ORIGINAL ARTICLE

Teprotumumab for the Treatment of Active Thyroid Eye Disease

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ABSTRACT

BACKGROUND

Thyroid eye disease is a debilitating, disfiguring, and potentially blinding periocular condition for which no Food and Drug Administration–approved medical therapy is available. Strong evidence has implicated the insulin-like growth factor I receptor (IGF-IR) in the pathogenesis of this disease.

METHODS

In a randomized, double-masked, placebo-controlled, phase 3 multicenter trial, we assigned patients with active thyroid eye disease in a 1:1 ratio to receive intravenous infusions of the IGF-IR inhibitor teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks; the last trial visit for this analysis was at week 24. The primary outcome was a proptosis response (a reduction in proptosis of ≥2 mm) at week 24. Prespecified secondary outcomes at week 24 were an overall response (a reduction of ≥2 points in the Clinical Activity Score plus a reduction in proptosis of ≥2 mm), a Clinical Activity Score of 0 or 1 (indicating no or minimal inflammation), the mean change in proptosis across trial visits (from baseline through week 24), a diplopia response (a reduction in diplopia of ≥1 grade), and the mean change in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire across trial visits (from baseline through week 24; a mean change of ≥6 points is considered clinically meaningful).

RESULTS

A total of 41 patients were assigned to the teprotumumab group and 42 to the placebo group. At week 24, the percentage of patients with a proptosis response was higher with teprotumumab than with placebo (83% [34 patients] vs. 10% [4 patients], P<0.001), with a number needed to treat of 1.36. All secondary outcomes were significantly better with teprotumumab than with placebo, including overall response (78% of patients [32] vs. 7% [3]), Clinical Activity Score of 0 or 1 (59% [24] vs. 21% [9]), the mean change in proptosis (–2.82 mm vs. –0.54 mm), diplopia response (68% [19 of 28] vs. 29% [8 of 28]), and the mean change in GO-QOL overall score (13.79 points vs. 4.43 points) (P≤0.001 for all). Reductions in extraocular muscle, orbital fat volume, or both were observed in 6 patients in the teprotumumab group who underwent orbital imaging. Most adverse events were mild or moderate in severity; two serious events occurred in the teprotumumab group, of which one (an infusion reaction) led to treatment discontinuation.

CONCLUSIONS

Among patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, Clinical Activity Score, diplopia, and quality of life than placebo; serious adverse events were uncommon. (Funded by Horizon Therapeutics; OPTIC ClinicalTrials.gov number, NCT03298867, and EudraCT number, 2017-002763-18.)

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N Engl J Med 2020;382:341-52.
DOI: 10.1056/NEJMoa1910434

Thyroid eye disease, also known as Graves' orbitopathy or thyroid-associated ophthalmopathy, is a rare, debilitating autoimmune disease with an incidence of 1.9 cases per 10,000 population per year.[1] The disease course transitions from an active progressive period characterized by inflammation to a stable and fibrotic (inactive) period after 1 to 3 years.[2] Remodeling of the orbit and upper face results in diverse presentations, including dry eyes, increased lacrimation, local irritation, and eyelid retraction in mild cases, but it can also manifest as pronounced proptosis, diplopia (due to uneven motility restriction), and optic nerve compression, with potential vision loss in more severe disease. Immunomodulatory agents may reduce inflammation in active disease but have limited effects on the long-term sequelae of thyroid eye disease, such as disfigurement and disability from proptosis and diplopia, which impair quality of life.[3-5] Patients with severe disease often require multiple remedial surgical procedures (e.g., orbital decompression, strabismus correction, and eyelid repair) as well as cosmetic procedures.

The causes of thyroid eye disease, a condition historically linked to Graves' disease, are incompletely understood.[1] Thyroid eye disease develops in approximately 40% of patients with Graves' disease.[1,6] Autoantibodies (thyroid-stimulating immunoglobulins) targeting the thyrotropin receptor drive hyperthyroidism in Graves' disease, but data indicate that additional autoantigens and antibodies are involved in the development of thyroid eye disease.[7] The insulin-like growth factor I receptor (IGF-IR), which is overexpressed by orbital fibroblasts and B and T cells in Graves' disease and thyroid eye disease, plays a central role.[7-9] Thyrotropin receptors and IGF-IRs form physical and functional complexes that cause thyroid eye disease, including hyaluronan accumulation and cytokine expression, resulting in inflammation, edema, and expansion of extraocular muscle and adipose tissue.[10-13] Teprotumumab, a fully human monoclonal antibody, attenuates signaling initiated at either receptor, thereby blocking pathologic immune responses in active thyroid eye disease.[10,13]

In the current trial (OPTIC), we investigated the efficacy and safety of teprotumumab, an IGF-IR inhibitor, as compared with placebo in patients with clinically active thyroid eye disease. Whereas the phase 2 trial evaluated proptosis as a component of the primary outcome,[14] the OPTIC trial focused on clinically meaningful reductions in proptosis as the primary outcome.

METHODS

TRIAL DESIGN AND OVERSIGHT

The OPTIC trial was conducted at 13 sites in the United States and Europe (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was approved by the Food and Drug Administration (FDA) and by the institutional review board or independent ethics committee at each trial site and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Horizon Therapeutics sponsored the trial; designed the trial with input from a steering committee of investigators; contributed to the collection, analysis, and interpretation of the data; and contributed to the writing and review of the manuscript and approval of the final version. All the authors made the decision to submit the manuscript for publication. Data were collected by the authors who were trial investigators. The conduct of the trial was overseen by a contract research organization (Syneos Health, formerly INC Research), and a data and safety monitoring board performed periodic assessments. Statistical analyses were prespecified and were overseen and reviewed by Horizon Therapeutics in agreement with the FDA. The manuscript was written by a team of authors under the leadership of the first two authors and the last author, with input from all the authors and editorial assistance from the employees of Horizon Therapeutics. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan (available at NEJM.org).

