

TEPROTUMUMAB FOR INJECTION

SPONSOR BRIEFING DOCUMENT

**DERMATOLOGIC AND OPHTHALMIC DRUGS
ADVISORY COMMITTEE**

MEETING DATE: DECEMBER 13, 2019

**ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE**

TABLE OF CONTENTS

Table of Contents	2
List of Tables	5
List of Figures	6
List of Abbreviations and Definition of Terms.....	7
1 Executive Summary	9
1.1 Background on Thyroid Eye Disease and Unmet Medical Need.....	9
1.2 Teprotumumab	10
1.3 Overview of Clinical Studies	10
1.4 Efficacy	13
1.5 Safety.....	18
1.6 Safety Experience in Oncology Populations	22
1.7 Benefit-Risk Summary.....	22
2 Thyroid Eye Disease and Current Treatment Options.....	24
2.1 Overview of Thyroid Eye Disease	24
2.2 Current Treatment Options.....	27
3 Overview of Teprotumumab Development	29
3.1 Regulatory Milestones in TED.....	29
3.2 Clinical Development Program.....	29
4 Mechanism of Action, Nonclinical Safety and Clinical Pharmacology	31
4.1 Mechanism of Action.....	31
4.2 Key Nonclinical Findings – Pregnancy.....	32
4.3 Clinical Pharmacokinetics.....	32
4.4 Rationale for Dose Selection.....	33
5 Clinical Efficacy	34
5.1 Study Design (Study 1 and Study 2)	35
5.1.1 Key Enrollment Criteria (Study 1 and Study 2).....	36
5.1.2 Efficacy Endpoints.....	36
5.1.2.1 Primary Endpoint.....	36
5.1.2.2 Secondary Endpoints	37
5.1.2.3 Description of Endpoint Measures	37

5.1.3	Statistical Analyses and Sample Size Calculations	39
5.1.3.1	Primary Endpoint.....	40
5.1.3.2	Secondary Endpoints	40
5.1.3.3	Sample Size Calculations	40
5.2	Patient Population	40
5.2.1	Patient Disposition.....	40
5.2.2	Demographics and Baseline Characteristics.....	41
5.3	Study Results.....	44
5.3.1	Proptosis Responder Rate (Study 2 Primary Endpoint).....	46
5.3.2	Overall Responder Rate (Study 1 Primary Endpoint).....	46
5.3.3	Change from Baseline in Proptosis.....	47
5.3.4	Change from Baseline in CAS.....	47
5.3.5	CAS Responder Rate	48
5.3.6	Diplopia Responder Rate	49
5.3.7	Change from Baseline in GO-QoL – Analysis from Individual Studies	49
5.3.8	Results in Non-Study Eye.....	49
5.4	Analyses of Pooled Data (Study 1 and Study 2 Combined)	50
5.4.1	Change from Baseline in GO-QoL	50
5.4.2	Efficacy in Subgroups.....	50
5.5	Persistence of Efficacy (Study 1).....	51
5.5.1	Assessment of Acute Rebound in Overall Response and Proptosis Response at Week 28	51
5.5.2	Maintenance of Response at Week 72	52
5.6	Efficacy Conclusions.....	52
6	Clinical Safety.....	53
6.1	Overview of Safety Analyses and Populations	54
6.2	Treatment Exposure	54
6.3	Overview of Adverse Events.....	55
6.3.1	Common Adverse Events	55
6.3.2	Severe or Life-Threatening Adverse Events.....	56
6.3.3	Adverse Events in Subgroups	57
6.4	Deaths.....	57

6.5	Serious Adverse Events.....	57
6.6	Treatment Emergent Adverse Events Leading to Discontinuation.....	60
6.7	Adverse Events of Special Interest.....	60
6.7.1	Hyperglycemia.....	61
6.7.2	Infusion Reactions	62
6.7.3	Diarrhea/Inflammatory Bowel Disease Exacerbation	64
6.7.4	Hearing Impairment.....	65
6.7.5	Muscle Spasm.....	68
6.8	Anti-Drug Antibodies.....	68
7	Benefit-Risk Conclusions	69
8	References.....	72
9	Appendices.....	79
9.1	Inclusion/Exclusion Criteria in Study 1 and Study 2.....	79
9.2	Brief Summaries of Non-Serious TEAEs Leading to Discontinuation.....	83
9.3	Adjudication Process Used to Identify Non-Anaphylactic Infusion Reaction.....	83

