 weeks	X		1

Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (flesh body at medial angle of the eye) *and/or plica**	X		1
Increase in proptosis greater than or equal to 2 mm		X	1
Decreased eye movements greater than or equal to 5° *(or greater than or equal to 8°)** in any direction		X	1
Decreased visual acuity greater than or equal to 1 line on Snellen chart		X	1

* Modifications for EUGOGO CAS in italics

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 13 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:
None

After review, 1 guideline comparison[22] was excluded as both guidelines have been previously reviewed.

New Formulations or Indications:
None

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts[4]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Teprotumumab	TEPEZZA	8/2025	Warnings and Precautions	Addition of new subsection: 5.2 Inflammatory Bowel Disease TEPEZZA may cause an exacerbation of inflammatory bowel disease (IBD). IBD has been reported in some patients without a prior diagnosis of IBD. Monitor patients for signs and symptoms of IBD. If IBD exacerbation is suspected, discontinue use of TEPEZZA.

Randomized Controlled Trials:
A total of 24 citations were manually reviewed from the initial literature search. After further review, 24 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 4**.

Clinical Efficacy:
Veligrotug (LUMVOA) is an IGF-1R inhibitor approved by the FDA for treatment of TED regardless of thyroid eye disease activity or duration in June 2026.[5] It is the second medication in this pharmacologic class with this indication after teprotumumab (TEPEZZA).[4] It is administered by IV infusion every 3 weeks for 5 total doses.[5]

The FDA approval of veligrotug was based on two, phase 3, double-blind, placebo controlled, RCTs called THRIVE (NCT05176639) and THRIVE 2 (NCT06021054).[1-3] THRIVE included patients with active TED while THRIVE-2, which is unpublished, enrolled patients with chronic TED. In THRIVE, patients were randomized 2:1 to 10 mg/kg veligrotug every 3 weeks by IV infusion (n=75) or matching placebo (n=38).[3] An early protocol allowed for a 5-time infusion and 8-time infusion regimen and this was amended to 5 infusions only.[3] Fourteen patients receiving more than 5 infusions were included in the week 15 efficacy and safety analysis and excluded from the week 52 durability analysis due to the additional doses.[3]

Efficacy endpoints varied by country/region.[3] The primary end point in North American was PRR at week 15, defined as 2 mm or more proptosis reduction from baseline in study eye without 2 mm or more increase in fellow eye.[3] Measurements were performed using Hertel exophthalmometry and by MRI/CT.[3] The overall responder rate (ORR) at week 15 was the primary endpoint in Europe and Australia, requiring a proptosis response plus a 2 or more point improvement

in the CAS without corresponding 2 or more increase in the fellow eye.[3] A 7-point CAS was used, including presence absence of signs and symptoms of inflammation.[3]

Baseline demographics were generally well matched. At week 15 patients taking veligrotug had improved rates of PRR versus placebo measured by Hertel exophthalmometry (70% vs. 5%; P < 0.001) and MRI/CT (71% vs. 9%; P < 0.001) and significantly improved ORR by Hertel (67% vs. 5%; P < 0.001) **(Table 5)**.[3] Response was maintained in 70% of patients (n=30 with data available) who received veligrotug at week 52.[3] Nineteen patients were not included in the week 52 results, 8 patients discontinued the follow-up or were missing week 52 data, and 11 patients that had been randomized to the 8-infusion veligrotug regimen.

Exact method of randomization (e.g., interactive web response system) was not described, and method for determining "normal" proptosis for race and sex was unclear in significant portion of patients listed without race information, making risk of selection bias difficult to assess. Unblinding could be possible with rapid response seen in some patient or side effects given continuity of Hertel examiner, however results correlated with MRI/CT proptosis response where blinding would not have been affected. The full protocol was not found online. Outcomes and NNT of 2 or 3 for most endpoints are similar to results seen in teprotumumab pivotal trials. Underlying thyroid status was not an inclusion criterion in the veligrotug trials in contrast to teprotumumab and onset of TED for treatment of acute disease varied between the two medications (within 9 months for teprotumumab and 15 months for veligrotug), though this is likely a clinically insignificant difference as both also have data for chronic disease.

THRIVE-2 was of similar design to THRIVE, with the inclusion of patients with chronic TED (onset more than 15 months before enrollment) rather than acute disease. The study is unpublished and was data extracted from a conference abstract[1], the prescribing information[5], and clinicaltrials.gov.[2] The primary endpoint of PRR was statistically significant compared to placebo (57% veligrotug vs. 8% placebo; 49% difference, 95% CI 38 to 60%; NNT 2).[1,5] Available results and trial details are available in **Table 5**.

