

Teprotumumab in Clinical Practice: Recommendations and Considerations From the OPTIC Trial Investigators

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Background: Thyroid eye disease (TED) is a vision-threatening and debilitating condition that until very recently had no Food and Drug Administration (FDA)-approved medical therapies. Teprotumumab has recently been approved to treat TED. We aim to provide guidance for its use, based on the input of the US investigators who participated in Phase 2 and Phase 3 clinical trials.

Methods: An expert panel was convened on October 11th and November 16th of 2019. All panel members had extensive experience as investigators in the Phase 2 and/or Phase 3 clinical trials of teprotumumab. Consensus

among those investigators was reached to determine patient characteristics most appropriate for teprotumumab treatment. Safety guidelines were also reviewed and agreed on.

Results: The authors recommend that teprotumumab be considered first-line therapy for patients with clinically significant ophthalmopathy, including those with disease duration exceeding 9 months. The clinical activity score (CAS) may be useful for longitudinal monitoring but should not be used to determine treatment eligibility. Criteria will likely be expanded after more experience with the drug. Using teprotumumab for patients with TED with substantial signs, symptoms, or morbidity without a CAS score of >4 (e.g., progressive proptosis, diplopia, and early compressive optic neuropathy) or more, could be considered. Diabetes mellitus and inflammatory bowel disease comorbidities should not be exclusionary, but stringent monitoring in these patients is recommended. Drug dosing, administration interval, and duration should adhere to the study protocol: 8 infusions, separated by 3 weeks. Patients with more severe disease may benefit from additional doses. Corticosteroids can be used before or during teprotumumab therapy. Clinical and laboratory monitoring should be consistent with good clinical practice for patients receiving teprotumumab.

Conclusions: Confirming the efficacy of teprotumumab usage outside the narrow parameters of the completed clinical trials will require rigorous scientific validation. As a step in that direction, we believe its on-label usage is appropriately applied to all patients with TED with substantial symptoms or morbidity, as judged by their physician.

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R. S. Douglas reports receiving consulting fees from Horizon Therapeutics. R. A. Dailey receiving consulting fees from Horizon Therapeutics. G. J. Harris receiving advisory board fees from Horizon Therapeutics. J. S. Schiffman and R. A. Tang receiving grant support and consulting fees from Immunovant Sciences. S. T. Wester receiving advisory board fees from Horizon Therapeutics. T. J. 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. The remaining authors report no conflicts of interest.

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Journal of Neuro-Ophthalmology 2021;41:461–468

doi: 10.1097/WNO.0000000000001134

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Thyroid eye disease (TED), also known as Graves ophthalmopathy or thyroid-associated ophthalmopathy, is a complex orbital inflammatory disease that can be sight threatening and disfiguring (1–3). Symptoms include dry eyes, red eyes, photophobia, diplopia, and pain with eye movement. Signs include proptosis (exophthalmos), lid edema/retraction, conjunctival injection/chemosis, restrictive myopathy, exposure keratopathy, and optic neuropathy

(4,5). The incidence of TED has been estimated to be 16 per 100,000 women and 2.9 per 100,000 men, with an approximate prevalence of 0.25% (4). However, for severe TED, the ratio of women to men inverts to 1:4 (4). In approximately 40% of patients with TED, onset of systemic symptoms of thyrotoxicosis occur simultaneously with ocular manifestations, and about 60% of all patients with hyperthyroidism will develop TED during their lifetime (1). Hyperthyroidism is present in 85% of patients with TED, hypothyroidism in 10%, and approximately 5% of patients are euthyroid (6).

Historical Guidance for Treatment of Thyrotoxicosis and Thyroid Eye Disease

The management of TED has focused historically on achievement of euthyroidism, nonspecific immunosuppression with corticosteroids, and surgical intervention when necessary. Until now, no medical therapy has achieved approval from the US Food and Drug Administration (FDA). The American Thyroid Association and European Thyroid Association agree that patients with TED should have their hyperthyroidism promptly controlled with anti-thyroid drugs and euthyroid state stably maintained. Patients treated with radioactive iodine (RAI) should receive steroid prophylaxis if mild active TED pre-exists or if there are increased risk factors for RAI-associated TED occurrence or progression. In patients with moderate-to-severe active TED, normalization of thyroid function should be a priority (7).