List of Tables

Table 1: Primary and Secondary Endpoints (Study 1 and Study 2).....	12
Table 2: Primary Endpoint in Study 1 and Study 2 (ITT Population)	13
Table 3: Change from Baseline Through Week 24 in GO-QoL (Study 1 and Study 2 Combined).....	17
Table 4: Primary Endpoint in Study 1 and Study 2 for Non-Study Eye (ITT Population)	18
Table 5: Overview of Safety	19
Table 6: Graves' Ophthalmopathy Quality of Life Questionnaire ¹	39
Table 7: Patient Disposition (Study 1 and Study 2).....	41
Table 8: Patient Demographics (Study 1 and Study 2)	42
Table 9: Patient Baseline Characteristics (Study 1 and Study 2).....	43
Table 10: Primary and Secondary Efficacy Endpoints (Study 1, ITT Population).....	44
Table 11: Primary and Secondary Efficacy Endpoints (Study 2, ITT Population).....	45
Table 12: Guide to Presentation of Efficacy Endpoints in Section 5.3	46
Table 13: Change from Baseline in CAS Value Through Week 24 (Study 1 and Study 2)	48
Table 14: Overall Response and Proptosis Response at Week 24 and Week 28 (Study 1).....	51
Table 15: Teprotumumab Exposure in Patients with TED (Safety Population).....	55
Table 16: TEAEs Occurring in $\geq 5.0\%$ of Patients in Either Treatment Group of the Double- Masked Population or in $\geq 5.0\%$ of Patients in OPTIC-X Population.....	56
Table 17: Serious Adverse Events (Double-Masked Population and OPTIC-X Population).....	58
Table 18: Non-Serious TEAEs Leading to Study Drug Discontinuation/Study Discontinuation (Double-Masked Population and OPTIC-X Population).....	60
Table 19: Hyperglycemia Events	62
Table 20: Infusion Reactions.....	63
Table 21: Diarrhea/IBD Exacerbation.....	65
Table 22: Hearing Impairment Events	66

List of Figures

Figure 1: Proptosis Responder Rate over Time (Study 1 and Study 2).....	14
Figure 2: Change from Baseline in Proptosis over Time (Study 1 and Study 2)	15
Figure 3: Diplopia Responder Rate over Time (Study 1 and Study 2).....	16
Figure 4: Pathophysiology of TED.....	25
Figure 5: Potential Presentations / Signs of TED	26
Figure 6: Mechanism of Action of Teprotumumab.....	32
Figure 7: Schematic of Study Design (Study 1 and Study 2).....	35
Figure 8: Overall Responder Rate over Time (Study 1 and Study 2).....	47
Figure 9: CAS Responder Rate over Time (Study 1 and Study 2).....	48
Figure 10: Change from Baseline in GO-QoL Overall Score over Time (Study 1 and Study 2)...	49
Figure 11: Proptosis Responder Rate at Week 24 by Subgroups (Placebo adjusted for Study 1 and Study 2 Combined)	51

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	anti-drug antibodies
AESI	adverse events of special interest
AKT	protein kinase B
AUC	area under the concentration-time curve
BID	twice daily
BL	Baseline
BP	blood pressure
DSMB	Data Safety Monitoring Board
CAS	Clinical Activity Score
CI	confidence interval
CFB	change from Baseline
C _{max}	peak concentration
CMH	Cochran-Mantel-Haenszel
CT	computed tomography
C _{trough}	trough concentration
EUGOGO	European Group on Graves' Orbitopathy
FDA	Food and Drug Administration
GO-QoL	Graves' Ophthalmopathy Quality of Life
HbA1c	glycated hemoglobin
HLT	high-level term
HR	heart rate
IBD	inflammatory bowel disease
IC ₅₀	half maximal inhibitory concentration
IGF-1R	insulin-like growth factor-1 receptor
ITT	intent-to-treat
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PI3K	phosphoinositide 3-kinase
PT	preferred term
Q3W	every 3 weeks
SAE	serious treatment emergent adverse event

SD	standard deviation
SE	standard error
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	Treatment -emergent adverse event
TED	thyroid eye disease
TSHR	thyroid stimulating hormone receptor
ULN	upper limit of normal

1 EXECUTIVE SUMMARY

Teprotumumab, an insulin-like growth factor-1 receptor (IGF-1R) inhibitor, is a fully human monoclonal antibody developed to address a significant unmet need in patients with Thyroid Eye Disease (TED), a progressive, vision-threatening autoimmune disease. Teprotumumab blocks the inflammatory/autoimmune pathophysiology that underlies TED and if approved, would be the first pharmacotherapy indicated for the treatment of TED.

Teprotumumab was effective across two adequate and well-controlled clinical studies, providing statistically significant and clinically meaningful improvements across multiple facets of this debilitating, vision-threatening and disfiguring disease. A large majority of patients achieved substantial improvements in proptosis, Clinical Activity Score (CAS), diplopia and quality of life with 24 weeks of therapy. Furthermore, most adverse events were graded as mild or moderate and were generally managed in the context of the trials without treatment discontinuation. Taken together, the data support a favorable benefit-risk profile for teprotumumab.

1.1 Background on Thyroid Eye Disease and Unmet Medical Need

TED (also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy, or Graves' orbitopathy) is a debilitating, vision-threatening autoimmune disease that often leads to irreversible disfigurement and disability. Sight can be threatened from optic nerve compression or severe corneal exposure in roughly 6% of patients with TED (Bartley 1996). The threat to functional vision is much more common, with diplopia (double vision) interfering with many activities of daily living such as reading, walking down stairs or driving a car, as well as the ability to work. The physical discomfort and facial disfigurement caused by TED can have a substantial and lasting impact on patients' quality of life; patients with TED are at increased risk of psychological disturbances such as anxiety and depression (Farid 2005; Kahaly 2005).