Clinical Safety:
Veligrotug has no label contraindications but warnings and precautions include the risk of infusion reactions, inflammatory bowel disease, hyperglycemia, and hearing impairment including hearing loss.[5] Risk of fetal harm in pregnancy is expected based on the mechanism of action with contraception recommended prior to, during, and for 6 months after treatment in patients of reproductive potential.

There were no serious adverse events reported in the THRIVE study.[3] Three patients in the veligrotug group discontinued due to adverse events.[3] These were dizziness and hyperthyroidism, both unrelated to treatment, and postmenopausal hemorrhage, considered mild and treatment related.[3] In addition to the special warnings in labeling, other outcomes of note were higher rates of menstrual disorders and muscle spasms in both studies **(Table 4)**.

Table 4: Adverse Reactions Occurring in 5% or more of patients treated with veligrotug and more frequent than placebo (THRIVE and THRIVE-2)[5]

Adverse reaction	**Veligrotug N=200 N (%)**	**Placebo N=101 N (%)**
Muscle Spasms	79 (40%)	7 (7%)
Headache	34 (17%)	14 (14%)
Hearing Impairment	29 (15%)	6 (6%)
Hyperglycemia	25 (13%)	5 (5%)

Fatigue	25 (13%)	11 (11%)
Diarrhea	22 (11%)	7 (7%)
Ear Discomfort	19 (10%)	3 (3%)
Infusion-related reaction	18 (9%)	2 (2%)
Nausea	15 (8%)	6 (6%)
Nasopharyngitis	14 (7%)	1 (1%)
Increased creatine phosphokinase (blood)	12 (6%)	1 (1%)
Dry skin	12 (6%)	2 (2%)
Hypertension	11 (6%)	5 (5%)

Look-alike / Sound-alike Error Risk Potential: Lumigan (bimatoprost) eye drops

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction of TED complications (including vision loss, need for surgery, need for orbital irradiation)
2) Change in Severity of TED
3) Improved Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Proptosis responder rate at week 15

Table 5**. Comparative Evidence Table.**

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/ NNT**	**Safety Outcomes**	**ARR/ NNH**	**Risk of Bias/ Applicability**
1. THRIVE[3] NCT05176639 Phase 3, PC, DB, MC, RCT	1. Veligrotug 10mg/kg IV every 3 weeks x 5 doses 2. Placebo IV every 3 weeks x 5 doses 2:1 randomization	Demographics: -Age ~ 49 y -Female:75% veligrotug, 82% placebo -White: 68% veligrotug, 50% placebo -Asian: 4% veligrotug, 16% placebo -Black: 5% veligrotug, 8% placebo -Unknown, other, or unreported: 23% veligrotug, 26% placebo	ITT: 1. 75 2. 38 Attrition: 1. 3 (4%) 2. 0	Primary Endpoint for North America: PRR at week 15 By Hertel: 1. 70% 2. 5% difference 65% (95% CI 52-78) P<0.001 By MRI/CT: 1. 71% 2. 9% difference 61% (95% CI 40-83)	65%/2 61%/2	AE: 1. 88% 2. 66% SAE: None Discontinuations due to AE: 1. 3 2. 0 Hearing impairment though week 15:	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization by "independent service provider". Method not detailed. Stratified by baseline proptosis (>/= 23 mm or not). Proptosis inclusion criteria required 3 mm or more above normal. Proptosis "normal" is defined by race and sex; 23% of patients were reported as unknown, other, or unreported race. Performance Bias: (Low) Patients and site personnel (except pharmacy) masked through week 15 (3 weeks after 5th infusion) and through week 52 for some patients when permitted by local authorities. Placebo and active infusions were indistinguishable.