PATIENTS

Patients were eligible for inclusion in the trial if they were 18 to 80 years of age, had received a diagnosis of Graves' disease, had active, moderate-to-severe thyroid eye disease (frequently associated with at least one of the following: lid retraction of ≥2 mm, moderate or severe soft-tissue involvement, proptosis of ≥3 mm above the normal values for race and sex, and periodic or con-

stant diplopia), had ocular symptoms that began within 9 months before the baseline assessment, and had a Clinical Activity Score of at least 4 (a description of the Clinical Activity Score is provided below) in the more proptotic (study) eye. Patients were required to be euthyroid, although mild hypothyroidism or hyperthyroidism was allowed at screening.

Key exclusion criteria were previous orbital irradiation or surgery for thyroid eye disease, decreasing visual acuity or a visual-field or color vision defect from optic nerve involvement within the previous 6 months, glucocorticoid use (cumulative dose equivalent to ≥1 g of methylprednisolone for the treatment of thyroid eye disease), and any previous treatment with rituximab or tocilizumab. The use of certain medications and therapies was restricted (Table S3), and exclusion criteria included specific preexisting medical conditions. A complete list of inclusion and exclusion criteria is provided in Table S2.

RANDOMIZATION AND MASKING

After screening, the patients were randomly assigned in a 1:1 ratio to receive intravenous infusions of either teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks for a total of eight infusions; the last trial visit of the treatment period was at 24 weeks (Fig. S1). Randomization was performed with the use of an interactive Web-response system (Bioclinica eClinical Solutions, a contract research organization). The patients, investigators, and trial-site personnel (excluding the formulating pharmacists) were unaware of the trial-group assignments and remained unaware through the follow-up data analysis and completion of the trial-site closeout visit.

OUTCOMES AND ASSESSMENTS

The primary outcome was a proptosis response (defined as a reduction in proptosis of ≥2 mm from baseline in the study eye without a corresponding increase of ≥2 mm in the fellow eye) at week 24. Key secondary outcomes were an overall response (defined as a reduction of ≥2 points in the Clinical Activity Score plus a reduction in proptosis of ≥2 mm without a corresponding increase [of ≥2 points or ≥2 mm] in the fellow eye) at week 24, a Clinical Activity Score of 0 or 1 (indicating no or minimal inflammation, respectively) at week 24, the mean change in proptosis (measured in millimeters) across trial visits (from baseline through week 24) and at each trial visit from baseline, a diplopia response (defined as a reduction in diplopia of ≥1 grade from baseline) at week 24, and the mean change in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire across trial visits (from baseline through week 24) and at each trial visit from baseline.[15] Outcomes were also evaluated in the contralateral eye.

At each trial site, proptosis was measured by the same observer using the same Hertel instrument. Inflammation was quantified according to the Clinical Activity Score,[16] which is based on seven components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side-to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica, and swelling of the eyelids. Each component is scored as present or absent (score of 1 or 0, respectively), and the Clinical Activity Score is given as the sum of the scores (range, 0 to 7, with higher scores indicating greater level of inflammation). A change of at least 2 points is considered clinically meaningful.[17]

Changes in diplopia grade were assessed with the use of the Gorman subjective diplopia score (range, 0 to 3),[17] which includes four categories: no diplopia (absent, scored as 0), diplopia in the primary position of gaze when the patient is tired or awakening (intermittent, scored as 1), diplopia at extremes of gaze (inconstant, scored as 2), and continuous diplopia in the primary or reading position (constant, scored as 3). A reduction of at least one grade is considered clinically meaningful.[17]

Patients completed the GO-QOL questionnaire, a 16-item questionnaire that is administered by the patients themselves. The questionnaire includes two subscales (8 questions each) that assess the effects of thyroid eye disease, as perceived by the patient, on visual functioning and appearance (i.e., psychosocial functioning related to changed physical appearance).[15] The sum of the scores on each subscale and an overall combined score were calculated, and each was transformed to a scale from 0 to 100: transformed score = [(sum of each score − number of

completed items) / (2 × number of completed items)] × 100. A mean change of at least 6 points on one or both subscales is considered clinically meaningful. For invasive treatments, a change of at least 10 points is considered clinically meaningful.[18]

We monitored safety, including adverse events of special interest (i.e., anaphylaxis, infusion-related reactions, hyperglycemia, muscle spasms, diarrhea, and hearing impairment) (Table S4, and see the protocol). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

After 24 weeks, the patients who did not have a proptosis response could enter an open-label extension study (OPTIC-X; ClinicalTrials.gov number, NCT03461211) and receive eight additional infusions of teprotumumab. The patients who were not included in the extension study were followed for 48 weeks. A patient who had a proptosis response but then had a relapse during the follow-up period could enter the extension study (Table S5). The follow-up and extension study are currently ongoing.

IMAGING

Orbital imaging (computed tomography or magnetic resonance imaging) was performed before and after teprotumumab treatment in six patients at one trial site in the United States. Extraocular muscle and orbital fat volumes were calculated by means of three-dimensional volumetric quantification in combination with validated Mimics software technology (Materialise). Two observers who were unaware of the trial-group assignments performed the manual tracings and volumetric analysis, measuring from the orbital apex to the globe insertion; each image was assessed twice to minimize interobserver and intraobserver variability.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of a phase 2 trial,[14] in which a 51 percentage-point difference in the percentage of patients who had a reduction in proptosis of at least 2 mm at week 24 was observed between those who received teprotumumab and those who received placebo. The sample size of 38 patients per trial group was estimated to provide the trial with 90% power to detect a 39 percentage-point difference between the teprotumumab group and the placebo group with respect to the same outcome, at a two-sided alpha level of 0.05; the sample size was adjusted to allow for a rate of discontinuation of 16%.

