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Teprotumumab Efficacy, Safety, and Durability in Longer-Duration Thyroid Eye Disease and Re-treatment

OPTIC-X Study

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Purpose: To evaluate teprotumumab safety/efficacy in patients with thyroid eye disease (TED) who were nonresponsive or who experienced a disease flare.

Design: The Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X) is a teprotumumab treatment and re-treatment trial following the placebo-controlled teprotumumab Phase 3 Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC) trial.

Participants: Patients who previously received placebo (n = 37) or teprotumumab (n = 14) in OPTIC.

Methods: OPTIC nonresponders or those who flared (≥2-mm increase in proptosis, ≥2-point increase in clinical activity score [CAS], or both) during follow-up were treated for the first time (previous placebo patients) or re-treated with teprotumumab in OPTIC-X with 8 infusions over 24 weeks.

Main Outcome Measures: Proptosis response and safety. Secondary outcomes included proptosis, CAS, subjective diplopia, and quality-of-life.

Results: Thirty-three of 37 placebo-treated OPTIC patients (89.2%) became proptosis responders (mean ± standard deviation, −3.5 ± 1.7 mm) when treated with teprotumumab in OPTIC-X. The responses were equivalent to the OPTIC study. In these responders, proptosis, CAS of 0 or 1, and diplopia responses were maintained in 29 of 32 patients (90.6%), 20 of 21 patients (95.2%), and 12 of 14 patients (85.7%), respectively, at follow-up week 48. The median TED duration was 12.9 months versus 6.3 months in those treated with teprotumumab in the OPTIC study. Of the 5 OPTIC teprotumumab nonresponders re-treated in OPTIC-X, 2 responded, 1 showed a proptosis reduction of 1.5 mm from OPTIC baseline, and 2 discontinued treatment early. Of the OPTIC teprotumumab responders who experienced flare, 5 of 8 patients (62.5%) responded when re-treated (mean proptosis reduction, 1.9 ± 1.2 mm from OPTIC-X baseline and 3.3 ± 0.7 mm from OPTIC baseline). Compared with published double-masked trials and their integrated follow-up, no new safety signals were identified. Mild hearing impairment was reported; 4 events occurred during the first course of treatment, and 2 events reoccurred after re-treatment.

Conclusions: Patients with TED of longer disease duration responded similarly to those treated earlier in the disease course. Patients with an insufficient initial response or flare may benefit from additional teprotumumab therapy. No new safety risk was identified; however additional postmarketing pharmacovigilance is ongoing. *Ophthalmology 2022;129:438-449 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Thyroid eye disease (TED) is a chronic, debilitating autoimmune disease commonly associated with Graves' disease. Thyroid eye disease presents with varying degrees of orbital inflammation and tissue expansion. Signs and symptoms of early TED include periorbital inflammation, retrobulbar pain, visual disturbance, diplopia, and proptosis. Over time, most patients experience quiescence of the acute inflammatory signs; however, proptosis and diplopia can persist

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chronically.[1] Furthermore, inflammatory signs can reoccur in a subset of patients. The morbidity burden can be considerable, with a marked impact on quality of life,[2,3] mental health,[4] and employment rate[5] leading to increased rates of suicide.[6]

The pathogenesis of TED is complex and not completely understood. One key insight is the overexpression and activation of the insulin-like growth factor 1 receptor (IGF-1R) in orbital fibroblasts and B and T cells.[7–9] A 3-fold increase in IGF-1R surface expression can be detected in orbital fibroblasts of patients with TED.[8] Insulin-like growth factor 1 receptor activation either directly or indirectly through the thyrotropin receptor in these cells results in increased cytokine production, including interleukin (IL)-1β, IL-1 receptor antagonist, IL-6, IL-12, IL-23, and tumor necrosis factor alpha α, which are all implicated in TED.[10–16] Depending on the inflammatory milieu, orbital fibroblasts can differentiate into adipocytes, myofibroblasts, chondrocytes, or osteoblasts.[13,17] A combination of these factors leads to inflammation and hydrophilic mucopolysaccharide (chiefly hyaluronan) accumulation within the orbit, contributing to tissue swelling. Recent evidence suggests that the increase in IGF-IR expression in acute TED persists into the chronic, nonprogressive phase.[18]

Teprotumumab (currently marketed as Tepezza), a novel, fully human monoclonal IGF-1R inhibitory antibody, binds to IGF-1R, inhibits downstream signalling, and provokes internalization of the antibody-receptor complex. Phase 2 and 3 randomized, placebo-controlled trials (ClinicalTrials.gov Identifiers, NCT01868997[19] and NCT03298867,[20] respectively) demonstrated marked improvement in proptosis, diplopia, and inflammation in patients with moderate to severe, active TED after 8 infusions of teprotumumab over a 24-week period. A subsequent study supported these findings by demonstrating a significant decrease in extraocular muscle and orbital fat volume after treatment with teprotumumab.[21]

Although the phase 2 and phase 3 trials have reported the safety and efficacy of teprotumumab in treating patients in the progressive, acute phase of TED, key questions remain unanswered: (1) Do patients with longer duration of TED respond equivalently, and is the response durable? (2) Do nonresponders at 24 weeks benefit from additional therapy? (3) Can those with disease exacerbations (flare) benefit from additional therapy? and (4) Is re-treatment with teprotumumab safe in these clinical circumstances?

To address these questions, patients in the phase 3 Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC) study (ClinicalTrials.gov identifier, NCT03298867) who were either nonresponders at week 24 of the OPTIC study or who experienced a disease flare during the 48-week follow-up period (within 51 weeks after last infusion) were eligible to enroll in the open label extension study, Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X; ClinicalTrials.gov identifier, NCT03461211). In the OPTIC-X study, patients received either an 8-infusion course of teprotumumab for the first time (previously treated with placebo) or a second course (re-treatment) of teprotumumab.

Methods

OPTIC Study Design

The OPTIC study was a phase 3, randomized, double-masked, placebo-controlled, parallel-group, multicenter clinical trial of the efficacy, safety, and tolerability of teprotumumab in patients with moderate to severe progressive, acute TED. The methods and results of this study have been described previously.[20] Using this protocol, the more severely affected (proptotic) eye was designated as the study eye.

The OPTIC study consisted of a 4-week screening period and a 24-week double-masked treatment period. The final study drug infusion was administered at week 21 of the treatment period with efficacy and safety assessments performed at week 24. A 48-week treatment-free follow-up was completed after the week 24 visit.

OPTIC-X Study Design

The OPTIC-X study was conducted in 7 States in the US and 5 European sites and was an open-label extension of the OPTIC study, in which patients who met the inclusion criteria could enter immediately after the OPTIC study or at any time during the follow-up period. All patients provided informed consent. The study was approved by local institutional review boards or independent ethics committees and was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice and the principles of the Declaration of Helsinki. This study was approved by the Western Institutional Review Board (Puyallup, WA) for the private practice sites and by the local institutional review boards of Cedars-Sinai Medical Center, University of Tennessee Health Science Center, Oregon Health & Science University, University of Miami Bascom Palmer Eye Institute, and The Medical College of Wisconsin. The independent ethics committees were as follows: Landesarztekammer Rheinland-Pfalz (State Medical Association of Rhineland-Palatinate), Milan Area 2 Ethics Committee, Comitato Etico Regione Toscana – Area Vasta Nord Ovest. A list of inclusion and exclusion criteria and a schedule of assessments are provided in Tables S1 and S2 (available at www.aaojournal.org).