Recommendations for treatment of TED have varied with disease activity and severity but typically use non-specific immunosuppression. None of the traditional therapies (most notably corticosteroids) reliably modifies proptosis and strabismus and primarily targets inflammation and symptomatic relief. Unfortunately, the use of high-dose steroids is fraught with serious adverse events in up to 30% of patients (8). The American Academy of Ophthalmology has not published a preferred practice pattern for TED, but ophthalmologists have been generally stringent in their use of toxic broad immunosuppression and have used a substantially wider range of medical options in the management of TED (Table 1) (2).

Emergence of Targeted Therapy With Teprotumumab

The insulin-like growth factor I receptor (IGF-IR) is over-expressed in multiple cell types (e.g., fibrocytes and orbital fibroblasts) in patients with TED (9,10). IGF-IR activity is critical to signaling downstream from both the IGF-IR and the thyroid-stimulating hormone receptor (10). In addition, antibodies against an IGF-IR have been detected in patients with TED, and these antibodies may directly activate an IGF-IR (9,11). Such activation may lead, directly or indirectly, to inflammation, putatively resulting in increased orbital fat and muscle volume and subsequent fibrosis of

extraocular muscles (11,12). These observations prompted clinical development of therapy for TED using a repurposed monoclonal antibody against an IGF-IR.

The anti-IGF-IR inhibitory antibody, teprotumumab, was evaluated in both Phase 2 and Phase 3 multicenter, double-blind, placebo-controlled trials in patients with active, moderate-to-severe TED (13,14). All patients had recent onset (≤ 9 months) TED. Both trials included patients who were randomized to receive either placebo or active drug administered intravenously once every 3 weeks for a total of 8 infusions. Pooled data comprise a total of 171 patients in the intent-to-treat analysis (84 patients receiving teprotumumab and 87 placebo) (Table 2). A greater proportion of patients who received teprotumumab (vs. placebo) had ≥ 2 mm reduction in proptosis (65/84 [73.8%] vs 13/87 [14.9%]) at Week 24. Patients who received teprotumumab had greater reduction of proptosis than placebo (-2.63 vs -0.31 mm) at 24 weeks. With a study inclusion requisite of clinical activity score (CAS) ≥ 4 , the percentage of patients achieving low CAS scores (0 or 1) was greater in the teprotumumab group (52/84 [61.9%] vs 19/87 [21.8%]) at Week 24. Furthermore, the diplopia responder rate (percentage of patients with ≥ 1 grades of improvement) was higher in the teprotumumab group than that of placebo (69.7% vs 30.5%). Improvement in the TED quality-of-life score was also greater with teprotumumab than that of placebo at 24 weeks (overall 15.55 vs 5.92).

Pooled data from both trials demonstrated that patients tolerated teprotumumab well. The most common side effects included muscle spasms, nausea, and alopecia. Please refer to Table 3 for list of adverse events. Suggested patient monitoring is discussed below.

Teprotumumab was approved for TED by the FDA on January 21, 2020. Although randomized clinical trials are widely regarded as the gold standard for determining the efficacy and safety of medications (15), their utility in guiding clinical practice is limited. The clinical use of teprotumumab as guided by its prescribing information extends beyond the drug's use in the 2 clinical trials. Additional comorbidities potentially present in patients with TED may not have been represented in the study population. Furthermore, the clinical trials excluded some antecedent and concomitant treatments in the study population. Gaps in the information provided by randomized controlled trials are often filled subsequently by collective clinical experience and postmarketing studies (16–18). When wide clinical experience with a medication is absent, advice emanating from investigators participating in those clinical trials can prove invaluable (19,20).