All efficacy analyses were performed in the intention-to-treat population (all patients who underwent randomization). Analyses to evaluate the sensitivity of the intention-to-treat analyses were performed in the per-protocol population (all patients who underwent randomization, received ≥1 infusion, had at least one postbaseline value, and completed the treatment period).

Week 24 efficacy data were included in the analyses, regardless of premature discontinuation of the trial drug or placebo. The trial drug or placebo was considered to have failed in patients who had missing week 24 data for binary outcomes. In the primary outcome analysis, we assessed the between-group difference, stratified according to tobacco use, in the percentage of patients who had a proptosis response. Cochran–Mantel–Haenszel weighting was used to estimate the percentage-point differences in risk and the standard error of the risk difference within strata of smoking status.

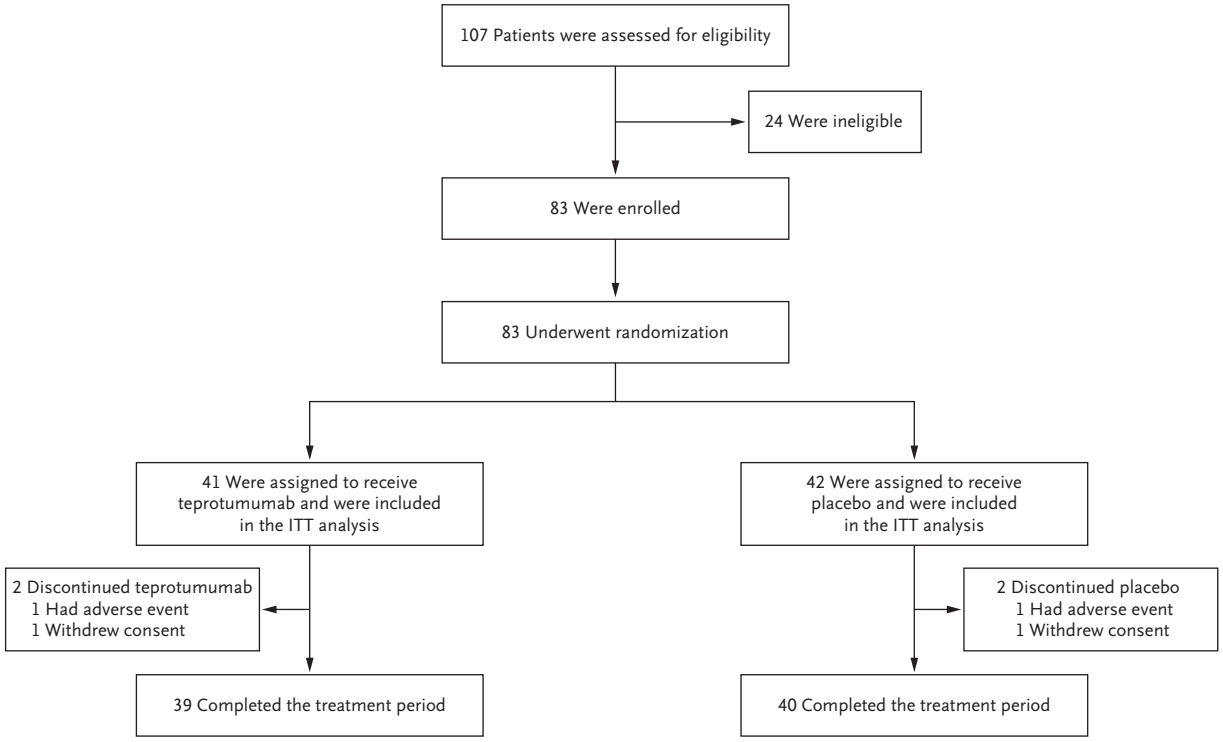
To reduce the type I error rate, all outcome measures were tested in a hierarchical stepwise fashion, as outlined in the statistical analysis plan. A mixed-model repeated-measures analysis of covariance was used to assess the secondary outcomes of change from baseline in proptosis and overall score on the GO-QOL questionnaire (continuous variables). Model terms included baseline assessment of proptosis and GO-QOL, tobacco use status (nonuser or user), trial group, visit, and visit-by-trial-group and visit-by-baseline-score interactions.

RESULTS

PATIENTS

Between October 24, 2017, and August 31, 2018, a total of 107 patients were screened and 83 underwent randomization (41 to the teprotumumab group and 42 to the placebo group [intention-to-treat population]) (Fig. 1A). All patients in the intention-to-treat population were included in the efficacy analyses. In each trial group, 95% of the patients completed the treatment period. Baseline characteristics were similar in the two groups (Table 1), as were the use of sulfur-containing imidazole derivatives for the treatment of Graves' disease and the use of