Patients Who Entered OPTIC-X

Nonresponders from the OPTIC Study. Placebo- and teprotumumab-treated proptosis nonresponders in the OPTIC trial (<2-mm decrease in the study eye at study week 24) were eligible to enter the OPTIC-X study immediately after completion of the OPTIC study. These nonresponders were eligible to receive teprotumumab for the first time (patients who had received placebo) or for the second time (teprotumumab nonresponders). All participants and investigators were masked to previous therapies; however, because the same ophthalmologist consistently completed proptosis measurements in both the OPTIC and OPTIC-X studies, it is possible that pretreatment measurements were available to them. Patients received 8 open-label infusions of teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions). During the open-label treatment period, teprotumumab infusions were scheduled for day 1 (OPTIC-X baseline) and at weeks 3, 6, 9, 12, 15, 18, and 21 (with a final study visit at week 24).

The active treatment period of the OPTIC-X study was followed by a 24-week follow-up period (27 weeks after the final

teprotumumab dose). The follow-up included clinic visits at 1, 3, and 6 months after week 24 of the open-label treatment period.

Patients from the OPTIC Follow-up Who Experienced a Disease Flare. Patients from the OPTIC study who demonstrated a proptosis response (reduction of ≥2 mm from baseline) entered a follow-up period scheduled for 48 weeks (ending on study week 72), which was 51 weeks after the final study drug infusion. During the OPTIC follow-up period, patients in either the placebo or teprotumumab treatment group who manifested disease flare (increase in proptosis in the study eye of ≥2 mm, increase in clinical activity score [CAS] of 2 points or more [description provided below] with a total CAS score of 4 or more in the study eye, or both) as measured from the end of the OPTIC study could enroll in the OPTIC-X study and receive a treatment course of teprotumumab. Patients who experienced a disease flare were eligible for 8 infusions of teprotumumab over 24 weeks, regardless of which treatment group they had been in during the OPTIC study (teprotumumab or placebo). In addition, these patients could enter the OPTIC-X study at any time during the 48-week OPTIC study follow-up period. Therefore, patients may have entered the OPTIC-X study at differing time points in the follow-up period. Patients who experienced a disease flare were not followed up beyond the OPTIC-X study treatment period so as not to prolong the study further.

Outcome Measures

The primary outcome measure for the OPTIC-X study was the proptosis responder rate at week 24 from entry into this trial. Proptosis was measured using the same Hertel exophthalmometer and by the same observer at each evaluation. Secondary efficacy end points included the percentage of patients with a CAS of 0 or 1 (disease inactivation) at week 24, mean change to week 24 in proptosis (in millimeters), diplopia responder rate, and mean change to week 24 in Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire aggregate score. The GO-QOL questionnaire is a 16-item questionnaire that assesses the impact of TED as perceived by the patient; the 2 subscales of the GO-QOL are visual functioning and appearance (8 questions for each).[22] The following were exploratory end points: overall responder rate (reduction of ≥2 points in the CAS and reduction in proptosis of ≥2 mm) and mean change to week 24 in the GO-QOL questionnaire visual functioning and appearance subscale scores.

Diplopia grade was assessed using the Gorman subjective diplopia score, and inflammation was quantified using the 7-point CAS represented by the presence of spontaneous retrobulbar pain, pain with eye movements, conjunctival and eyelid redness, chemosis, swelling of the caruncle or plica, or eyelid swelling.

Adverse events (AEs) and concomitant medications were inquired about at each visit as required in clinical trials for regulatory submission. Events of special interest were followed up, and patient narratives were created for these events to characterize them further. Hyperglycemia was monitored prospectively through laboratory testing, with glucose levels obtained at each study visit and hemoglobin A1c levels obtained every 12 weeks. Hearing impairment and alopecia AEs were captured through patient reporting.

OPTIC-X Follow-up

Responder rates and maintained responder rates (proptosis, overall response, CAS of 0 or 1, and diplopia) were calculated at each visit during the follow-up. Maintained responders were those who were OPTIC-X responders for the variable at week 24 and who continued to meet the response definition for the OPTIC-X study with no additional TED treatment at weeks 28, 36, and 48. Patients missing values at a visit were considered nonresponders at that visit.

Statistical Analysis

Analysis was conducted on the intention-to-treat population. Any participant whose week 24 assessment was affected by the coronavirus disease 2019 (COVID-19) pandemic was not included in any categorical analysis. Patients were analyzed according to treatment received in the OPTIC study (placebo or teprotumumab). Results are presented as mean and standard deviation (standard error in graphs displaying continuous variables). All efficacy and safety end points were summarized using descriptive statistics (SAS software version 9.4; SAS Institute).

Results

Patients with Longer Duration of TED

Do Patients with Longer Duration of TED Respond to Teprotumumab Treatment?. Forty-two patients were randomized to placebo in the OPTIC study, with 40 completing the study. Four of these showed a clinically significant reduction in proptosis at week 24 and therefore entered the treatment-free follow-up period for the OPTIC study. Of these 4 patients, 1 met flare criteria (week 28 visit) and was enrolled in the OPTIC-X study. The remaining 36 nonresponder placebo-treated patients entered the OPTIC-X study (Fig 1A).

At the OPTIC baseline visit, patients randomized to placebo had a mean ± standard deviation (SD) CAS of 5.3 ± 1.0, mean ± SD proptosis of 23.2 ± 3.2 mm, and a mean ± SD duration of TED of 6.4 ± 2.4 months (median, 6.8 months; interquartile range [IQR], 4.9−8.6 months). In comparison, those patients entering the OPTIC-X study had a mean ± SD CAS of 3.6 ± 1.7 and a mean ± SD TED duration of 12.3 ± 2.5 months (median, 12.9 months; IQR, 10.9−14.4 months; maximum, 16 months). The mean ± SD proptosis remained unchanged from the OPTIC baseline visit at 23.0 ± 3.1 mm (Fig 1B).

Of the 23 OPTIC placebo patients experiencing diplopia at the OPTIC-X study baseline, 12 were unchanged, 7 had worsened diplopia, 3 had new-onset diplopia, and 1 improved between the start of the OPTIC study and the start of the OPTIC-X study. Of the 37 patients entering the OPTIC-X study, 36 completed the treatment period (1 discontinued treatment because of an AE, entered the follow-up and completed OPITC-X follow-up).