Expert Panel Process

Early guidance regarding the appropriate use of teprotumumab is deemed as essential for moving forward into an era where the drug becomes widely used in clinical practice. To

TABLE 1. Treatments for thyroid eye disease

Therapy	Mode of Action	Pros and Cons	Common Doses
Mild active disease			
Topical solutions			
Artificial tears	Maintain tear film	Rapid action and minimal side effects	
Glucocorticoids	Reduce inflammation	Rapid action and minimal side effects	
Avoidance of wind, light, dust, and smoke	Reduces ocular surface desiccation and reduces irritation		
Elevation of head during sleep	Reduces orbital congestion		
Avoidance of eye cosmetics	Reduces irritation	Benefits not yet confirmed	
Selenium	Uncertain	Benefits not yet confirmed	
Moderate or severe active disease			
Systemic glucocorticoids			
Oral	Reduce inflammation and orbital congestion	Hyperglycemia, hypertension, and osteoporosis	Up to 100 mg of oral prednisone daily, followed by tapering of the dose
Intravenous	Reduce inflammation and orbital congestion	Rapid onset of anti-inflammatory effect, fewer side effects than oral delivery, and liver damage on rare occasions	Methylprednisolone, 500 mg/week for 6 weeks, followed by 250 mg/week for 6 weeks
Orbital irradiation	Reduces inflammation	Can induce retinopathy	2 Gy daily for 2 weeks (20 Gy total)
B-cell depletion*	Reduces autoreactive B-cells	Very expensive; risks of infection, cancer, and allergic reaction	Two 1,000 mg doses of intravenous rituximab 2 weeks apart
Emergency orbital decompression†	Reduces orbital volume	Surgical procedure with inherent risks, such as postoperative diplopia	
Stable disease (inactive)			
Orbital decompression (fat removal)	Reduces orbital volume	Postoperative diplopia and pain	
Bony decompression of the lateral and medial walls	Reduces proptosis by enlarging orbital space	Postoperative diplopia, pain, sinus bleeding, and cerebrospinal fluid leak	
Strabismus repair	Improves eye alignment and reduces diplopia	Surgical procedure with inherent risks	
Eyelid repair	Improves appearance, reduces lagophthalmos, and improves function	Surgical procedure with inherent risks, including orbital hemorrhage	

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*B-cell depletion with the use of rituximab is not approved by the Food and Drug Administration for this indication.

†Emergency orbital decompression is indicated for optic neuropathy or severe corneal exposure.

TABLE 2. Pooled results of efficacy end points from Phase 2 and Phase 3 teprotumumab trials

	Teprotumumab	Placebo	P Value
Primary end point			
% Proptosis responder Week 24	65/84 (73.8%)	13/87 (14.9%)	<0.001
Secondary end points			
% With CAS 0 or 1 Week 24	52/84 (61.9%)	19/87 (21.8%)	<0.001
Change in proptosis from baseline through Week 24 (mm)	-2.63	-0.31	<0.001
Diplopia responder Week 24	46/66 (69.7%)	18/59 (30.5%)	<0.001
Change in GO-QOL from baseline through Week 24	15.55	5.92	<0.001

CAS, clinical activity score.

this end, a panel of experts convened on October 11th and November 16th of 2019. These individuals participated as investigators who treated patients enrolled in Phase 2 and/or Phase 3 clinical trials of teprotumumab. These studies were integral components of the clinical development program for the drug in TED. The panelists have provided their aggregate recommendations and considerations for safe and effective use of teprotumumab. The consensus results from conference-based and face-to-face deliberations are given below.

The panel addressed a series of questions, including which patients might be suitable for treatment with teprotumumab, guidelines for drug administration, and definition of appropriate patient monitoring. Each topic was discussed until a consensus was achieved. These guidelines are based on the best available data and the clinical expertise of the panel members.

Consensus Statement and Rationale

1. Teprotumumab should be considered as first-line therapy in patients with significant Graves ophthalmopathy.

Rationale: The experts advocate the usage of teprotumumab as first line therapy on the basis that it is more effective and safer than other options, such as corticosteroids (Table 4) (21). They conclude that inclusion/exclusion criteria used in the clinical trials were too restrictive for clinical practice. Thus, these guidelines are offered to aid clinicians in navigating the use of the drug. In this article, significant TED is defined as physician-determined disease associated with consequential symptoms and morbidity. Please refer to Appendix A for inclusion/exclusion criteria.