A



B

Efficacy Outcomes	Teprotumumab	Placebo	Difference (95% CI)	P Value
Primary outcome of proptosis response at wk 24				
In the ITT population — % of patients (no./total no.)	83 (34/41)	10 (4/42)	73 (59 to 88)	<0.001
In the per-protocol population — % of patients (no./total no.)	88 (29/33)	12 (4/34)	76 (61 to 92)	<0.001
Secondary outcomes in the ITT population				
Overall response at wk 24 — % of patients (no./total no.)	78 (32/41)	7 (3/42)	71 (56 to 86)	<0.001
Clinical Activity Score of 0 or 1 at wk 24 — % of patients (no./total no.)	59 (24/41)	21 (9/42)	36 (17 to 55)	<0.001
Mean change in proptosis from baseline through wk 24 — mm	−2.82±0.19	−0.54±0.19	−2.28 (−2.77 to −1.80)	<0.001
Diplopia response at wk 24 — % of patients (no./total no. with diplopia at baseline)	68 (19/28)	29 (8/28)	39 (16 to 63)	0.001
Mean change in GO-QOL score from baseline through wk 24	13.79±2.07	4.43±2.10	9.36 (4.08 to 14.64)	<0.001

Figure 1. Enrollment, Randomization, and Follow-up and Efficacy Outcomes at Week 24.

Panel A shows the enrollment, randomization, and follow-up of the patients through the treatment period. The patients were randomly assigned to received intravenous infusions of either teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks for a total of eight infusions; the last trial visit was at week 24. Panel B shows the efficacy outcome results. Cochran–Mantel–Haenszel weighting was used to estimate the percentage-point differences in risk and corresponding 95% confidence intervals with respect to the primary outcome (i.e., the percentage of patients with a proptosis response [defined as a reduction in proptosis of ≥2 mm]) and the secondary outcomes of the percentage of patients with an overall response (defined as a reduction of ≥2 points in the Clinical Activity Score [scores range from 0 to 7, with higher scores indicating greater level of inflammation] plus a reduction in proptosis of ≥2 mm), the percentage of patients with a Clinical Activity Score of 0 or 1 (indicating no or minimal inflammation, respectively), and the percentage of patients with a diplopia response (defined as a reduction in diplopia of ≥1 grade; 28 patients in each trial group had diplopia at baseline). The least-squares mean change (±SE) was calculated for the secondary outcomes of change from baseline in proptosis and change from baseline in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire (continuous variables) with the use of a mixed-model repeated-measures analysis of covariance model with an unstructured covariance matrix that included the following terms: baseline score, tobacco use status (nonuser or user), trial group, visit, and visit-by-trial-group and visit-by-baseline-score interactions. The GO-QOL questionnaire includes two subscales (8 questions each) that assess the effects of thyroid eye disease, as perceived by the patient, on visual functioning and appearance. The sum of the scores on each subscale and an overall combined score were calculated, and each was transformed to a scale from 0 to 100: transformed score=[(sum of each score−number of completed items) / (2×number of completed items)]×100. All efficacy analyses were controlled for multiplicity.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Teprotumumab (N=41)	Placebo (N=42)
Sex — no. (%)		
Male	12 (29)	11 (26)
Female	29 (71)	31 (74)
Age — yr	51.6±12.6	48.9±13.0
Race — no. (%)†		
White	35 (85)	37 (88)
Black	4 (10)	2 (5)
Asian	2 (5)	1 (2)
Other	0	2 (5)
Duration of thyroid eye disease — mo.	6.2±2.3	6.4±2.4
Duration of Graves' disease — yr	3.5±6.1	2.2±3.2
Smoking status — no. (%)		
Smoker	9 (22)	8 (19)
Nonsmoker	32 (78)	34 (81)
Proptosis measurement — mm	22.62±3.32	23.20±3.21
Clinical Activity Score‡	5.1±0.9	5.3±1.0
Thyroid hormone level — pmol/liter		
Free triiodothyronine	5.1±1.8	5.3±1.7
Minimum–maximum	3.3–13.0	3.3–11.1
Free thyroxine	16.5±5.3	16.2±4.8
Minimum–maximum	6.3–34.2	8.8–32.2
Thyrotropin level — mIU/liter	1.75±4.16	1.42±2.17
Minimum–maximum	0.01–25.77	0.01–7.99

* Plus–minus values are means ±SD. To convert the values for free triiodothyronine to nanograms per deciliter, divide by 15.4. To convert the values for free thyroxine to nanograms per deciliter, divide by 12.87. The normal range for free thyroxine is 11.5 to 22.7 pmol per liter; for free triiodothyronine, 3.5 to 6.5 pmol per liter; and for thyrotropin, 0.55 to 4.78 mIU per liter.

† Race was reported by the patient.

‡ The Clinical Activity Score is based on seven components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side-to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica, and swelling of the eyelids. Each component is scored as present or absent (score of 1 or 0, respectively), and the Clinical Activity Score is given as the sum of the scores (range, 0 to 7, with higher scores indicating greater level of inflammation).

thyroid hormones, both before and during the trial.

OUTCOMES

The results of the efficacy outcomes in the intention-to-treat population are provided in Figure 1B. With respect to the primary outcome, 83% of the patients in the teprotumumab group had a proptosis response, as compared with 10% of the patients in the placebo group (between-group difference, 73 percentage points; 95% CI, 59 to 88; P<0.001). The results of the sensitivity analysis in the per-protocol population were similar to those of the primary outcome analysis. The response was observed early and occurred in an increasing percentage of patients throughout the trial (Fig. 2A). The initial response occurred at week 6 (±3 days) in the majority of patients in the teprotumumab group; the median time to response was 6.4 weeks. At week 24, the mean change from baseline in proptosis among the patients in the teprotumumab group was –3.32 mm (between-group difference, –2.79 mm; 95% CI, –3.40 to –2.17) and was greater than that in the placebo group at all time points (Fig. 2B). Between-group differences and corresponding 95% confidence intervals at intermediate time points, which were not controlled for multiplicity, are provided in Figure S2.