As an autoimmune disease TED is systemic in nature. It can affect both eyes, and presents initially as an inflammatory (referred to as "active") condition, with a cascade of negative effects including inflammation, accumulation of extracellular matrix and cellular proliferation mediated by IGF-1R activity in the orbital tissues behind the eye. Patients with active TED may present with orbital pain, periorbital edema and erythema, conjunctival redness and eyelid retraction, with vision-impairing symptoms such as proptosis (bulging eyes), strabismus (misalignment of the eyes) and diplopia. (Wiersinga 1989; Strianese 2013). When signs and symptoms of inflammation have waned, the disease is generally considered to be "inactive," but proptosis, strabismus and diplopia generally persist as irreversible manifestations of the subsequent fibrosis, or scarring of orbital tissues behind the eye.

There are currently no FDA-approved medical treatments indicated for TED and no current consensus in the U.S. on how to treat this disease. Treatment approaches for active TED include high-dose glucocorticoids, which treat some elements of inflammation, but are associated with serious side effects and safety concerns; immunosuppressive therapies which are limited by a lack of placebo-controlled clinical data; and local measures such as artificial tears, ointments, use of sunglasses and selenium supplementation. None of these treatment options have been shown

to be effective on proptosis, diplopia or the associated disfigurement. Surgery can be performed to address persistent, clinical manifestations of proptosis and diplopia. However, multiple sequential surgeries (e.g., orbital decompression, strabismus surgery and eyelid surgery) are often required and patients rarely return to their pre-TED state.

There is a significant unmet need for a pharmacologic treatment that reduces proptosis, diplopia and inflammation and has a favorable benefit-risk profile in this debilitating, vision-threatening and disfiguring disease.

1.2 Teprotumumab

Teprotumumab is a fully human immunoglobulin IgG1 monoclonal antibody that binds IGF-1R, a tyrosine kinase cell surface receptor that is overexpressed in the orbital fibroblasts of TED patients (Tsui 2008). TED is driven by the IGF-1R mediated signaling cascade in the tissues behind the eye, including cytokine production, hyaluronic acid accumulation and extracellular matrix deposition and adipogenesis (Pritchard 2002; Pritchard 2003; Smith 2004; Iyer 2012; Kumar 2012). These events, in turn, cause enlargement of ocular muscles, expansion of orbital tissue and fat and forward displacement of the eye, resulting in proptosis and inflammation (Wang 2014; Smith 2017). Teprotumumab targets and binds to IGF-1R, inhibits IGF-1R autophosphorylation, reduces cell surface expression of IGF-1R and inhibits downstream signaling. Based on its mechanism of action as an IGF-1R inhibitor, teprotumumab was hypothesized to decrease inflammation and tissue expansion and produce clinically meaningful reductions in the signs and symptoms of TED (Chen 2014; Chen 2015; Smith 2018; Douglas 2019).

1.3 Overview of Clinical Studies

The efficacy and safety of teprotumumab for the treatment of TED was evaluated in two randomized, double-masked, placebo-controlled studies, each conducted at sites in the U.S. and Europe, with both studies designed to demonstrate treatment differences of statistical significance:

- Study TED01RV (NCT01868997), hereafter referred to as “Study 1,” enrolled and randomized 88 patients (43 to teprotumumab [42 of whom were treated] and 45 to placebo)
- Study HZNP-TEP-301 (NCT03298867), hereafter referred to as “Study 2,” enrolled and randomized 83 patients (41 to teprotumumab and 42 to placebo)

Both Study 1 and Study 2 were designed to evaluate the efficacy and safety of a course (8 infusions) of teprotumumab compared to that of placebo during a 24-week Double-Masked Treatment Period. Both studies also contain an off-treatment Follow-up Period. Study 1 has completed. The Treatment Period of Study 2 has been completed and the off-treatment Follow-up Period is currently ongoing.

The primary evidence supporting the efficacy and safety of teprotumumab comes from Study 1 and Study 2, including analyses of the individual studies and data from the two studies combined.

A third study (Study HZNP-TEP-302 [NCT03461211], hereafter referred to as “OPTIC-X”) is ongoing. In this study, patients from Study 2 who were Week 24 non-responders or who were Week 24 responders and subsequently lost response will receive open-label treatment with a course of teprotumumab (8 infusions). To date, 46 patients from Study 2 have been enrolled (37 from the placebo group and 9 from the teprotumumab group). Available safety information from this study is included.

Study 1 and Study 2 Design

In both Study 1 and Study 2, patients were randomized to receive 8 infusions of teprotumumab (10 mg/kg for the first infusion to assess tolerability of a new biologic entity before escalating to the target dose of 20 mg/kg for all subsequent infusions) Q3W or placebo administered Q3W during the Double-Masked Treatment Period. After completing the 24-week Treatment Period, patients entered an off-treatment Follow-up Period.

Local supportive measures for TED, simple analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory therapies) and medications/supplements for conditions other than TED were permitted during the study. Steroids for the treatment of TED were prohibited, but topical steroids and inhaled steroids were allowed for non-TED conditions. Oral corticosteroid use was restricted to patients who experienced infusion related adverse events. Lastly, selenium and biotin supplements were not allowed although taking a multivitamin that included selenium and/or biotin was allowed.

Enrolled Population

In both studies, patients were required to have a CAS ≥ 4 for the study eye and onset of symptoms within 9 months prior to Baseline. The CAS is a 7-point scale used to measure the inflammatory signs and symptoms of TED. Patients were euthyroid or had free thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Prior surgical treatment for TED was not permitted. Previous steroid use with a cumulative dose of < 1000 mg of methylprednisolone or equivalent, with a minimum 4-week washout period, was allowed.