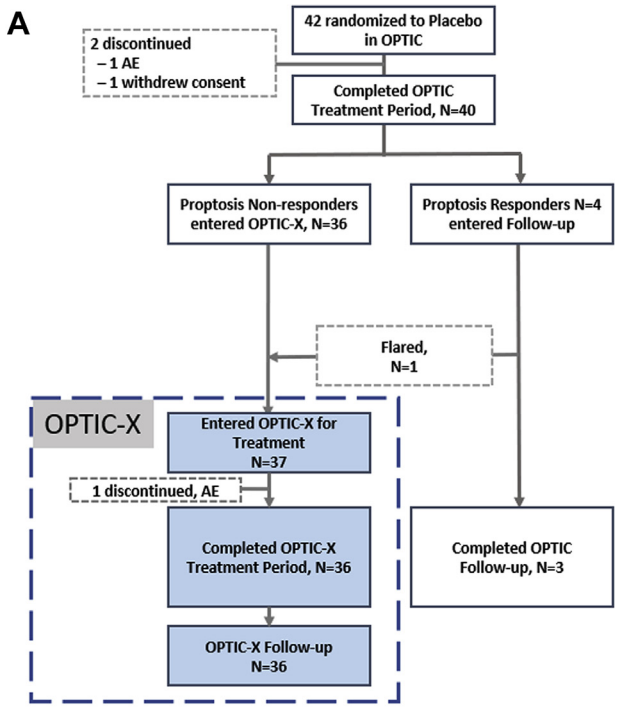
Outcomes. Proptosis (Fig 2A), diplopia (Fig 2B), CAS (0 or 1; Fig 2C), and overall responses (Fig 2D) to teprotumumab in OPTIC-X patients who previously received placebo during the OPTIC study closely mirrored the responses of patients receiving teprotumumab in the OPTIC study.

Proptosis Response. Eighty-nine percent of patients (33/37) were proptosis responders at week 24 (Fig 2A). The median time to proptosis response (reduction of ≥2 mm) was 6.4 weeks (IQR, 6.1−12.1 weeks), and the mean change from baseline at week 24 in the OPTIC-X study was −3.5 ± 1.7 mm, similar to results reported in the OPTIC study (Fig 2E).

Diplopia Response. In patients with diplopia, 14 of 23 patients (60.9%) showed improvement of 1 grade or more (Fig 2B), and 13 of 23 patients (56.5%) showed complete resolution of diplopia at week 24.

Clinical Activity Score Response. Of 32 patients entering the OPTIC-X study with a CAS of more than 1, 65.6% (21/32) achieved a CAS of 0 or 1 at week 24 (Fig 2C). Of those patients who entered the OPTIC-X study with minimal or no

A



B

Patient Demographics	1st Course (OPTIC Placebo) N=37
Age, Mean (SD)	48.5 (13.5)
Gender, n (%)	
Female	27 (73.0%)
Male	10 (27.0%)
Race, n (%)	
White	33 (89.2%)
Black	1 (2.7%)
Asian	1 (2.7%)
Other	2 (5.4%)
Years Since Diagnosis of Graves' Disease, Median (range)	1.4 (0.58 – 15.29)
Months Since Diagnosis of Thyroid Eye Disease, Median (range)	12.9 (7.01 – 15.86)
Smoking Status, n (%)	
Non-smoker	29 (78.4%)
Smoker	8 (21.6%)
Clinical Activity Score, mean ± SD	3.6 ± 1.7
Proptosis measurement, mm, mean ± SD	23.0 ± 3.1
Thyroid hormone level, pmol/L	
Free triiodothyronine (FT3), mean ± SD	5.0 ± 1.0
Patients with Normal FT3	32 (86.5%)
Patients with Low FT3	1 (2.7%)
Patients with High FT3	4 (10.8%)
Free thyroxine (FT4), mean ± SD	16.0 ± 3.8
Patients with Normal FT4	32 (86.5%)
Patients with Low FT4	3 (8.1%)
Patients with High FT4	2 (5.4%)
Thyrotropin (TSH) level, mIU/L, mean ± SD	1.43 ± 1.46
Patients with Normal TSH	22 (59.5%)
Patients with Low TSH	14 (37.8%)
Patients with High TSH	1 (2.7%)

AE, adverse event; Normal ranges: free thyroxine is 11.5 to 22.7 pmol/L; free triiodothyronine, 3.5 to 6.5 pmol/L; for thyrotropin, 0.55 to 4.78 mIU/L

Figure 1. OPTIC-X Study patients from OPTIC Placebo Group: (**A**) Consolidated Standards of Reporting Trials flow diagram and (**B**) table showing demographic characteristics. OPTIC = Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study; OPTIC-X = Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study; SD = standard deviation.

inflammation (n = 5; CAS, 0 or 1), 4 showed reductions in proptosis at week 24, with 3 meeting proptosis responder criteria.

Graves' Ophthalmopathy-Specific Quality-of-Life Scores. The combined and visual functioning and appearance subscale GO-QOL scores improved with teprotumumab over the course of the study in patients who previously received placebo in the OPTIC study (Fig 2F). The mean ± SD change from baseline was 11.7 ± 22.5 and 15.1 ± 20.3 in the visual functioning and appearance subscales, respectively, indicating moderate clinical changes[23] at 24 weeks.

Is the Response Durable in Patients with Longer Duration of TED?. In short-term follow-up 7 weeks after the final teprotumumab dose (week 28 visit), 92% of patients (33/36) showed a proptosis response. The response remained high at week 48 (32/36 [89%], 27 weeks after final dose; Fig 3A). Proptosis reduction (in millimeters) was sustained across the OPTIC-X study follow-up visits (Fig 3B). Other outcomes also were consistent across the follow-up, with more than 90% reaching the overall response criteria at each visit. At the final visit, disease inactivation (CAS of 0 or 1) occurred in more than 80% (25/31), and 64% (14/22) showed a diplopia response (Fig 3A). The mean ± SD change from baseline at week 48 was 17.5 ± 17.5 and 16.7 ± 20.3 in the GO-QOL visual functioning and appearance subscales, respectively, indicating maintenance of moderate to large clinical changes.[23]

In patients with a 24-week response, each response was re-evaluated at the week 28, 36, and 48 follow-up visits, with a large percentage of all outcomes being maintained; more than 90% maintained proptosis, disease inactivation, and overall responses at each visit (Fig 3C). Diplopia improvement of 1 Gorman grade or more was maintained in 86% of patients (12/14) at the final visit. Furthermore, maintenance of diplopia score of 0 (i.e., no diplopia) was achieved in 77% of patients (10/13) at week 48 (illustrative example of proptosis and diplopia response and maintenance is provided in Fig 4).

Nonresponders to First Course

Do Nonresponders to a First Course of Teprotumumab Benefit from Additional Therapy?. Forty-one patients were randomized to teprotumumab in the OPTIC study, and 39 completed the 24-week double-masked treatment period. Five teprotumumab-treated patients were proptosis nonresponders at week 24 in the OPTIC study and entered the OPTIC-X study (Fig 5A; demographics in Fig 5B). Two patients discontinued early from the OPTIC-X treatment period, 1 because of lack of efficacy (exophthalmometer of 15.5 mm at the OPTIC-X study baseline and 15 mm at week 18; CAS of 3 at the OPTIC-X study baseline and week 18; diplopia of grade 1 at the OPTIC-X study baseline and grade 0 at week 18) but completed the follow-up period. Discontinuation of the other patient was the result of a serious AE (intracerebral hemorrhage, further described in "Safety").