The key secondary outcomes were significantly better among the patients in the teprotumumab group than in the placebo group (Fig. 1B). The percentage of patients with a Clinical Activity Score of 0 or 1 and the percentage with an overall response increased in the teprotumumab group throughout the treatment period and were higher than those in the placebo group at all trial visits (Fig. 2C and 2D). In each trial group, 28 patients had diplopia at baseline. A diplopia response (i.e., a reduction in diplopia of ≥1 grade) was observed in a higher percentage of patients in the teprotumumab group than in the placebo group at the first visit and each subsequent visit (Fig. 2E). Further analysis indicated that the better diplopia response in the teprotumumab group occurred regardless of the severity of diplopia at baseline.

The overall score on the GO-QOL questionnaire was better among the patients in the teprotumumab group than among those in the placebo group over the course of the trial (Fig. 2F). The 95% confidence intervals of the between-group differences did not cross zero for any of the outcome measures at any visit, with the exception of the GO-QOL score at week 6 (Fig. S2 in Supplementary Appendix).

The orbital imaging performed in the six patients in the teprotumumab group (performed at one trial site) showed that the reduction in proptosis was associated with a reduction in extraocular muscle volume, orbital fat volume, or both. All six patients had significantly decreased extraocular muscle volume, with a mean

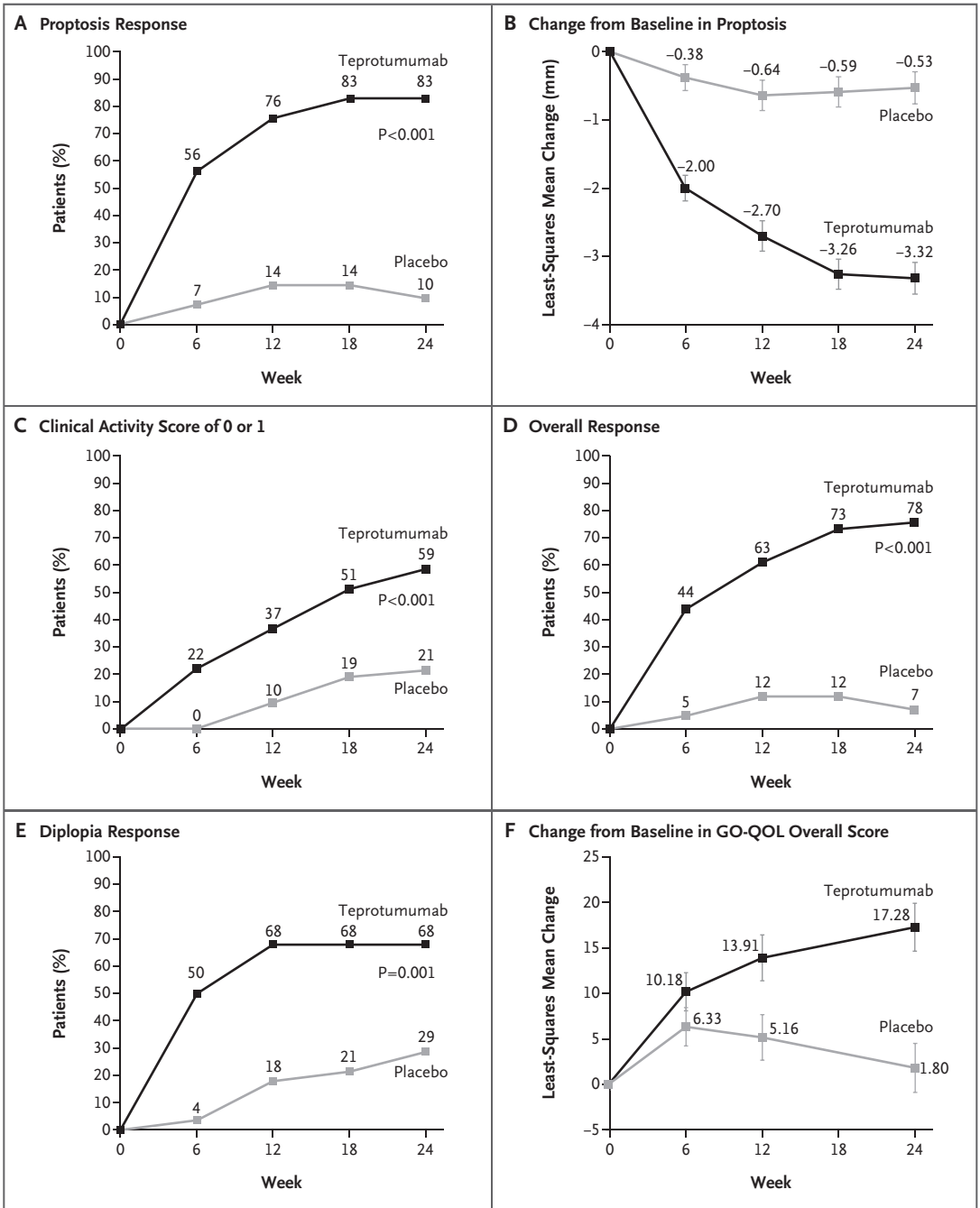


Figure 2. Efficacy Outcomes over the Course of the Trial.