Efficacy Endpoints

In Study 1, the primary efficacy endpoint was the overall responder rate at Week 24, which was defined as the percentage of patients with a ≥ 2 mm reduction from Baseline in proptosis in the study eye (more severely affected eye at Baseline) and with a ≥ 2 -point reduction in CAS, without deterioration in the non-study eye (≥ 2 mm increase in proptosis or ≥ 2 -point increase in CAS).

In Study 2, the primary efficacy endpoint was the proptosis responder rate at Week 24, defined as the percentage of patients with a ≥ 2 mm reduction from Baseline in proptosis in the study

eye, without deterioration in the non-study eye (≥ 2 mm increase in proptosis). The primary endpoint for Study 2 was prospectively agreed with FDA to represent proptosis response which was the most objective part of the composite primary endpoint from Study 1.

A change of at least 2 mm in proptosis is considered to constitute a response to therapy (Wiersinga 2006).

In each study, secondary endpoints were tested sequentially, comparing teprotumumab versus placebo, to control for type 1 error. The rank-ordered secondary endpoints are listed in Table 1.

Table 1: Primary and Secondary Endpoints (Study 1 and Study 2)

Efficacy Endpoint	Study 1	Study 2
Primary	Overall responder rate at Week 24	Proptosis responder rate at Week 24
Secondary (analyzed in a sequential order in individual studies)	<ol style="list-style-type: none"> 1. Mean CFB to Week 24 in GO-QoL overall score 2. Mean CFB to Week 24 in proptosis measurements in the study eye 3. Mean CFB to Week 24 in CAS in the study eye 4. Mean CFB to Week 24 in GO-QoL visual functioning subscale score 5. Mean CFB to Week 24 in GO-QoL appearance subscale score 	<ol style="list-style-type: none"> 1. Overall responder rate at Week 24 2. CAS responder at Week 24 3. Mean CFB to Week 24 in proptosis measurement in the study eye 4. Diplopia responder rate at Week 24 5. Mean CFB to Week 24 in the GO-QoL overall score
Responder definitions		
Proptosis	Patients with a ≥ 2 mm reduction from Baseline in proptosis in the study eye, without deterioration (≥ 2 mm increase) of proptosis in the non-study eye at Week 24	
Overall	Patients with a ≥ 2 mm reduction in proptosis AND a ≥ 2 -point reduction in CAS from Baseline in the study eye, without deterioration (≥ 2 mm increase in proptosis or ≥ 2 -point increase in CAS) in the non-study eye at Week 24	
CAS	Patients with a reduction to a CAS of 0 or 1 (no or minimal inflammation) in the study eye at Week 24	
Diplopia	Patients with Baseline diplopia grade > 0 in the study eye who have a reduction of ≥ 1 -grade with no corresponding deterioration (≥ 1 -grade worsening) in the non-study eye at Week 24	

Patients missing the Week 24 evaluation were considered non-responders.

CAS = Clinical Activity Score; CFB = change from Baseline; GO-QoL = Graves' Ophthalmopathy Quality of Life

Enrolled Patients

In both Study 1 and Study 2, the intention-to-treat (ITT) principle was used to define the primary population used for efficacy analysis, but they were defined slightly differently. The ITT population in Study 1 comprised all patients who were randomized and received at least one dose of study drug (N=42, teprotumumab [1 patient randomized to teprotumumab was never treated]);

N=45, placebo). In Study 2, the ITT population comprised all patients who were randomized (N=41, teprotumumab; N=42, placebo).

Demographics and baseline characteristics were generally similar between the teprotumumab and placebo groups in each individual study, with minor exceptions in Study 1: sex (higher proportion of females for placebo), tobacco use (higher percentage of users for placebo) and diplopia (higher incidence for teprotumumab). Patients had been living with TED for an average of 6 months and approximately two-thirds had diplopia.

1.4 Efficacy

The results from Study 1 and Study 2 demonstrated that teprotumumab was effective in patients with TED, with the large majority of patients achieving improvements in primary and secondary endpoints of proptosis, diplopia, CAS and quality of life with 24 weeks of therapy.

In the individual studies, statistically significant and clinically meaningful differences favoring teprotumumab were observed on the primary endpoint (Table 2) and the first 4 of the 5 ranked secondary endpoints in Study 1 (Table 10) and all 5 secondary endpoints in Study 2 (Table 11).

In order to show the consistency of the results across both Study 1 and Study 2, the outcomes of the individual studies are presented side-by-side by endpoint measure (as opposed to sequential order of statistical testing, which varied by individual study) in the following text. Conclusions of statistical significance are made based on prespecified testing strategies within each analysis.

Results of the study eye (the eye more severely affected by TED) are presented as applicable; results of the non-study eye generally followed the same pattern of improvement as the study eye (Table 4).