Both trials required that a CAS ≥ 4 using a 7-point scale in the more severely affected (study) eye (Smith, 2017; Douglas, 2020). Both retrospective and prospective analyses have shown that a CAS ≥ 4 has a high-specificity and high-positive predictive value for favorable response to immunosuppressive treatment (22). However, lower CAS scores do not preclude response to these agents. CAS measurements are subjective and relatively nonspecific. More objective measurements may be required (e.g., progressive

proptosis, diplopia, and compressive optic neuropathy as well as positive imaging findings) (23). The panel also agreed that a CAS is not used frequently in clinical practice, and its grading is imprecise and variable, therefore limiting its utility in evaluating novel therapies. Perhaps most importantly, patients with debilitating diplopia, extreme proptosis, and compressive optic neuropathy—who potentially may benefit the most from teprotumumab—may score low on the CAS scale. The consensus recommendation was that the CAS system alone may be unhelpful in stratifying patients for teprotumumab use.

Hypothetically, teprotumumab might have better efficacy in patients with early vs long-standing disease, but there are no data currently to support this hypothesis. Patients treated with teprotumumab in the Phase 2 trial had ocular symptoms for a mean of 4.7 months at enrollment (13), whereas those in the Phase 3 study had a disease duration ranging from 0.97 to 9.67 months (14). Recommendation was made in accordance with the FDA labeling that physicians should use their judgment regarding time from onset in considering use of teprotumumab. The consensus recommendation was that patients with significant disease (despite a longer duration of disease) should be considered candidates for teprotumumab.

TABLE 3. Adverse events from combined Phase 2 and Phase 3 trials

Adverse Event, N (%)	Teprotumumab (N = 85)	Placebo (N = 86)
Muscle spasm	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue	10 (12%)	6 (7%)
Hyperglycemia	8 (10%)	1 (1%)
Hearing impairment*	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

*Hearing impairment includes deafness, Eustachian tube dysfunction, hyperacusis, hypoacusis, and autophony.

TABLE 4. Summary of recommendations on usage of teprotumumab for thyroid eye disease

	Recommendations
Treatment population	Age: adults; use with in caution in postpubertal adolescents Thyroid status: any, can be started concomitantly with attempts to achieve euthyroidism TED status: progressive disease TED severity: clinically significant Previous treatment of thyroid/TED: any
Contraindications	Poorly controlled diabetics, pregnant or planning to become pregnant, nursing mothers, and prepubertal children Those on concomitant biologics, or those who received rituximab within 6 months Patients with inflammatory bowel disease should be treated with caution and comanaged with gastroenterologists
Dose and duration	1st infusion: 10 mg/kg (over 90 minutes) 2nd infusion: 20 mg/kg (over 90 minutes) Subsequent infusions: 20 mg/kg (over 60 minutes) Total of 8 infusions (every 3 weeks) Early discontinuation if no improvement at 4–6th infusion Additional doses if severe disease with continued improvement
Pre-infusion screen	Complete medical (including weight and BP measurement) and ophthalmic examination Baseline laboratory results: fasting blood glucose, HgA1c, LFTs, and CBC Baseline EKG
Drug monitoring	In patients with diabetes: fasting blood glucose after each of the 1st 2 infusions. Self-monitoring at least twice a day. Work in conjunction with endocrinologist.

BP, blood pressure; CBC, complete blood count; EKG, electrocardiography; HgA1c, hemoglobin A1c; LFTs, liver function tests; TED, thyroid eye disease.

2. Teprotumumab for TED can be started concomitantly with attempts to achieve euthyroid status.

Rationale: The entry criteria for clinical trial participation required euthyroid status (13,14). However, the experts felt that teprotumumab administration could commence concomitantly with initiation of antithyroid medication. Delaying teprotumumab therapy until an euthyroid state was achieved was considered unnecessary. This recommendation is based on the absence of evidence that thyroidal status impacts efficacy or safety of the drug.