A total of 41 patients were randomly assigned to the teprotumumab group, and 42 to the placebo group. Panel A shows the primary outcome of the percentage of patients with a proptosis response; Panel B, the change from baseline in proptosis (I bars indicate the standard error); Panel C, the percentage of patients with a Clinical Activity Score of 0 or 1; Panel D, the percentage of patients with an overall response; Panel E, the percentage of patients with a diplopia response; and Panel F, the change from baseline in the overall score on the GO-QOL questionnaire (I bars indicate the standard error). The P values for the between-group differences at week 24 (Panels A, C, D, and E) were adjusted for multiplicity. The mean changes in proptosis measurement and GO-QOL overall score from baseline to each visit were significantly better in the teprotumumab group, with the exception of the GO-QOL score at week 6 (Fig. 1B and Fig. S2). The between-group differences and 95% confidence intervals for each time point are provided in Figure S2 in the Supplementary Appendix.

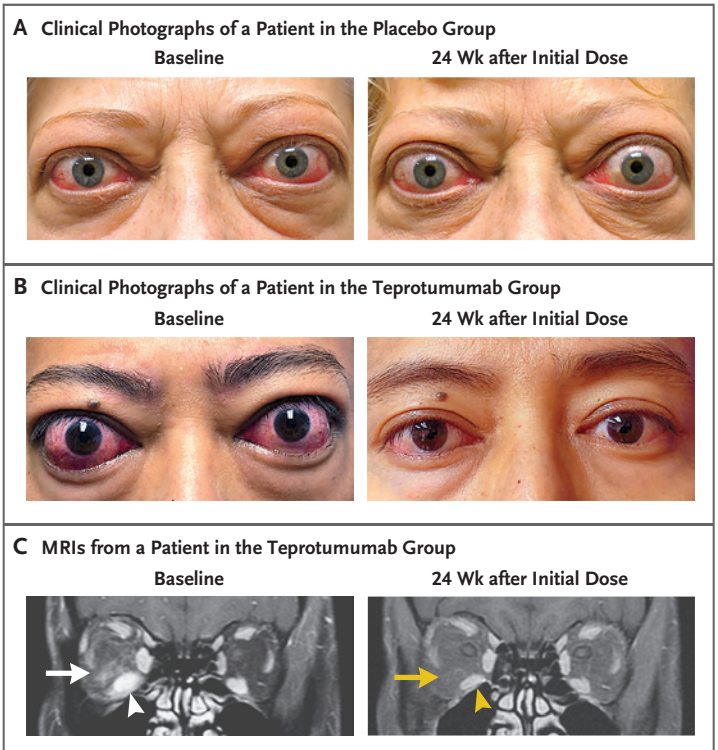


Figure 3. Clinical Photographs and MRIs at Baseline and 24 Weeks after the Initial Dose of Placebo or Teprotumumab.

Panel A shows the clinical photographs of a patient in the placebo group. At baseline, the patient had considerable proptosis (29 mm in the left eye and 27 mm in the right eye), edema, and multiple inflammatory signs (Clinical Activity Score of 7 in the left eye and 5 in the right eye). At week 24, the patient still had considerable proptosis (28 mm in the left eye and 26 mm in the right eye) and inflammatory signs (Clinical Activity Score of 5 in the left eye and 5 in the right eye). Panel B shows the clinical photographs of a patient in the teprotumumab group. At baseline, the patient had considerable proptosis (24 mm in each eye), upper and lower eyelid retraction, edema, and multiple inflammatory signs (Clinical Activity Score of 5 in each eye). At week 24, the patient had considerable reductions in both proptosis (–5 mm) and Clinical Activity Score (–4 points) in each eye. Panel C shows coronal, contrast-enhanced, fat-saturated, T1-weighted magnetic resonance images (MRIs) from a patient in the teprotumumab group. At baseline, the MRI showed marked enhancement of the inferior rectus muscle (white arrowhead) and orbital fat (white arrow), findings indicative of inflammation and edema. In addition, the inferior rectus muscle is shown to be enlarged (white arrowhead). The patient had a proptosis measurement of 23 mm, a Clinical Activity Score of 5, and a Gorman subjective diplopia score of 3 (range, 0 [no diplopia] to 3 [continuous diplopia in the primary or reading position]). At week 24, the MRI showed resolution of the enhancement of the inferior rectus muscle (yellow arrowhead) and orbital fat (yellow arrow). The size of the inferior rectus muscle was reduced by 49% according to volumetric analysis (yellow arrowhead), and the volume of the medial rectus muscle was reduced by 41%. The patient had a proptosis measurement of 18 mm, a Clinical Activity Score of 0, and a Gorman subjective diplopia score of 0.

percentage decrease of 35% (Table S6). The inferior rectus muscle volume exhibited the largest reduction in four of the six patients. The mean percentage decrease in volume of the most affected muscle was 45% (range, 27 to 62), with a 48% decrease in the mean absolute volume (an illustrative example is provided in Fig. 3). Orbital fat volume was reduced by 44% in one patient and by 40% in another.

SAFETY

Adverse events that occurred in at least 5% of the patients in either trial group within 21 days after the final dose are listed in Table 2. Most of the adverse events that occurred during this period were of grade 1 or 2. Potential infusion reactions were noted in six patients in the teprotumumab group and in four patients in the placebo group. Two of these events were considered to be infusion reactions to teprotumumab; one patient had a nonanaphylactic reaction during the initial infusion and discontinued the trial drug; the other patient was premedicated, received subsequent infusions at a slower rate, and completed the treatment period.

Adverse events of special interest that occurred in less than 5% of the patients in either trial group within 21 days after the last dose included the development of hyperglycemia in two patients (<5%) in the teprotumumab group (both cases were mild). Hearing impairment was reported in five patients in the teprotumumab group: two had hypoacusis, which resolved; one had deafness, which resolved; one had autophony (bilateral intermittent echoing of the patient's own voice that occurred in conjunction with sore throat), which resolved; and one had mild patulous eustachian tube, which resolved. No auditory issues occurred in the placebo group. Five patients (four women) in the teprotumumab group had a body-weight loss of at least 5.0 kg during the trial. At baseline, the body weights of these patients ranged from 59.9 kg to 98.2 kg, and overall weight loss ranged from –5.7 kg to –19.0 kg. The 19-kg weight loss was intentional. No adverse events associated with decreased body weight were reported in these patients through 21 days after the final dose.