Proptosis Response. The 5 teprotumumab nonresponder patients in the OPTIC study experienced proptosis reductions ranging from 1 to 1.5 mm at week 24. After re-treatment in the OPTIC-X study, 2 of 5 of these patients (40%) exhibited a reduction of 2 mm or more from the OPTIC-X study baseline (Fig S1A, available at www.aaojournal.org) and thus were considered proptosis responders. Of the 3 nonresponders, 1 patient showed a 0.5-mm proptosis reduction during the OPTIC-X study with a 1.5-mm cumulative reduction from the OPTIC study baseline. The other 2 patients discontinued early. The mean ± SD change in proptosis

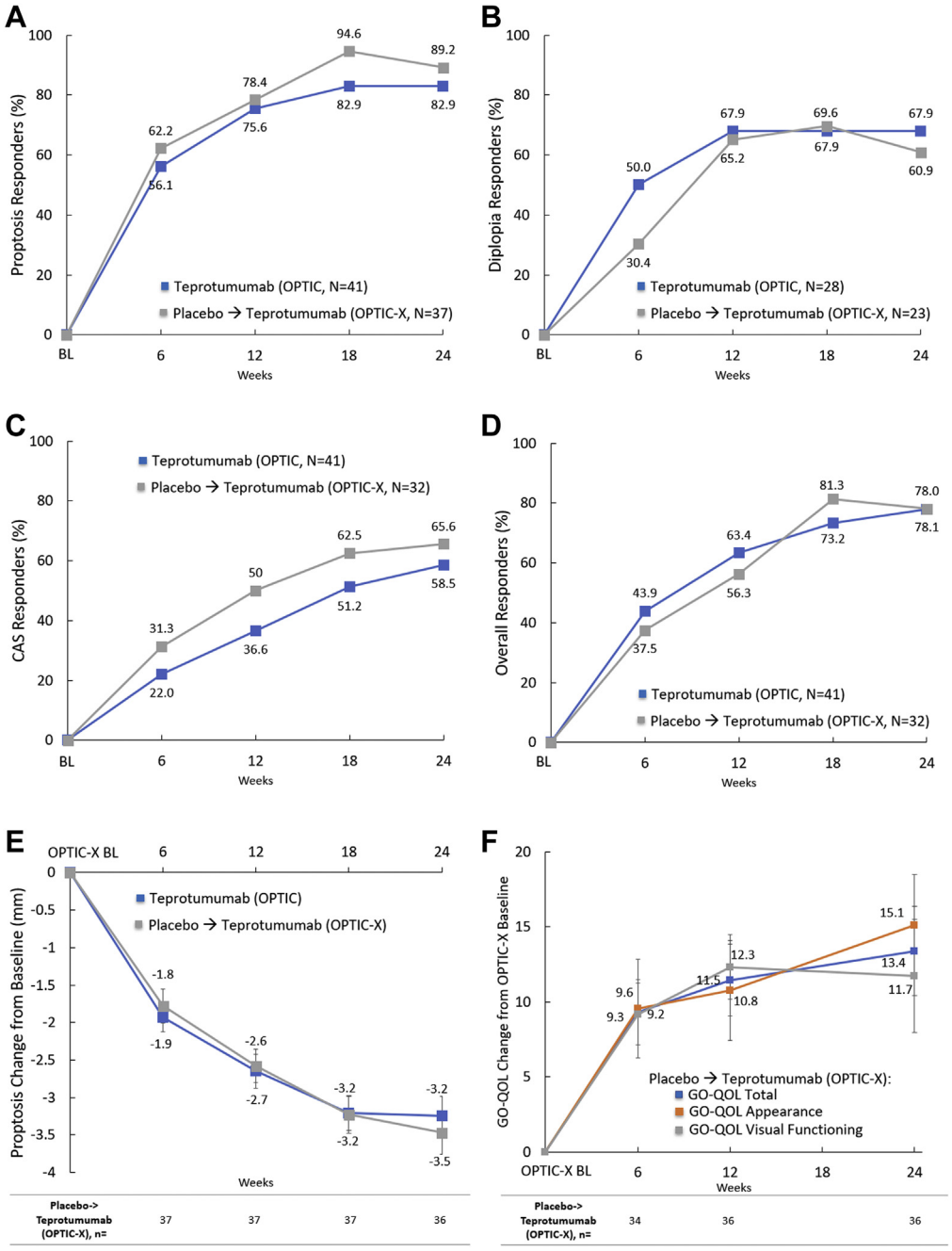


Figure 2. Line graphs showing the OPTIC study placebo-treated patient response to a first course of teprotumumab in the OPTIC-X study (median thyroid eye disease [TED] duration, 12.9 months) compared with those receiving teprotumumab in the OPTIC study (median TED duration, 6.3 months): (**A**) proptosis response, (**B**) diplopia response, (**C**) clinical activity score (CAS) of 0 or 1 response, (**D**) overall response, (**E**) proptosis change overlaid on the change from baseline in the OPTIC study, and (**F**) Graves' ophthalmopathy-specific quality-of-life (GO-QOL) total and subscale score changes during the OPTIC-X study. Note that proptosis response was defined as a 2-mm reduction or more from OPTIC-X baseline in proptosis in the study (more severely affected) eye, without deterioration of proptosis in the fellow eye. Diplopia response was defined as an improvement in 1 or more grades in those with baseline diplopia. Clinical activity score and overall response were determined for patients with CAS of more than 1 entering the OPTIC-X study. Continuous end points are presented as mean ± standard error. Proptosis change from baseline in the OPTIC-X study patients overlaid on the unadjusted change from baseline in the OPTIC study. BL = baseline; OPTIC = Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study; OPTIC-X = Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study.