		-Current tobacco use: 17% veligrotug, 16% placebo -Reduced hearing: 13% veligrotug, 8% placebo -Proptosis (Hertel): 23.2mm both groups -Proptosis (MRI/CT): 22.5mm veligrotug, 22.4mm placebo -CAS: 4.5 veligrotug, 4.8 placebo -Time since TED onset (months): 8.2 veligrotug, 7.6 placebo -Diplopia ~67-68% <u>Key Inclusion Criteria</u>: -≥ 18 years of age -moderate-severe, active TED -symptom onset < 15 months of screening -CAS ≥ 3 -proptosis ≥ 3 mm above normal -1 or more symptoms: --lid retraction 2mm or more --moderate-severe soft tissue involvement --inconstant or constant diplopia --spontaneous retrobulbar pain or pain on eye movement --swelling of conjunctiva, eyelids, or plica --redness of eyes or plica (in study eye) -HbA1C <8.5% <u>Key Exclusion Criteria</u> -prior orbital irradiation		P<0.001 <u>Primary Endpoint (outside North America)</u>: ORR at week 15 1. 67% 2. 5% difference 62% (95% CI 49-75) P<0.001 <u>Other endpoint:</u> Proptosis change from baseline at week 15 1. -2.9 mm 2. -0.5 mm difference -2.4 (95% CI -3.0 to -1.8) P<0.01 Proptosis response durability at week 52 1. 21/30 (70%) 2. NR	62%/2 NA	1. 12 (8=tinnitus, 2=hypoacusis, 1=grade 2 neurosensory deafness, 1=autophony) 2. 4 (tinnitus) <u>Hyperglycemia:</u> 1. 11 2. 3 <u>Menstrual disorders:</u> 1. 8 2. 1 <u>Muscle spasms:</u> 1. 33 2. 2		<u>Detection Bias</u>: (Unclear) Hertel exophthalmometry done by same assessor using same instrument at each, possibility allowing unblinding of patients with significant response or side effects (e.g., muscle spasms). Imaging analyzed by independent masked readers at central reading center using double reading with adjudication paradigm. <u>Attrition Bias</u>: (Low) Low overall attrition. Multiple imputation used to account for missing data in follow-up period. <u>Reporting Bias</u>: (Unclear) Protocol not available. <u>Other Bias:</u> (Unclear) Most authors are employees of or receive financial support from manufacturer. Manufacturer funded and participated in design, conduct, data management, data analysis and interpretation, and preparation and approval of the manuscript. **Applicability**: <u>Patient</u>: Significant portion of population with "unknown/other/unreported" race information. Otherwise representative of TED population. <u>Intervention</u>: The 10-mg/kg dose was selected based on nonclinical pharmacologic studies predicting that this dose would achieve target-tissue exposures in more than 95% of patients, healthy volunteer safety data and phase 2 proof-of-concept safety and efficacy data for TED. <u>Comparator</u>: Proptosis appropriate surrogate, study not designed to study long term reduction of TED induced vision loss. <u>Outcomes</u>: Appropriate based on previous trials for other therapies for TED. <u>Setting</u>: 29 sites in North America, Europe, and Australia.

		prior use of anti-IGF-1R mAbs -clinically significant hearing impairment -inflammatory bowel disease -use of systemic corticosteroids or selenium (except in MVI) for any reason within 2 weeks of study drug -other immunosuppressant withing 8 weeks						
2. THRIVE 2[1,2,5] NCT06021054 Phase 3, PC, DB, MC, RCT Data from: Abstract, PI Clinicaltrials.gov	1. Veligrotug 10mg/kg IV every 3 weeks x 5 doses 2. Placebo IV every 3 weeks x 5 doses 2:1 randomization	Demographics: -Median age 50 y -Female 75% -White 76% -Black 10% -Asian 3% -Other 4% -Tobacco (current use) 26% -Proptosis: 24.3 mm veligrotug, 23.8 mm placebo Diplopia: 52% veligrotug, 59% placebo -CAS ≥ 3, 57% veligrotug, 52% placebo Key Inclusion Criteria: -moderate-severe chronic TED (onset > 15 mo, proptosis ≥ 3 mm, any CAS [0-7]) Key Exclusion Criteria: -clinically significant hearing impairment -inflammatory bowel disease	ITT: 1. 125 2. 63	Primary Endpoint: PRR at week 15 By Hertel: 1. 57% 2. 8% difference 49% (95% CI 38 to 60) P<0.0001 Proptosis change from baseline 1. -2.34 mm 2. -0.46 mm difference -1.9 (95% CI -2.4 to -1.4) P<0.0001 By MRI/CT: 1. 48% 2. 3% P<0.0001 ORR at week 15 1. 56% 2. 7% P<0.0001	49%/2 NA 45%/3 49%/2	Muscle spasms: 1. 36% 2. 6% Menstrual disorders (for menstruating participants): 1. 33% 2. 10% Hearing impairment: 1. 13% 2. 3%. Serious TEAEs: 1. 2% 2. 3%	NA for all	Unable to assess risk of bias **Risk of Bias (low/high/unclear)**: Selection Bias: Performance Bias: Detection Bias: Attrition Bias: Reporting Bias: Other Bias: **Applicability**: Patient: Intervention: Comparator: Outcomes: Setting:

Abbreviations: AE = adverse events; ARR = absolute risk reduction; CAS = clinical activity score; CI = confidence interval; CT = computed tomography; DB = double-blind; HbA1C = hemoglobin A1C; IGF-1R = insulin-like growth factor-1 receptor; ITT = intention to treat; IV = intravenous; mAbs = monoclonal antibodies; MC = multicenter; mITT = modified intention to treat; mo = months; MRI = magnetic

resonance imaging; N = number of subjects; MVI = multivitamin; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; ORR = overall responder rate; PC = placebo-controlled; PI = prescribing information; PP = per protocol; PRR = proptosis responder rate; RCT = randomized controlled trial; SAE = serious adverse event; TEAE = treatment emergent adverse event; TED = thyroid eye disease; y = years.

References:

1. Jain AP, Cockerham K, Abrams J, et al. THRIVE-2 Phase 3 Trial of Veligrotug (VRDN-001) in Chronic Thyroid Eye Disease (TED): Efficacy and Safety at 15 weeks [Abstract citation ID: bvaf149.2240]. JEndocrine Soc. 2025; Volume 9 (Supplement 1): A1181-A1182. doi:10.1210/jendso/bvaf149
2. Viridian Therapeutics, Inc. An Efficacy, Safety, and Tolerability Study of Veligrotug (VRDN-001), in Participants With Chronic Thyroid Eye Disease (TED) (THRIVE-2). Clinicaltrials.gov identifier: NCT06021054. Updated 10/23/2025. Accessed: 8/12/26. Available at: https://clinicaltrials.gov/study/NCT06021054?term=NCT06021054&viewType=Card&rank=1#study-overview
3. Yen MT, Cockerham K, Saeed P, et al. THRIVE: A Phase 3, Randomized, Double-Masked, Placebo-Controlled Study of Veligrotug for Active Thyroid Eye Disease. *Ophthalmology*. Jun 1 2026;doi:10.1016/j.ophtha.2026.04.022
4. Tepezza (teprotumumab-trbw) prescribing information. Horizon Theraputics. Dubland, Ireland. 9/2025. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761143s030lbl.pdf.
5. Lumvoa (veligrotug-vvze). Prescribing Information. Viridian Therapetuics. Waltham, MA. 6/2026. Accessed at: accessdata.fda.gov/drugsatfda_docs/label/2026/761530Orig1s000lbl.pdf.
6. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. Multicenter Study Randomized Controlled Trial. *New England Journal of Medicine*. 376(18):1748-1761.
7. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. Clinical Trial, Phase III Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't. *New England Journal of Medicine*. 382(4):341-352.
8. Douglas RS, Couch S, Wester ST, et al. Efficacy and Safety of Teprotumumab in Patients With Thyroid Eye Disease of Long Duration and Low Disease Activity. Randomized Controlled Trial. *Journal of Clinical Endocrinology & Metabolism*. Dec 21 2023;109(1):25-35. doi:https://dx.doi.org/10.1210/clinem/dgad637
9. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. Oct 2016;26(10):1343-1421. doi:10.1089/thy.2016.0229
10. Liu ZW, Masterson L, Fish B, Jani P, Chatterjee K. Thyroid surgery for Graves' disease and Graves' ophthalmopathy. *Cochrane Database of Systematic Reviews*. 2015;(11)doi:10.1002/14651858.CD010576.pub2
11. National Institute for Health and Care Excellence. Retrobulbar irradiation for thyroid eye disease. Interventional procedures guidance. Dec 2005. Available at: nice.org.uk/guidance/ipg148. Accessed July 14, 2020.
12. US National Library of Medicine. Search term: Thyroid eye disease. (Accessed July 14, 2020 at: www.ClinicalTrials.gov).
13. Minakaran N, Ezra DG. Rituximab for thyroid-associated ophthalmopathy. *Cochrane Database of Systematic Reviews*. 2013;(5)doi:10.1002/14651858.CD009226.pub2