No deaths occurred. Two serious adverse events occurred in the teprotumumab group: pneumo-

Table 2. Safety.*

Adverse Event	Teprotumumab (N=41)	Placebo (N=42)	Summary of Adverse Events in the Teprotumumab Group
	no. of patients (%)		
Muscle spasm	13 (32)	4 (10)	All events were nonserious; most were mild in severity, and 3 were moderate.
Alopecia	8 (20)	5 (12)	All events were mild in severity, except for 1 event of moderate severity.
Nausea	6 (15)	4 (10)	All events were mild in severity.
Fatigue	5 (12)	1 (2)	Two patients had fatigue of moderate severity; other events were mild.
Diarrhea	4 (10)	5 (12)	No event was suggestive of inflammatory bowel disease.
Headache	4 (10)	4 (10)	All events were mild in severity and nonserious.
Dry skin	4 (10)	0	All events were mild in severity and nonserious.
Dysgeusia	4 (10)	0	All events were mild in severity.
Stomatitis	3 (7)	1 (2)	All events were mild in severity and nonserious.
Amenorrhea	3 (7)	0	All events were nonserious; 2 were mild in severity and 1 was moderate.
Dizziness	3 (7)	0	All events were nonserious; 2 were mild in severity and 1 was moderate.
Cough	2 (5)	3 (7)	Both events were mild in severity and nonserious.
Upper abdominal pain	2 (5)	3 (7)	All events were mild in severity and nonserious.
Influenza	1 (2)	3 (7)	The 1 event was moderate in severity.
Any adverse events	35 (85)	29 (69)	
Infusion reaction	1 (2)	0	A grade 2 event occurred on day 1 and was considered by an investigator to be possibly related to the trial drug. The event resolved with hydrocortisone treatment, and the patient discontinued the trial.
Pneumothorax	1 (2)	0	A grade 4 event occurred on day 113 and was considered by an investigator unrelated to the trial drug. The event resolved with treatment, and the patient completed the treatment period.
Visual-field defect	0	1 (2)	Not applicable (occurred in a patient receiving placebo).
Any serious adverse event	2 (5)	1 (2)	

* Shown are the adverse events that occurred in 5% or more of patients in either study group within 21 days after the final dose of the trial drug or placebo.

thorax (probably unrelated to the trial drug, as determined by an investigator) and an infusion reaction that led to withdrawal from the trial. One patient in the placebo group reported a serious adverse event (a visual-field defect in need of decompression surgery) and was withdrawn from the trial. No antidrug antibodies were detected in the patients who received teprotumumab.

At baseline, eight patients in the teprotumumab group had abnormal findings on slit-lamp examinations, which included clinically significant abnormalities consistent with thyroid eye disease, primarily keratitis, punctate keratopathy, and punctate epithelial erosions. At the last assessment, three of these patients had normal slit-lamp examination findings, one had abnormal, clinically nonsignificant findings, and four had abnormal, clinically significant findings.

Three patients in the placebo group had abnormal findings on slit-lamp examination at baseline. At the last evaluation, one of these patients had abnormal, clinically nonsignificant findings, and two had abnormal, clinically significant findings. No worsening of the abnormalities found on slit-lamp examinations at baseline occurred in either group.

DISCUSSION

In this trial involving patients with active thyroid eye disease, the primary and all secondary outcomes were better among those who received teprotumumab than among those who received placebo, with meaningful between-group differences in proptosis response, Clinical Activity Score, diplopia response, and overall response. The effect of teprotumumab was rapid for each outcome, which was evident at the first post-baseline assessment at week 6, and the outcomes continued to improve over the 24-week treatment period.

With respect to the primary outcome, the percentage of patients who had a proptosis response corresponded to a number needed to treat of 1.36, which shows that nearly all the patients who received teprotumumab, as compared with a few patients (4 of 42) who received placebo, had a reduction in proptosis of at least 2 mm. Indeed, all the patients who received teprotumumab had some reduction in proptosis at week 24 (Fig. S3). The efficacy of teprotumumab was shown, regardless of the initial severity of proptosis (Fig. S4). Among the patients in the teprotumumab group, the least-squares mean change in proptosis at week 24 (–3.32 mm) is similar to the best results attained with single-wall orbital decompression surgery.[19]

Teprotumumab led to better patient-reported outcomes, as evidenced by the overall scores and scores on the visual and appearance subscales of the GO-QOL questionnaire, all of which were significantly better with teprotumumab than with placebo at week 24. The least-squares mean change at week 24 in the scores on the visual-functioning and appearance subscales were 15 points and 19 points, respectively, in the teprotumumab group, and 3 points and less than 1 point, respectively, in the placebo group. The threshold for clinical importance with a noninvasive therapy such as teprotumumab is a change of at least 6 points.[14,18]

The percentage of patients with a Clinical Activity Score of 0 or 1, which is widely accepted as indicative of absence of disease activity, was significantly higher in the teprotumumab group than in the placebo group. The percentage of patients with an overall response (a composite outcome of a reduction in both proptosis and Clinical Activity Score) and the percentage with a diplopia response (a reduction in diplopia of ≥1 among those who had diplopia at baseline) were significantly higher in the teprotumumab group at all time points and mirrored the phase 2 trial outcomes.[14] No clinically significant differences in changes in thyroid function values from baseline were observed between the placebo group and the teprotumumab group, and no consistent trends were noted throughout the trial (Table S7).