3. Teprotumumab usage can be expanded to include select adolescents and the elderly.

Rationale: Although both Phase 2 and 3 trials were restricted to adult patients (ages 18–75 years in Phase 2 and 18–80 years in Phase 3), the experts felt that teprotumumab treatment could be considered for carefully selected older adolescents with TED whose linear growth had ceased. As with all such issues, the risk must be weighed against benefits. Furthermore, a pediatric endocrinologist should be consulted before initiating teprotumumab treatment, as acknowledging its safety has yet to be established in these younger patients.

4. Teprotumumab for TED can be used with caution in patients with diabetes mellitus.

Rationale: The IGF-IR pathway co-regulates glucose homeostasis with that of insulin (24). The Phase 2 trials revealed that Grade 2 or 3 hyperglycemia occurred in some

patients with diabetes receiving teprotumumab. However, this was well controlled after adjustment of diet and diabetes medication. Glycemic control, assessed by glycated hemoglobin (hemoglobin A1c) levels, returned to baseline after completion of teprotumumab treatment (13). Two patients in Phase 3, neither previously diagnosed with diabetes, developed mild hyperglycemia that resolved after completion of the trial (14).

The panel members viewed pre-existing diabetes as an indication for close glycemic monitoring and control during treatment with teprotumumab. Consistent with good practices, hemoglobin A1c and blood glucose should be closely followed during treatment. Self-monitoring is advised, consistent with good medical practices as advised by each patient's endocrinologist. Ketoacidosis-prone diabetics should be excluded.

5. Teprotumumab should be avoided in pregnant women, those planning to become pregnant, women of reproductive ages not using effective birth control measures, and lactating mothers.

Given the potential for growth retardation and developmental anomalies, teprotumumab should not be used during pregnancy or by lactating mothers. The panel recommended counseling, pregnancy testing, and patient instruction concerning birth control before initiation of therapy. The panel also recommended male birth control and pregnancy avoidance for 6 months after treatment.

6. Teprotumumab for TED should be used with caution in patients with inflammatory bowel disease.

Patients with inflammatory bowel disease (IBD) were excluded from the Phase 3 trial. In selected cases with stable IBD comorbidity, teprotumumab could be considered but close monitoring and comanagement with a gastroenterologist is strongly recommended.

7. Dose and duration of treatment:

Dosing in both clinical trials involved 8 infusions over 6 months. The initial dosage of teprotumumab was 10 mg/kg body weight by IV infusion delivered over a 90-minute period while infusions 3 through 8 were administered over 60 minutes (if no infusion-related reactions). Infusions 2 to 8 were dosed at 20 mg/kg. The panel advised adherence to this regimen but acknowledged the potential indication for additional dosing in more severe and persistent disease. Guidance regarding prolonging treatment may emerge from data generated in the open-label extension (OPTIC-X) of the Phase 3 study. The panel noted that the risk of relapse after treatment seems small (14). Recurrence-driven retreatment was offered to 3 patients in the Phase 3 trial (14). Results from the OPTIC-X indicate that relapse could be effectively managed by resuming teprotumumab (unpublished data).

Early discontinuation of therapy (less than 24 weeks) could be considered in patients failing to improve from baseline after 12–18 weeks (4–6 doses). This recommendation is based on the observation that the mean time to onset of clinical response in the Phase 2 trial was 10 weeks (13). A response for proptosis was observed after 2 infusions in 56% of patients in the Phase 3 study (14).

Patients with severe disease who continue demonstrating response at 24 weeks to teprotumumab can be considered for additional infusions using the same dosing schedule. The total number of additional infusions should be determined by the prescribing physician based on relative risks and benefits.

8. Concomitant Medications/Treatments.

Biologics: Concomitant use of teprotumumab with another biologic agent is strongly discouraged. Rituximab-treated patients have depleted B-cell counts for 6 months after their last treatment (25). Therefore, a 6-month wash-out period between the most recent rituximab dosing and initiation of teprotumumab is advocated because no information currently exists regarding potential infectious risks with concurrent treatment. If available, the peripheral B-cell count can be obtained to confirm that the biological impact of rituximab has disappeared before treatment with teprotumumab.

Corticosteroids: Corticosteroids can be used as a prelude to teprotumumab therapy and the 2 might be administered concomitantly.