Table 2: Primary Endpoint in Study 1 and Study 2 (ITT Population)

	Teprotumumab	Placebo	Odds Ratio	95% CI	p-value
Study 1¹	(N = 42)	(N = 45)			
Overall responder rate at Week 24, n (%)	29 (69.0)	9 (20.0)	8.86	3.29, 23.8	< 0.001
Study 2²	(N = 41)	(N = 42)	Difference	95% CI	p-value
Proptosis responder rate at Week 24, n (%)	34 (82.9)	4 (9.5)	73.5 (7.4)	58.9, 88.0	< 0.001

1. Odds ratio, 95% CI and p-value were from a logistic regression with treatment and tobacco use status (non-user vs user) as covariates.

2. Stratified difference is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights. Test statistic calculated by dividing the stratified difference by the SE. Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

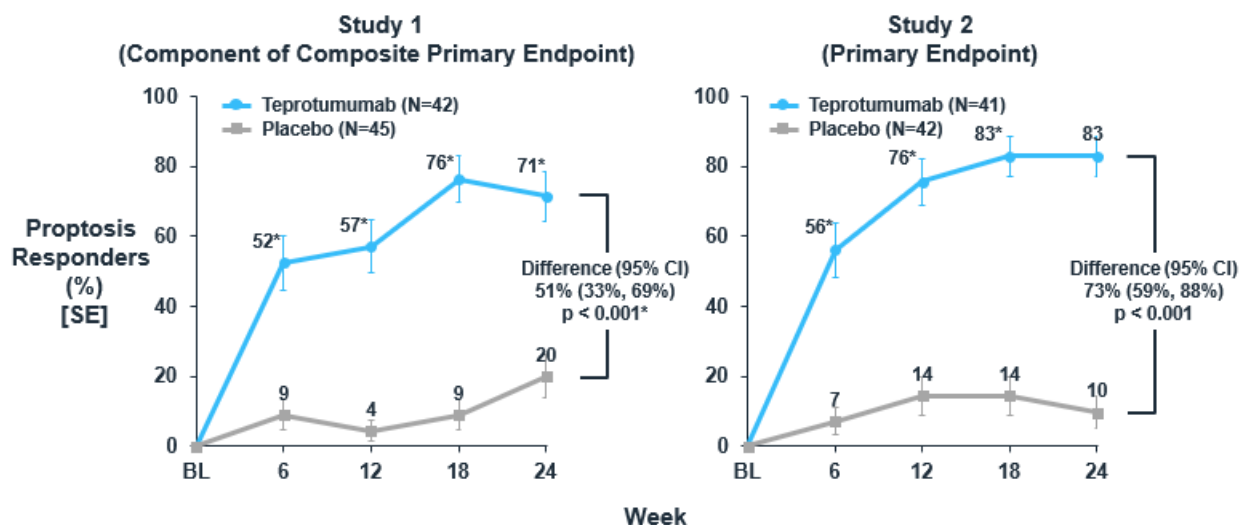
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; SE = standard error

Proptosis Responder Rate

In each individual study, a greater proportion of patients treated with teprotumumab were proptosis responders compared with patients who received placebo not only at the end of the 24-

week Treatment Period, but at all study visits starting at Week 6, the first post-Baseline efficacy assessment (Figure 1).

Figure 1: Proptosis Responder Rate over Time (Study 1 and Study 2)



* Nominal p-value: $p < 0.001$

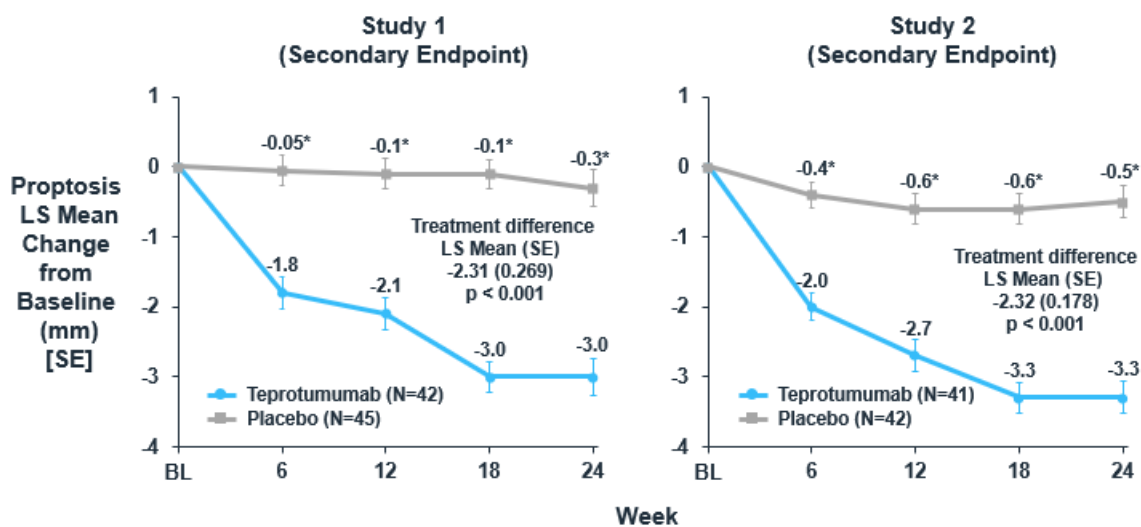
BL = Baseline; CI = confidence interval; SE = standard error

Overall (Proptosis AND CAS) Responder Rate

Similarly, a greater proportion of patients treated with teprotumumab were overall responders (achieved ≥ 2 mm reduction in proptosis AND ≥ 2 -point reduction in CAS from Baseline in the study eye) compared with patients who received placebo at all post-Baseline time points (Figure 8).