14. Hamed Azzam S, Kang S, Salvi M, Ezra DG. Tocilizumab for thyroid eye disease. *Cochrane Database of Systematic Reviews*. 2018;(11)doi:10.1002/14651858.CD012984.pub2
15. FDA Center for Drug Evaluation and Research. BLA 761143 Tepezza (teprotumumab-trbw) Clinical Review. Review completion date Jan 13, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761143Orig1s000MedR.pdf Accessed: July 8, 2020.
16. European Group on Graves O. Consensus Statement of the European Group on Graves' Orbitopathy (EUGOGO) on Management of Graves' Orbitopathy. *Thyroid*. 2008;18(3)doi:10.1089/thy.2007.0315
17. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velazquez-Villoria A, Galofre JC. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. *J Ophthalmol*. 2015;2015:249125. doi:10.1155/2015/249125
18. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. Research Support, Non-U.S. Gov't. *Clinical Endocrinology*. 1995;42(1):45-50.
19. Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. *Eur Thyroid J*. Dec 1 2022;11(6)doi:10.1530/ETJ-22-0189
20. MP M, MF P, WM W, L K. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clinical Endocrinology*. 1997;47:9-14.
21. European Group on Graves O, Wiersinga WM, Perros P, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. *Eur J Endocrinol*. Sep 2006;155(3):387-9. doi:10.1530/eje.1.02230
22. Bartalena L, Gallo D, Kahaly GJ, Marino M, Tanda ML. Comparison of the 2021 EUGOGO guidelines and the 2022 ATA/ETA consensus statement for the management of Graves' orbitopathy. Comparative Study Review. *European Thyroid Journal*. 12 01 2025;14(6):01. doi:https://dx.doi.org/10.1530/ETJ-25-0318

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
veligrotug-vvze	LUMVOA	INTRAVEN	VIAL	
teprotumumab-trbw	TEPEZZA	INTRAVEN	VIAL	N

Appendix 2: Medline Search Strategy

Search through 8/5/26

☐	1	Veligrotug.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	4
☐	2	teprotumumab.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	460
☐	3	limit 2 to yr="2024 -Current"	212
☐	4	limit 3 to (english language and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review"))	35
☐	5	1 or 4	39

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUMVOA safely and effectively. See full prescribing information for LUMVOA.

LUMVOA (veligrotug-vvze) injection, for intravenous use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
LUMVOA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of thyroid eye disease regardless of thyroid eye disease activity or duration. (1)

----------DOSAGE AND ADMINISTRATION----------
- 10 mg/kg every three weeks for a total of 5 infusions (2.1)
- Administer LUMVOA by intravenous infusion over 30 to 45 minutes (2.3)
- See full prescribing information for dose preparation and administration instructions (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Infusion Reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)
- Inflammatory Bowel Disease (IBD): Monitor patients for signs and symptoms of disease, including patients without a history of IBD; discontinue LUMVOA if IBD is suspected (5.2)
- Hyperglycemia: Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with LUMVOA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving LUMVOA. Continue monitoring after treatment for patients who experience hyperglycemia while on LUMVOA (5.3)
- Hearing Impairment including Hearing Loss: LUMVOA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patient's hearing before, during, and after treatment with LUMVOA and consider the benefit-risk of treatment with patients (5.4)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence of 5% or more) are muscle spasms, headache, hearing impairment, hyperglycemia, fatigue, diarrhea, ear discomfort, infusion-related reaction, nausea, nasopharyngitis, blood creatine phosphokinase increased, dry skin, and hypertension (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Viridian Therapeutics, Inc. at 1-866-321-VRDN (1-866-321-8736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Females of Reproductive Potential: Appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of LUMVOA (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Dose Preparation
2.3 Administration Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infusion Reactions
5.2 Inflammatory Bowel Disease
5.3 Hyperglycemia
5.4 Hearing Impairment Including Hearing Loss
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 Immunogenicity
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

Appendix 4. Pharmacology and Pharmacokinetic Properties of Veligrotug

Parameter	
Mechanism of Action	Humanized IgG1 monoclonal antibody that binds to IGF-1R and inhibits IGF-1R signaling by blocking ligand-induced receptor autophosphorylation. Mechanism in patients with thyroid eye disease not fully characterized.
Oral Bioavailability	NA
Distribution	2.8 L central Vd, 2.5 L peripheral Vd
Protein Binding	NR
Elimination	Not fully characterized
Half-Life	18 days
Metabolism	Expected to be metabolized by proteolysis

Abbreviations: L = liter; IGF1R = insulin-like growth factor-1 receptor; IgG1 = immunoglobulin G1; NA = not applicable; NR = not reported; Vd = volume of distribution.