Surgical orbital decompression and orbital radiation: Patients demonstrating persistent significant or progressive disease after surgery or orbital irradiation can receive teprotumumab, if needed, based on individual risks/benefits.

PRETREATMENT SAFETY EVALUATION AND PATIENT MONITORING

Initial Assessment

Patient assessment before the initiation of teprotumumab should include the following: medical and surgical history (including history of diabetes and IBD), physical examination (including measurement of weight and blood pressure), complete ophthalmologic examination (including exophthalmometry, extraocular motility, strabismus measurements, and fundus examination), standard clinical laboratory evaluation (including complete blood count, liver function tests, fasting blood glucose, and hemoglobin A1c), and an electrocardiogram.

On-Treatment Monitoring

The safety profile for teprotumumab documented in patients with TED differs substantially from that in cancer patients treated with the drug. Adverse events noted in those Phase 1 cancer trials included hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, hypotension, and rash (pruritus) (26–28). None of these was detected in either of the TED trials. Please refer to Table 3 for list of adverse events.

Neither Phase 2 nor Phase 3 trials generated safety signals requiring special clinical or laboratory monitoring. However, diabetic and prediabetic patients should be carefully monitored throughout the treatment period for abnormalities in blood glucose. This management should be conducted by the attending endocrinologist and diabetes medication should be adjusted as needed, consistent with best practices. Hyperglycemia was detected predominately in several patients with pre-existing carbohydrate intolerance or diabetes (13,14). There were no cases of diabetic ketoacidosis. These adverse events were mild or moderate in intensity, and none resulted in discontinuation of teprotumumab.

No clinically significant abnormality in electrolytes (including calcium and magnesium) or hepatic transaminases were noted for subjects who experienced muscle spasms.

Only a single infusion reaction, occurring in the Phase 3 trial, resulted in one patient discontinuing the study. A second patient experienced elevated blood pressure that may have represented an infusion reaction. It was managed with steroid pretreatment for subsequent infusions (14). Routine premedication before infusions is not recommended, but blood pressure elevations should be managed with

appropriate therapy. Emergency equipment should be readily available. Antidrug antibodies were not detected in patients receiving teprotumumab.

Integrated Patient Management

The expert panel strongly recommends multidisciplinary team management of patients treated with teprotumumab focused on individual patient needs (29–31). Primary management of these patients should be by ophthalmologists, neuro-ophthalmologists, and endocrinologists. Treatment with teprotumumab and other biologic agents may involve rheumatologists as well. The goal is to provide all patients with optimal coordinated subspecialty care (30).

Potential Impact on Treatment Costs

Teprotumumab, like virtually all biological therapeutics, represents a relatively costly drug, the consequence of the substantial research and development process. The issue of attendant costs of teprotumumab has been commented on by the American Association of Ophthalmology (32). The financial burdens of this therapy must be considered whenever contemplating its use in patients with clinically significant TED.

CONCLUSIONS

Teprotumumab can be used safely and effectively to treat TED. A wider range of patients than that included in the 2 clinical trials, such as those with a longer duration of disease and more broadly defined activity and severity, should be considered. The panel arrived at the consensus that teprotumumab is appropriate first-line therapy for use in patients with clinically significant TED. The rationale for this “first-line” designation derives from its substantially better effectiveness and improved safety profile when compared with corticosteroids and other less-frequently used drugs. Teprotumumab administration in combination with urgent, high-dosage corticosteroids in cases of compressive optic neuropathy can be considered, given their different mechanisms of action. It should not be administered to pregnant, lactating women, or those of child-bearing age not on birth control. Benefits and risks should be weighed when contemplating teprotumumab treatment of adolescents, diabetics, and those with IBD. In those cases, comanagement with relevant health care providers is strongly recommended.

The panel recognizes the substantial cost of teprotumumab therapy compared with that of corticosteroids. Although substantial, the peripheral economic challenges associated with traditional treatment approaches, including corticosteroids, multistaged rehabilitative surgeries, and protracted recovery lead to incalculable financial and social burdens. As experience with teprotumumab expands, we anticipate the accumulation of necessary data for meaningful cost analysis.

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