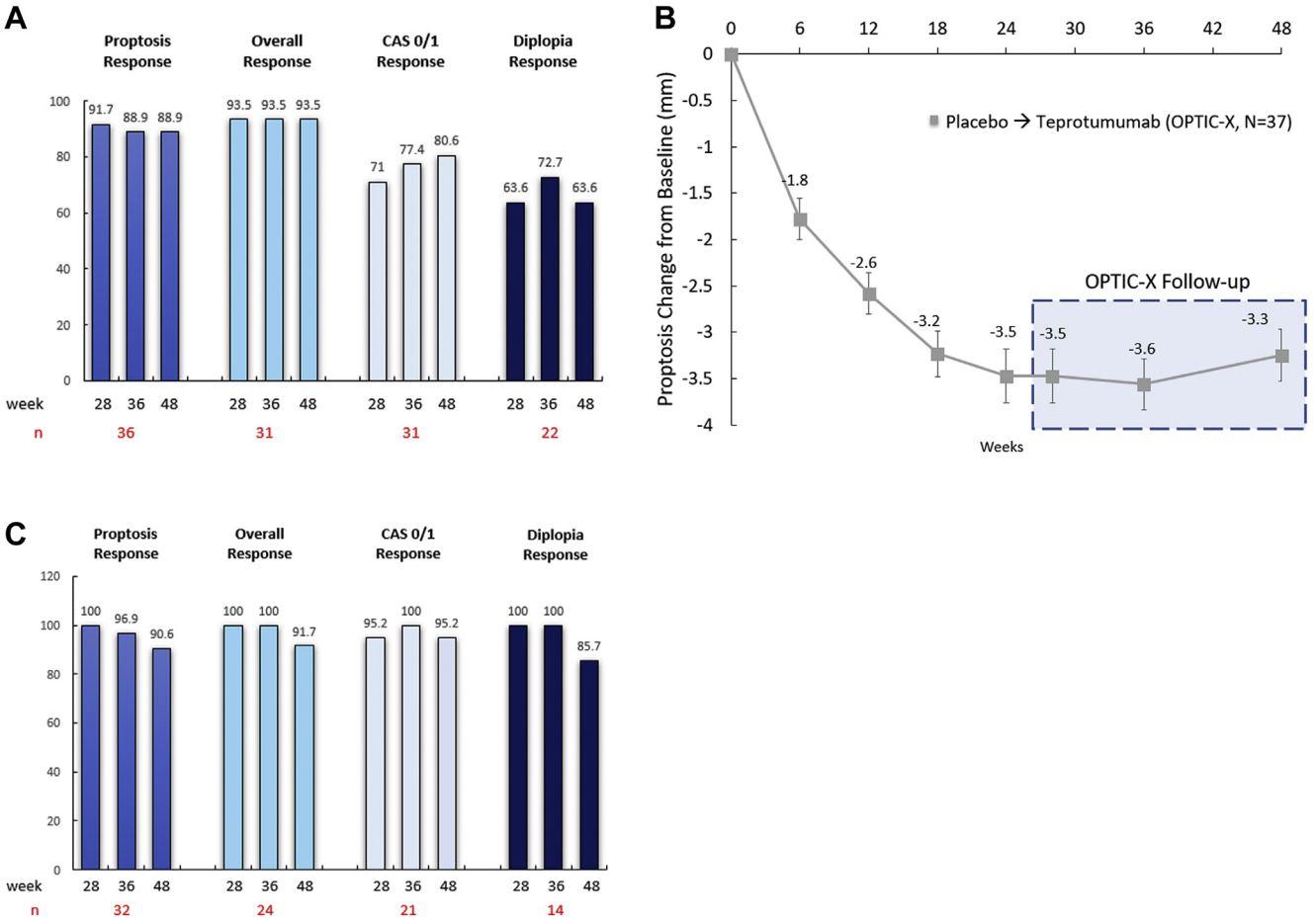


Figure 3. Graphs showing follow-up of first-course treatment patients (previous placebo patients): (**A**) response in all patients, (**B**) change from baseline in proptosis at follow-up, and (**C**) follow-up response for week 24 responders (percentage of those with week 24 responses remaining responders at weeks 28, 36, and 48). CAS = clinical activity score; OPTIC-X = Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study.

in this group from the OPTIC-X study baseline until its completion was −1.5 ± 0.9 mm (Fig S1B) with an overall mean change in proptosis from the OPTIC study baseline of −2.5 ± 0.9 mm (n = 3; Fig S1C).

Other End Points. Only 1 of 5 OPTIC teprotumumab nonresponders exhibited diplopia at the OPTIC-X study baseline. This patient responded at weeks 6, 12, and 18 but did not undergo measurements at week 24. Of the 3 OPTIC nonresponders who completed the OPTIC-X study, all showed CAS reductions during the OPTIC-X study, but none met the CAS of 0 or 1 responder criteria.

Patients with Exacerbation of Disease

Can Patients with an Exacerbation of Disease (Flare) Benefit from Another Course?. Thirty-four teprotumumab-treated patients in the OPTIC study met the primary (proptosis) response (reduction of ≥2 mm) at week 24. Of these, 33 of 34 patients (97%) continued in the treatment-free OPTIC study follow-up period. One additional patient who did not complete the double-masked treatment period of the OPTIC study continued in the follow-up. Ten of 34 patients (29.4%) experienced a disease flare; 7 did so at week 48, 2 did so at week 60, and 1 did so at week 72. Five of the 10 who experienced a disease flare experienced isolated proptosis flare (increase of ≥2 mm in the study eye since week 24), 4 met proptosis and CAS flare criteria (increase of 2 points or more after week 24 with a CAS of ≥4 in the study eye), and 1 met the isolated CAS flare criterion. Nine of the 10 who experienced a disease flare enrolled in the OPTIC-X study (Fig 5A, B). One patient became ineligible after the development of acute dysthyroid optic neuropathy. That patient required treatment with high-dose intravenous glucocorticoids. All 9 patients who experienced disease flare completed the treatment period; however, 1 patient was excluded from all week 24 summaries because of COVID-19 (visit delayed).

Proptosis Response. In those 8 patients who experienced disease flare and contributed data at week 24, 5 showed 2-mm or more improvement in proptosis during the second course of teprotumumab (Fig S1A; patients 4−8 in Fig S2, available at www.aaojournal.org). The 3 patients not achieving a 2-mm or more improvement in proptosis during the OPTIC-X study showed reductions relative to their OPTIC study baseline measurements of 3 mm, 3 mm, and 4 mm (Fig S2, patients 1−3, respectively). The patient who completed treatment but was excluded from the efficacy analysis because of a 3-month delay in the week 24 visit owing to COVID-19 achieved a 5-mm reduction in proptosis (Fig