Author: Fletcher Date: October 2026

Appendix 5: Key Inclusion Criteria

Population	Adults or children with thyroid eye disease (acute or chronic)
Intervention	Teprotumumab, Veligrotug
Comparator	Corticosteroids, orbital irradiation, surgery (e.g., strabismus surgery, orbital decompression)
Outcomes	Proptosis, Clinical Activity Score, diplopia, blindness, adverse events
Timing	Any
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Insulin-like Growth Factor-1 Receptor (IGF-1R) Inhibitors

Goal(s):
- To ensure appropriate use of teprotumumab and veligrotug in patients with Thyroid Eye Disease (TED)

Length of Authorization:
- 1 lifetime treatment course, allow 9 months to complete treatment (teprotumumab 8 total doses OR veligrotug 5 total doses)

Requires PA:
- Teprotumumab and veligrotug (pharmacy and provider administered claims)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the patient an adult (18 years or older)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the medication being ordered by, or in consultation with, an ophthalmologist or specialized ophthalmologist (e.g. neuro-ophthalmologist or ocular facial plastic surgeon)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have **moderate**, **severe**, or **sight-threatening** TED? • Defined by the Graves' Orbitopathy Severity Assessment. Possible severity ratings are mild, moderate, severe, and sight-threatening.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have **active** TED? • Defined as Clinical Activity Score (CAS) of 3 or higher on 7-point scale within past 3 months.	**Yes:** Go to #6 CAS score:_____ Score date:_____	**No:** Go to #8

Approval Criteria		
6. Does the patient have <u>any</u> of the following: • active viral hepatitis, chronic liver disease, or a significant chronic infection <u>or</u> • a contraindication or severe side effect* to intermediate or high dose* corticosteroids <u>or</u> • failed to respond to 6 weeks of low-dose corticosteroid prophylaxis after radioactive iodine treatment <u>or</u> • failed to respond/relapsed after at least 3 weeks of intermediate or high dose* (IV or oral) corticosteroids *Note: • IGF-1R inhibitors are associated with hyperglycemia which may necessitate diabetic medication changes and may not be an appropriate alternative when avoiding steroids in patients with uncontrolled diabetes mellitus. • Steroid regimens may vary. Example intermediate steroid regimen: 0.5 g/week for 6 weeks then 0.25 g/week for additional 6 weeks for cumulative dose 4.5 g IV methylprednisolone over ~ 3 months. Example high-dose steroid regimen: IV methylprednisolone 0.75 g/week for 6 weeks then 0.5 g/week for 6 weeks.	**Yes:** Go to #9	**No:** Go to #7
7. Dose the patient have documentation of diplopia or significant proptosis*? *Note: significant proptosis is defined as ≥ 3 mm above the upper limit for race and sex or < 3 mm but of sufficient severity to impact daily quality of life.	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have **inactive** TED?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the patient of childbearing potential? Not considered of childbearing potential any of the following: • Onset of menopause >2 years before current date or • Non-therapy-induced amenorrhea >12 months before current date or • Surgically sterile (absence of ovaries and/or uterus, or tubal ligation) or • Not sexually active	**Yes:** Go to #10	**No:** Go to #12
10. Is there documentation of negative pregnancy test within past 4 weeks?	**Yes:** Go to #11 Type of test (urine or serum): _____ Date of test:_____	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the provider attested that the patient has been counselled on risk of fetal harm AND agreed to use at least one reliable form of contraceptive for entire duration of drug therapy and for 180 days (6 months) after final dose? • Reliable forms of birth control have less than 1% failure rate/year with consistent and correct use • Examples include: implants, injectables, combined oral/intravaginal/transdermal contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner • Hormonal methods should be started at least one full menstrual cycle prior to initiation of IGF-1R inhibitor.	**Yes:** Go to #12 Contraceptive method:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is there documentation that there has been a risk/benefit discussion with the patient related to risk of potentially permanent hearing impairment AND documentation of a plan to assess/monitor hearing before, during, and after treatment?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Has the patient previously received any doses of an IGF-1R inhibitor? Note: There is not adequate data to support retreatment of the same or a different IGF-1R medication after a full treatment course. If therapy is being changed prior to course completion (e.g., side effect) use clinical judgement for number of remaining doses with alternative agent.	**Yes:** Approve balance to allow full treatment course for requested medication† (Full course dose # – previous # doses = current approval #) Previous number of doses_____	**No:** Approve full treatment course based on requested medication†

† All approvals will be referred for and offered optional case management

P&T/DUR Review: 10/26 (SF) 4/24 (SF); 12/20 (SF)
Implementation: 1/1/27; 5/1/24; 1/1/2021