Change from Baseline in Proptosis

Improvement of proptosis as measured by mean change from Baseline was observed as early as 6 weeks and continued to improve through Week 24 as shown in Figure 2. The level of proptosis reduction observed at Week 24 in patients treated with teprotumumab (-3.0 mm and -3.3 mm in Study 1 and Study 2, respectively) approached mean levels attained with decompression surgery (-3.8 mm; Rootman 2017; Wu 2017).

Figure 2: Change from Baseline in Proptosis over Time (Study 1 and Study 2)

*Nominal p-value: $p < 0.001$

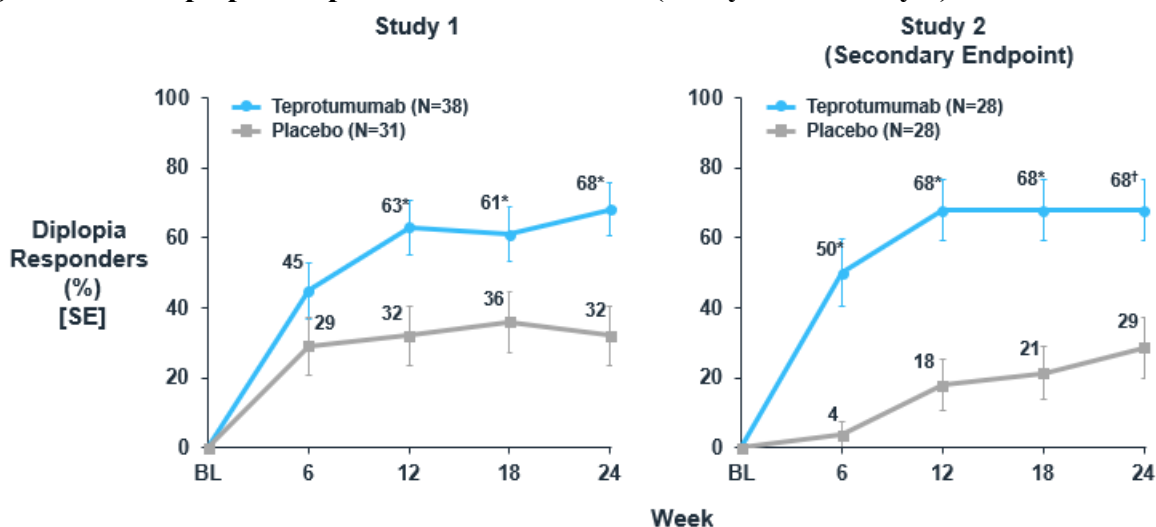
LS = least squares; SE = standard error

CAS Responder Rate

A greater proportion of patients treated with teprotumumab were CAS responders (had a CAS of 0 or 1 [no or minimal inflammation]) compared with patients who received placebo at all post-Baseline visits in each individual study (Figure 9). The CAS responder rates at Week 24 for teprotumumab versus placebo were 67% versus 22% in Study 1 and 59% versus 21% in Study 2.

Diplopia Responder Rate

In each study, diplopia was evaluated on a 4-grade scale (0 = no diplopia, 1 = intermittent [diplopia in primary position of gaze, when tired or when first awakening], 2 = inconstant [diplopia at extremes of gaze], 3 = constant diplopia), where a decrease of 1 grade or more represents a clinically meaningful improvement (Wiersinga 2006). Among patients with Baseline diplopia (> 0 in study eye), a greater proportion achieved a ≥ 1 -grade improvement with teprotumumab than did with placebo (Figure 3). The diplopia responder rate (proportion of patients with ≥ 1 -grade decrease in study eye without corresponding deterioration in the non-study eye at Week 24) for teprotumumab compared to placebo was 68% versus 32% in Study 1 and 68% versus 29% for placebo in Study 2.

Figure 3: Diplopia Responder Rate over Time (Study 1 and Study 2)

*Nominal p-value: $p < 0.05$

†Ranked endpoint: $p = 0.001$

BL = Baseline

Change from Baseline in Graves' Ophthalmopathy Quality of Life

The Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire was used in both Study 1 and Study 2. GO-QoL is a 16-item patient self-administered questionnaire comprising 2 subscales, one measuring the consequences of TED on visual functioning and one measuring the psychosocial consequences of a changed appearance. The overall score and the individual subscales are transformed into a scale that ranges from 0 to 100, with 0 representing worst health and 100 representing best health.

In each individual study, teprotumumab was associated with improvements on the GO-QoL overall score (Figure 10). The improvements over placebo were statistically significant and clinically meaningful. The change through Week 24 among teprotumumab-treated patients in Study 1 (16.8 points) and Study 2 (13.8 points) was larger than 6 points, the minimal clinically important difference for the GO-QoL instrument (Terwee 2001).

Patients treated with teprotumumab reported greater improvement in both subscales of visual functioning and appearance compared with patients in the placebo group. The improvements in the separate subscales were apparent in each individual study and reached statistical significance in the integrated analysis of both studies (Table 3).