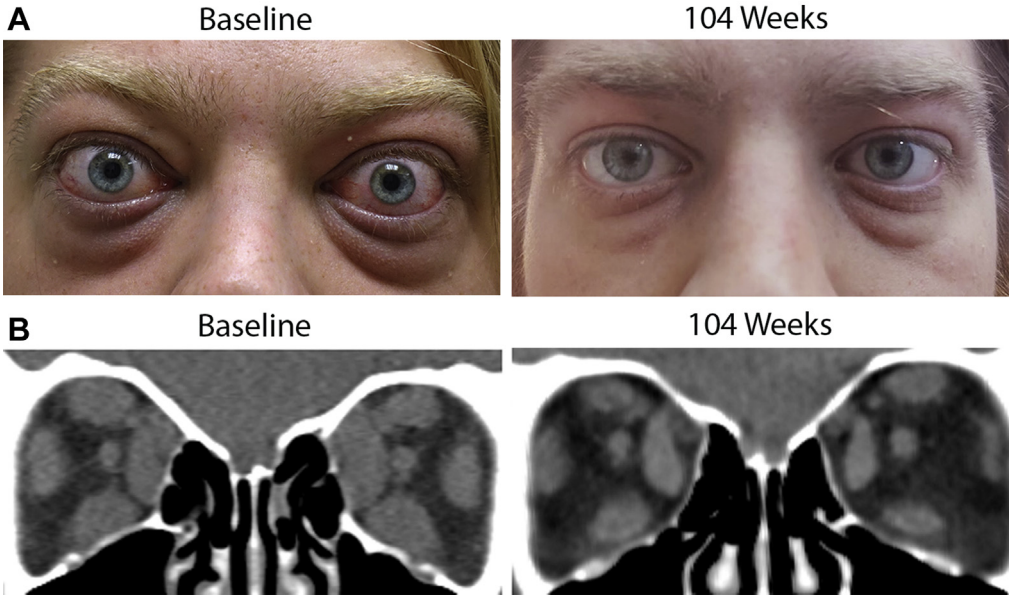
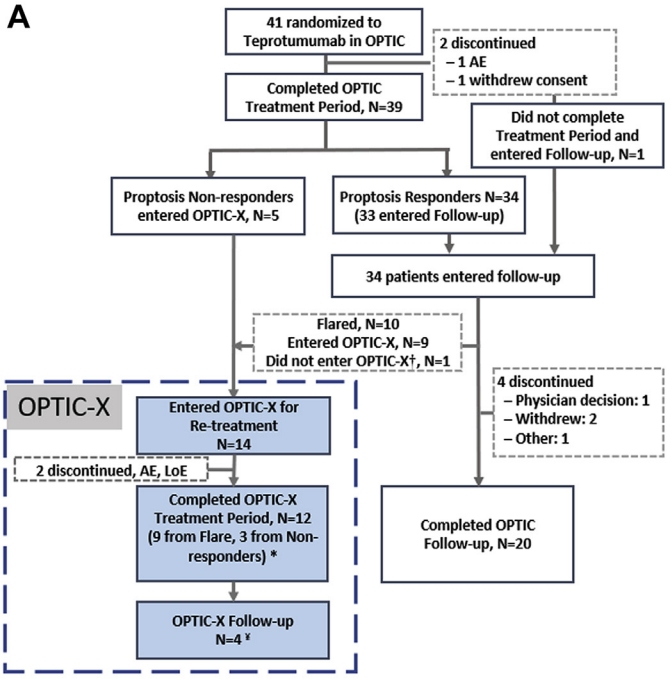


Figure 4. **A**, Clinical photographs of a patient with thyroid eye disease at baseline and 104 weeks (83 weeks after last infusion). **B**, Noncontrast computed tomography orbital images of the same patient at baseline and 104 weeks. At baseline of the Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X) study, the previously placebo-treated patient demonstrated proptosis of 29 mm (study eye or left eye) and 28 mm (right eye), clinical activity score (CAS) of 4 in each eye, and constant diplopia. After 8 infusions of teprotumumab (week 24 visit) and at week 48, the diplopia had resolved completely, and CAS was reduced to 0. The proptosis was 22 mm (study eye or left eye) and 22 mm (right eye) at weeks 24 and 48, which remained stable (22 mm in both eyes) at week 104 with no diplopia. In the right eye, compared with baseline at 104 weeks, the inferior rectus, superior rectus, and superior oblique muscles are decreased in volume. In the left eye, compared with baseline at 104 weeks, the inferior rectus, medial rectus, superior oblique, and lateral rectus muscles are decreased in volume.

A



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Patient Demographics	2nd Course/Retreatment (OPTIC Teprotumumab) N=14
Age, Mean (SD)	56.1 (11.5)
Gender, n (%)	
Female	11 (78.6%)
Male	3 (21.4%)
Race, n (%)	
White	11 (78.6%)
Black	1 (7.1%)
Asian	2 (14.3%)
Other	0
Years Since Diagnosis of Graves' Disease, Median (range)	1.7 (0.79 - 28.78)
Months Since Diagnosis of Thyroid Eye Disease, Median (range)	16.5 (8.52 - 22.50)
Smoking Status, n (%)	
Non-smoker	11 (78.6%)
Smoker	3 (21.4%)
Clinical Activity Score, mean ± SD	3.5 ± 1.6
Proptosis measurement, mm, mean ± SD	21.0 ± 4.2
Thyroid hormone level, pmol/L	
Free triiodothyronine (FT3), mean ± SD	4.7 ± 0.8
Patients with Normal FT3	14 (100%)
Patients with Low FT3	0
Patients with High FT3	0
Free thyroxine (FT4), mean ± SD	16.5 ± 3.2
Patients with Normal FT4	13 (92.9%)
Patients with Low FT4	0
Patients with High FT4	1 (7.1%)
Thyrotropin (TSH) level, mIU/L, mean ± SD	2.47 ± 2.46
Patients with Normal TSH	10 (71.4%)
Patients with Low TSH	3 (21.4%)
Patients with High TSH	1 (7.1%)

† Patient flared and received intravenous methylprednisolone for optic neuropathy, followed by decompression surgery, * Efficacy analyses in OPTIC-X based on ITT; patients with missing data were considered non-responders with the exception of 1 flare patient whose week 24 assessment was delayed due to COVID (this patient was excluded from week 24 analysis); AE, adverse event; LoE, lack of efficacy; Normal ranges: free thyroxine is 11.5 to 22.7 pmol/L; free triiodothyronine, 3.5 to 6.5 pmol/L; for thyrotropin, 0.55 to 4.78 mIU/L. ¥The non-responder who discontinued the treatment period due to LoE returned for the follow up

Figure 5. Patients re-treated with teprotumumab: (**A**) Consolidated Standards of Reporting Trials flow diagram and (**B**) table showing demographic characteristics. AE = adverse events; OPTIC = Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study; OPTIC-X = Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study; SD = standard deviation.

S2, patient 9) and 4-point reduction in CAS in both eyes from the OPTIC-X baseline to the final assessment. Had this patient been included in the week 24 efficacy evaluation, the response rate would have been 6 of 9. The mean ± SD change in proptosis from beginning to the end of the OPTIC-X study was −1.9 ± 1.2 mm (Fig S1B) with an overall mean change in proptosis from the OPTIC study baseline of −3.3 ± 0.7 mm (n = 8) (Fig S1C).

Other End Points. Only 3 of 9 OPTIC patients who experienced disease flare manifested diplopia at the OPTIC-X study baseline. All 3 patients achieved a diplopia response at weeks 12, 18, and 24, and all 3 were complete responders (Gorman grade 0 or no diplopia) at week 24. In the OPTIC flare patients with a CAS of more than 1, 4 of 7 showed a CAS of 0 or 1 at week 24 of the OPTIC-X study. Patients who experienced a flare in proptosis, CAS, or both showed a mean ± SD improvement in quality of life of 17.9 ± 12.4 points (a moderate to large change) after re-treatment with teprotumumab (Fig S1D). Patients showed a mean improvement of 28.0 points (SD, 28.0 points; median, 25 points) in the GO-QOL visual functioning subscale (a large change), for a mean score of 95.3 points (SD, 7.3 points; median, 100 points) at week 24 (Fig S1E). The appearance-related GO-QOL subscale score improved by 7.8 points (11.5 points [SD], a clinically significant change; Fig S1F).

Overall GO-QOL Results in Patients Completing the OPTIC-X Study

Of the 47 patients who completed the OPTIC-X study (1 patient did not have a week 24 value because of COVID-19), the median overall GO-QOL score was 88 (IQR, 68.8–93.8) of a possible 100.