Active thyroid eye disease remains an inadequately treated, life-altering, and potentially sight-threatening disease for which no FDA-approved pharmacotherapy is available. Teprotumumab, as compared with placebo, led to striking physical changes in patients who had considerable proptosis (Fig. 3), and those with the highest levels of proptosis had the largest reductions. Data showing similar effects with glucocorticoids or other immunomodulators are lacking.[20-24]

With the exception of sight-threatening dysthyroid optic neuropathy, surgical procedures for proptosis and diplopia (i.e., orbital decompression and extraocular muscle [strabismus] repair, respectively) are not recommended during active disease. Patients may be offered occlusion or prisms for diplopia while waiting (sometimes for years) for their thyroid eye disease to become inactive before undergoing remedial surgery.

The use of teprotumumab in patients with active thyroid eye disease was predicated on in vitro studies that showed consequential interactions between circulating autoantibodies against thyrotropin receptor and IGF-IR displayed on orbital fibroblasts[7,25] and provided evidence that thyrotropin receptors and IGF-IRs form physical and functional signaling complexes.[10,13] The current clinical trial provides insights into the in vivo mechanisms and tissue-targeting involved in the action of teprotumumab. Teprotumumab

mediates the reduction in extraocular muscle volume (with associated reductions in proptosis and diplopia) as well as the effects on orbital fat (reduction in proptosis). These findings are consistent with the critical roles played by the IGF-I pathway in maintaining the integrity and function of both adipocytes[26] and muscle cells.[27]

Most adverse events were of grade 1 or 2 and were similar to those reported previously.[14] Adverse events of special interest, including potential infusion-related reactions, hyperglycemia, muscle spasms, diarrhea, and hearing impairment, that occurred within 21 days after the final dose were of grade 1 or 2, and with the exception of a single teprotumumab infusion–related reaction, none led to discontinuation of the trial drug.

Limitations of this trial include the lack of long-term follow-up (i.e., the number of patients in need of orbital decompression, surgical procedures for strabismus correction, or both). The collection of data on the durability of efficacy is ongoing. Additional data are being collected from the patients in either trial group who did not have a proptosis response and from those who had a proptosis response but then had a relapse during follow-up. In the phase 2 trial, the efficacy of teprotumumab was maintained for up to 48 weeks of follow-up in most of the patients who had a proptosis response and a diplopia response.[28,29]

The results of the current trial show that teprotumumab, administered once every 3 weeks, was significantly more effective than placebo with respect to the primary outcome and all key secondary outcomes that were evaluated in this 24-week assessment of moderate-to-severe, active thyroid eye disease. Objective measures of thyroid eye disease and patient-reported quality of life were significantly better with teprotumumab in most patients, and the effects of the trial drug occurred rapidly; serious adverse events were uncommon with teprotumumab.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by Horizon Therapeutics.

Dr. Douglas reports receiving consulting fees from Horizon Therapeutics; Drs. Sile, Thompson, Vescio, and Holt and Ms. Perdok, being employed by and owning stock in Horizon Therapeutics; Dr. Dailey, receiving consulting fees from Horizon Therapeutics; Drs. Schiffman and Tang, receiving grant support and consulting fees from Immunovant Sciences; Dr. Salvi, receiving travel support from Immunovant; Dr. Wester, receiving advisory board fees from Horizon Therapeutics; Dr. Sherman, being employed by and serving as chief medical officer for Horizon Therapeutics; and Dr. Smith, receiving consulting fees from Immunovant and Horizon Therapeutics, holding patents 6936426 and 7998681 on detection of antibody-mediated inflammatory autoimmune disorders, holding patent 8153121 on diagnosis and therapy of antibody mediated inflammatory autoimmune disorders, and holding patent 8178304 on diagnostic methods related to Graves' disease and other autoimmune disorders. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients for participating in this trial and the following persons for assisting in the trial conduct: Katharina A. Ponto, M.D., Anna Beck, M.D., and Michaela Riedl, Ph.D. (Johannes Gutenberg University Medical Center, Mainz, Germany); Angela Sframeli, M.D., Poupak Fallahi, M.D., Giovanna Rotondo Dottore (graduate student), Ilaria Bucci, Ph.D., and Ilaria Ionni, M.D. (University of Pisa, Pisa, Italy); Nicola Currò, M.D., Danila Covelli, M.D., and Elisa Lazzaroni, M.D. (Departments of Internal Medicine and Endocrinology, Fondazione IRCCS Cà Granda, Milan, Italy); Sang H. Hong, M.D., and Tim S. Wells, M.D. (Medical College of Wisconsin, Milwaukee); Mareile Stohr, M.D., and Harald Lahner, M.D. (University Hospital Essen, University Duisburg-Essen, Essen, Germany); Chad Soreson and Jennifer Murdock, M.D. (Oregon Health and Sciences University, Portland); Andrew Meador, M.D., and Paula S. McCune, R.N. (University of Tennessee Center for the Health Sciences, Memphis); and Andrew Rong, M.D. (Bascom Palmer Eye Institute, Miami). We acknowledge the following employees of Horizon Therapeutics: Naina Barretto, Ph.D., for writing and editorial assistance, Megan Francis-Sedlak, Ph.D., for analytic, writing, and editorial assistance, Teresa M.Y. Kok, R.Ph., M.B.A., for analytic and editorial assistance, and Melanie Gloria and Julie Ball, M.S., for trial support.

APPENDIX

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