Table 3: Change from Baseline Through Week 24 in GO-QoL (Study 1 and Study 2 Combined)

Change from Baseline Through Week 24 in GO-QoL ¹	Combined Analyses	
	Teprotumumab (N = 84)	Placebo (N = 87)
GO-QoL Overall Score		
LS Mean (SE)	15.6 (1.6)	5.9 (1.5)
Difference (95% CI)	9.6 (5.5, 13.7)	
p-value	< 0.001	
GO-QoL Visual Functioning		
LS Mean (SE)	16.8 (2.0)	6.1 (2.0)
Difference (95% CI)	10.7 (5.4, 16.0)	
p-value	< 0.001	
GO-QoL Appearance		
LS Mean (SE)	13.5 (1.9)	5.8 (1.8)
Difference (95% CI)	7.7 (2.9, 12.6)	
p-value	0.002	

1. Results from an MMRM with an unstructured covariance matrix including the following terms: Baseline score, tobacco use status, treatment group, visit, visit-by-treatment interaction, visit-by-Baseline value interaction and study. A change from Baseline of 0 was imputed at the first post-Baseline visit for any patient without a post-Baseline value.

CI = confidence interval; GO-QoL = Graves' Ophthalmopathy Quality of Life; LS = least squares; MMRM = mixed model repeated-measures; SE = standard error

Efficacy in Subgroups

Examination of subgroups defined by age, sex and region (U.S. and Europe) did not identify differences in response to teprotumumab based on these characteristics. There were too few Black or African-American and Asian patients to adequately assess differences in effects in those populations. Reduction in proptosis was similar between tobacco users and non-users in both studies.

Efficacy in Non-Study Eye

Similar efficacy results were observed for the non-study eye in both Study 1 and Study 2 (Table 4).

Table 4: Primary Endpoint in Study 1 and Study 2 for Non-Study Eye (ITT Population)

	Teprotumumab	Placebo	Odds Ratio	95% CI	p-value
Study 1¹	(N = 42)	(N = 45)			
Overall responder rate at Week 24, n (%)	22 (52.4)	6 (13.3)	7.10	2.5, 20.5	< 0.001
Study 2²	(N = 41)	(N = 42)	Difference	95% CI	p-value
Proptosis responder rate at Week 24, n (%)	27 (65.9)	1 (2.4)	63.5	48.3, 78.7	< 0.001

1. Odds ratio, 95% CI and p-value were from a logistic regression with treatment and tobacco use status (non-user vs user) as covariates.

2. Stratified difference is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights. Test statistic calculated by dividing the stratified difference by the SE. Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; SE = standard error

Maintenance of Efficacy

Following completion of study treatment in Study 1, 53% of patients (16 of 30 patients) who were proptosis responders at Week 24 maintained response criteria 51 weeks after the last infusion of teprotumumab, while 73% still showed reduced proptosis from Baseline without the need for additional treatment for TED. Similarly, of patients who had improved at least 1 grade in diplopia by Week 24, 69% (18 of 26) were still responders at Week 72, nearly a year after the last dose of teprotumumab.

The off-treatment Follow-up Period of Study 2 is currently ongoing.

1.5 Safety

Exposure to Teprotumumab

The safety of teprotumumab has been assessed in a total of 121 unique patients with TED who received treatment with teprotumumab as of the 120-day safety update (data cut-off 28 June 2019), including 84 patients from Study 1 and Study 2 and 46 patients from OPTIC-X (9 of whom also received teprotumumab during Study 2). Follow-up information for serious adverse events or adverse events of special interest after the 120-day safety update is also included where available as of October 29, 2019. The safety of teprotumumab was primarily evaluated based on the Double-Masked Population, which includes Study 1 and Study 2, augmented by data available from the OPTIC-X Population.

Among the 84 patients who received teprotumumab in the Double-Masked Treatment Period of Study 1 and Study 2, 75 (89.3%) completed a full course of 8 infusions compared to 80 (93.0%) of the 86 patients in the placebo group. In OPTIC-X, patients had completed a median of 8 infusions at the time of the data cutoff.

Overview of Treatment-Emergent Adverse Events

In the Double-Masked Population, the percentage of patients who reported at least one treatment-emergent adverse event (TEAE) was greater among teprotumumab patients (79.8%) than among placebo patients (69.8%) (Table 5).

The most commonly reported TEAEs in the teprotumumab group, occurring in $\geq 5.0\%$ of patients, were *Muscle spasms* (25.0%), *Nausea* (16.7%), *Alopecia* (13.1%), *Diarrhoea* (11.9%), *Fatigue* (9.5%), *Dysgeusia*, *Headache*, *Dry skin* (each 8.3%), *Hyperglycaemia* (7.1%) and *Rash* (6.0%); all of these, with the exception of *Rash*, occurred at a higher rate for teprotumumab than placebo. Similar TEAEs were observed in the OPTIC-X Population.

Table 5: Overview of Safety

		Double-Masked Population		OPTIC-X
		Teprotumumab (N = 84)	Placebo (N = 86)	Teprotumumab (N = 46)
Patients with Events, n (%)				
TEAEs		67 (79.8)	60 (69.8)	39 (84.8)
Mild to moderate intensity TEAEs		63 (75.0)	59 (68.6)	39 (84.8)
Severe or higher intensity ¹ TEAEs	Any	4 (4.8)	1 (1.2)	1 (1.2) ²
	Reported as Related	1 (1.2)	0	0
TEAEs leading to study drug discontinuation/study discontinuation	Any	5 (6.0) ³	2 (2.3)	2 (4.3) ²
	Reported as Related	2 (2.4)	0	1 (2.2)
Serious adverse events ⁴	Any	7 (8.3)	1 (1.2)	1 (2.2) ²
	Reported as Related	3 (3.6)	0	0
Death		0	0	0

1. Includes severe (resulting in the inability to work or perform normal daily activity), life-threatening (immediate threat to life).