Safety

OPTIC Placebo Patients Treated for the First Time in the OPTIC-X Study. Adverse events occurring in more than 10% of patients (4 patients or more) during the OPTIC-X study treatment are listed in Table 1. All AEs were mild or moderate, and no patients experienced a serious AE. Three patients experienced potential infusion reactions (includes AEs that occur within 2 hours after infusion initiation) characterized as dysgeusia during multiple infusions in 1 patient, generalized pruritus during the second infusion in 1 patient, and hypertension after infusion in 1 patient. All 3 patients completed the course of therapy. Three patients experienced AEs associated with hyperglycemia during the treatment period; 2 demonstrated new-onset type 2 diabetes mellitus that persisted at the end of the study, and 1 patient experienced increased blood glucose concentrations that resolved without medication. In the 2 patients reporting AEs of type 2 diabetes, fasting glucose and hemoglobin A1c levels at baseline were indicative of the presence of prediabetes (levels over time presented in Table S3, available at www.aaojournal.org). Hearing impairment was reported in 4 patients as mild AEs: 2 patients with hypoacusis that resolved, 1 patient with tinnitus that resolved, and 1 patient with tinnitus that continued at last visit and was accompanied by muscle spasms (bilateral lower leg) of moderate severity that led to treatment discontinuation after the sixth infusion. In the last patient, both muscle spasms and the tinnitus were considered treatment related. Both patients with AEs of tinnitus underwent audiogram evaluations. In 1 patient, pure tone audiography revealed borderline normal hearing at the 2-kHz threshold in the right ear, and all other thresholds in both ears were deemed normal. Word recognition score was 96% for both ears. The tinnitus was considered mild and resolved within 8 months. The other patient, who had a family history of hearing loss, showed normal hearing sensitivity on pure tone audiography with the exception of a mild sensorineural hearing loss at 500 Hz only in both ears. Ultra–high-frequency thresholds were not obtained. Furthermore, word recognition was excellent (90%–100%) in both ears. Five patients had experienced a body weight loss of 5 kg or more during the treatment period. No AEs associated with decreased weight were reported.

Re-treatment (Nonresponder or Patient with Disease Flare). Adverse events occurring in more than 10% of patients (≥2 patients) during the OPTIC-X study treatment are listed in Table 1. One patient taking a nonsteroidal anti-inflammatory drug (ibuprofen 400 mg twice daily) experienced a serious, life-threatening (grade 4) AE after 3 infusions of teprotumumab in the OPTIC-X study (last dose approximately 12 days before the event). This patient was a smoker. She experienced an intracerebral and subarachnoid hemorrhage and underwent emergency neurosurgery for hematoma evacuation. No aneurysm, arteriovenous malformation, or vasculitis was identified. The patient recovered with sequelae and entered rehabilitation after hospital discharge, precluding her continuation in the study. The relationship between the teprotumumab infusion and this rare AE event is uncertain. The reporting study investigator and his hospital consultants suggested that the event may be related to the patient's underlying medical condition and that it was not related to the study medication. This singular occurrence requires further pharmacovigilant surveillance to determine if this is of general concern or rather an event related to the complex medical history of this particular patient. All other AEs were mild or moderate, and none led to study drug

Table 1. Safety during Teprotumumab Treatment Period in the OPTIC-X Study Categorized by Treatment Received in the OPTIC Study

Variable	Second Course (OPTIC Teprotumumab) n = 14	First Course (OPTIC Placebo) n = 37
Any serious adverse events	1 (7.1)	0 (0)
Cerebral hemorrhage	1 (7.1)	0 (0)
Any adverse event	11 (78.6)	32 (86.5)
Adverse events in >10% of patients		
Muscle spasm	4 (28.6)	18 (48.6)
Arthralgia	2 (14.3)	0 (0)
Back pain	2 (14.3)	0 (0)
Nasal dryness	2 (14.3)	0 (0)
Alopecia	2 (14.3)	4 (10.8)
Dry skin	2 (14.3)	4 (10.8)
Hearing impairment	2 (14.3)	4 (10.8)
Diarrhea	1 (7.1)	5 (13.5)
Fatigue	0 (0)	4 (10.8)
Dysgeusia	0 (0)	4 (10.8)
Onychoclasis	0 (0)	4 (10.8)
Any adverse events of special interest <10%*		
Potential infusion-related reaction	1 (7.1)	3 (8.1)
Anaphylactic reaction	0 (0)	0 (0)
Hyperglycemia	0 (0)	3 (8.1)

Data are presented as no. (%). OPTIC = Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study; OPTIC-X = Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study.
*Diarrhea, hearing impairment, and muscle spasm adverse events of special interest are included in the section adverse events in >10% of patients.

discontinuation. One patient experienced a body weight loss of 5 kg or more during the treatment period.

Adverse events of special interest occurring during the OPTIC-X study treatment were evaluated also (Table 1). One patient experienced potential infusion reactions (includes AEs occurring within 2 hours after initiating an infusion), characterized as eye pain during the first infusion and asthenia during the second, but continued the study, receiving the full 8-infusion course of teprotumumab. No AEs associated with hyperglycemia were reported during treatment. Hearing impairment was reported in 2 patients and persisted at the end of the study; 1 patient had an AE of mild autophony described as intermittent echoing in the left ear, and the other patient experienced mild hypoacusis. Both patients previously reported hearing impairment events earlier during the OPTIC study that resolved during that study. No antidrug antibodies were detected during the OPTIC-X study.

Discussion

Data presented here provide evidence that teprotumumab may be effective in patients with longer TED duration than previously studied. Furthermore, evidence also suggested that re-treatment with teprotumumab in the OPTIC-X study in initial nonresponders or those who experienced disease flare during OPTIC follow-up showed improved proptosis by at least 2 mm from the OPTIC study baseline in nearly 80% of patients (11/14).

The previously published controlled trials with teprotumumab in patients with relatively recent TED onset (within 9 months) demonstrated significant efficacy with regard to a wide range of outcomes. Herein, the results from the OPTIC-X study provide additional insight into patients treated later in the TED course (up to 1.3 years of history). Patients who previously were in the OPTIC placebo group and received teprotumumab during the OPTIC-X study showed nearly a 7-month longer median disease course and lower CAS score (mean, 3.6 vs. 5.1) than patients treated with teprotumumab in the OPTIC study while demonstrating equivalent efficacy. Additionally, 5 patients previously treated with placebo in the OPTIC study demonstrated more chronic, inactive TED (CAS score, 0 or 1) at the OPTIC-X study baseline. Of these patients, most achieved reductions in proptosis at week 24 of the OPTIC-X study, with 3 meeting proptosis responder criteria. This finding provides exploratory evidence that patients with inactive disease also may benefit from teprotumumab; this currently is under investigation (ClinicalTrials.gov identifier, NCT04583735). Additional support for this conclusion derives from finding that patients with chronic TED maintain an IGF-1R overexpression.[18]

Integrated findings from those patients who were treated with an 8-infusion course of teprotumumab during the previously published pivotal trials indicate similar efficacy to those observed in the OPTIC-X study during the 24-week active treatment period. Likewise, follow-up results seen in OPTIC placebo patients who received teprotumumab initially during the OPTIC-X study, reported herein, were similar to those identified in the integrated off-treatment period (7−51 weeks) from the earlier trials.[24] The proptosis and diplopia responses of 85% and 74%, respectively, 27 weeks after the last infusion, as reported in the integrated follow-up data from those 2 randomized, double-masked, placebo-controlled trials,[24] compare favorably with the results reported herein.

In those patients receiving placebo in the OPTIC study and treated with teprotumumab in the OPTIC-X study, 91% of proptosis responders at week 24 maintained the proptosis response 27 weeks after last infusion in the OPTIC-X study follow-up. Furthermore, in those with baseline diplopia and a diplopia response at week 24, more than 80% maintained their response through the follow-up.

Consistent with the previously published pivotal studies with teprotumumab,[19,20] the clinical outcome improvements reported herein were associated with improved QOL as measured by the GO-QOL and its subscales for vision and appearance-related changes. Those patients receiving placebo in the OPTIC study and treated for the first time in the OPTIC-X study and those who were re-treated demonstrated or maintained moderate to large improvements in quality of life.

The overall safety profile in the OPTIC-X study and its follow-up was similar either in patients treated initially with teprotumumab or in those re-treated. Although the numbers of patients treated in the trial is small, no clinically meaningful differences were identified among these patients when compared with those reported either in the OPTIC study[20] or in the integrated analysis of the 2 pivotal trials.[23] In the patients who were re-treated, no evidence was found that the additional drug exposure produced any additional harm. Circulating growth hormone and insulin-like growth factor 1 levels both reliably increase as a consequence of IGF-1R inhibition in patients[25,26] and mice[27] with effects that are transient. No biological rationale exists for concern that the increases from baseline occurring as a consequence of 16 infusions of teprotumumab might have a materially different biological impact on neoplastic disease than those from the shorter 8-infusion protocol. The insulin-like growth factor 1 pathway does not involve metabolic or molecular imprinting, and therefore, long-term effects are unlikely. Finally, the class of insulin-like growth factor 1 inhibitors (including teprotumumab) were developed initially as anticancer drugs because cancer progression frequently is associated with increased expression of the IGF-1R and early investigations were promising. However, most of these investigations have been discontinued because of lack of efficacy. Furthermore, in a safety analysis of 772 patients treated with IGF-1R inhibitors, no evidence was cited for tumor progression.[28]

One patient, who was a smoker and taking concomitant NSAIDs, experienced a serious AE of an intracerebral hemorrhage. Despite the investigator deeming it as unrelated to teprotumumab, the relationship of teprotumumab infusion and this rare AE event is uncertain. Post-marketing pharmacovigilance monitoring as with any prescription medicine is ongoing to collect and assess further all serious AEs observed with teprotumumab treatment. No new AEs, or AEs of special interest, were detected in this study. Six patients in the OPTIC-X study experienced mild hearing impairment AEs (defined as discomfort with no disruption of normal daily activity), with 3 whose impairment resolved and 3 whose impairment had continued at the last visit (tinnitus, autophony, hypoacusis). Four patients were undergoing their first course of teprotumumab and 2 were

receiving a second course with hearing-related AEs reoccurring with re-treatment. Further research and longer observation are needed to understand this risk better.

The results reported herein from the OPTIC-X study continue to support a positive benefit-to-risk assessment of teprotumumab for the treatment of longer-term TED or re-treatment of TED in those few patients who experience disease flare or fail to respond initially. Treatment decisions require taking into account the burden of the disease, cost of treatment, and quality of life. Although the direct cost of teprotumumab ($14 900/vial or $342 700 for 8 infusions for a 70-kg patient at wholesale acquisition cost) is higher than that of other treatments for TED, this should be balanced by both the direct and indirect cost burden of the disease. Many patients who need surgeries to correct the consequences of undertreated TED have to wait months to years for the inflammation to subside to have these needed procedures, which can affect their quality of life profoundly. A 2012 study in Germany evaluated both the direct and indirect costs of TED and, although much smaller than those in the United States, can be extrapolated to more than $4 billion/year in 2021 United States dollars.[5] Data from the United States nationwide inpatient sample database indicate that mean charges for TED hospitalizations were $59 103 (95% CI, $50 106−$58 100) in 2017.[29] Furthermore, using data from the United States national ambulatory surgery sample, the mean charge for each TED-specific surgical encounter was $21 875 (95% CI, $19 066−$24 684) in 2018.[30]

The limitations of this study pertain to its open-label design because patients became aware of the treatment they were receiving. This may have influenced responses to the GO-QOL questionnaires. Patients and investigators were masked to the previous treatment received in the OPTIC study, although presence of muscle spasms or other AEs more common in teprotumumab-treated patients than patients receiving placebo may have indicated which treatment the patient received previously. Furthermore, the number of patients qualifying for re-treatment was small, and therefore, further efficacy and safety assessments are needed in this patient subset. The planned postmarketing study (ClinicalTrials.gov identifier, NCT05002998) will evaluate further the safety and efficacy of different teprotumumab treatment durations as well as the need for re-treatment in a larger number of patients with TED. Finally, although efficacy was achieved in those patients with a longer TED duration presented herein, more controlled study data are needed to document the efficacy of teprotumumab in those patients with chronic, longer-standing fibrotic disease. A randomized, placebo-controlled study in a patient population with chronic TED recently was initiated (ClinicalTrials.gov identifier, NCT04583735). Consistent with other regulatory placebo-controlled trials, AE data were collected prospectively, and patients with serious or severe AEs were followed up for their outcomes. As the safety profile of the drug emerges, more longitudinal analyses of those few events with a significant prevalence greater than that associated with placebo, such as muscle spasms (18%; 95% CI, 7.3%−28.7%), hearing loss (10%), and hyperglycemia (8%; 95% CI, 1.7%−15.0%)[24] need to be performed.

Conclusions

The OPTIC-X study evaluated the safety and efficacy of teprotumumab treatment and re-treatment in patients from the double-masked OPTIC study. This has allowed a more complete understanding of outcomes associated with (1) patients with longer disease duration, (2) re-treatment efficacy in initial nonresponders or those who experience disease flare, and (3) additional safety evaluations in these populations. Patients who had a longer duration of disease (previous placebo patients in the OPTIC study) responded similarly to those who were treated with teprotumumab in the phase 2 and phase 3 (OPTIC) studies. Most patients re-treated with teprotumumab showed clinically significant reductions in proptosis and diplopia, although the number of patients was small. These results require additional confirmation. Finally, although the number of patients treated in this study was small, no new safety concerns were found in any group during longer-term follow-up. This analysis adds to previous studies that have suggested that teprotumumab has disease-modifying activity and durability in patients with TED.[24]

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Abbreviations and Acronyms:
AE = adverse event; **CAS** = clinical activity score; **COVID-19** = coronavirus disease 2019; **GO-QOL** = Graves' ophthalmopathy-specific quality-of-life; **IGF-1R** = insulin-like growth factor 1 receptor; **IL** = interleukin; **OPTIC** = Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study; **IQR** = interquartile range; **OPTIC-X** = Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study; **SD** = standard deviation; **TED** = thyroid eye disease.

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