2. Includes additional information subsequent to 120-day safety update: cerebral hemorrhage (already noted at 120-day safety update and in this table as SAE) was changed in severity from moderate to life-threatening and resulted in study discontinuation.

3. One additional patient in the teprotumumab group of the Double-Masked Population discontinued due to an adverse event that started more than 21 days after the last dose of study drug, falling outside the definition of TEAE, and is therefore not included in the count but is included in description of all discontinuations.

4. A serious event results in any of the following outcomes: death, is life-threatening, results in persistent or significant disability or incapacity, inpatient hospitalization or prolongation of an existing hospitalization, congenital anomaly or birth defect, or is considered medically important according to appropriate medical judgment and may require medical or surgical intervention to prevent one of the outcomes listed above.

TEAE = treatment-emergent adverse event

In the Double-Masked Population, serious, severe or life-threatening TEAEs and those leading to discontinuation of study drug were more frequently reported with teprotumumab than placebo.

The SAEs were reported as unique medical concepts in single patients, though 2 patients experienced SAEs that were consistent with exacerbation of inflammatory bowel disease (IBD). Given the heterogeneous nature of the reported events, the data are described in detail in [Section 6.5](#) (serious) and [Section 6.3.2](#) (severe).

There have been no deaths in the teprotumumab TED clinical program.

Adverse Events of Special Interest

Adverse events of special interest (AESI) were defined for teprotumumab to provide a more comprehensive understanding of the safety profile of teprotumumab. They were generally identified on the basis of previous clinical experience or by what might be expected with systemic administration of a monoclonal antibody (infusion reactions). Mechanism of action and biologic plausibility were considered for all AESI; the only event of interest clearly identified as mechanistically related was hyperglycemia.

Hyperglycemia

In the Double-Masked Population, events of hyperglycemia, which included preferred terms of *Blood glucose increased* and *Hyperglycaemia*, were reported more frequently for teprotumumab compared to placebo (9.5% vs 1.2%). All events were non-serious, did not result in hospitalization or other complication and were mild or moderate in severity. Hyperglycemia was more commonly reported in patients with pre-existing diabetes mellitus or impaired glucose tolerance compared to patients without pre-existing disease (50.0% versus 4.1%, respectively). All events resolved and no patients discontinued due to hyperglycemia.

The highest blood glucose value observed in any patient was 303 mg/dL and occurred at the Week 4 visit (Day 29) in a Study 1 patient with a medical history of glucose intolerance (HbA1c at baseline was 7.2%). This patient was managed with metformin and glipizide without further complication. The highest glycosylated hemoglobin (HbA1c) value observed in any patient was 7.9% at the Week 24 visit (Day 168) in a patient without a medical history of glucose intolerance (HbA1c was 5.8% at baseline). This patient was managed with metformin and the TEAE was reported as resolved at the Week 72 visit (now off metformin).

In OPTIC-X, *Blood glucose increased*, *Diabetes mellitus* and *Type 2 Diabetes mellitus* were reported in 3 patients. All events were mild to moderate in severity and managed with diet and/or metformin.

During the off-treatment Follow-up Period, *Diabetes mellitus*, *Hyperglycaemia*, *Glucose tolerance impaired* and *Glycosylated haemoglobin increased* were reported in 3 patients, including one patient with a previously reported event of hyperglycemia. All events were mild to moderate in severity and managed with diet and/or metformin.

Additional information on hyperglycemia is provided in [Section 6.7.1](#).

Infusion Reactions

Patients were not routinely premedicated for hypersensitivity reactions prior to infusion of teprotumumab. Infusion reactions occurred in 3 teprotumumab-treated patients and all were mild or moderate in severity. No patient was reported as having an anaphylactic reaction.

A single patient with an SAE of *Infusion-related reaction* experienced symptoms approximately 6 minutes into the first infusion of teprotumumab and the patient discontinued from the study. A second patient experienced a non-serious infusion reaction following the second dose of teprotumumab. At the next visit, a similar reaction occurred following premedication but before study drug administration, and the patient was withdrawn from the study. The third patient experienced a non-serious infusion reaction, continued study treatment with premedication and a slower infusion rate and tolerated all subsequent infusions. All infusion reactions resolved on the same day.

Additional information regarding infusion reactions is provided in [Section 6.7.2](#).

Diarrhea/Exacerbation of Inflammatory Bowel Disease

In the Double-Masked Population, Diarrhea occurred in 12 (14.3%) patients in the teprotumumab group and 7 (8.1%) patients in the placebo group. As described above, 2 teprotumumab-treated patients experienced SAEs consistent with exacerbation of pre-existing IBD, which led to discontinuation of study drug. The remaining events of diarrhea were mild or moderate in severity; none represented cases of new-onset IBD or led to study drug discontinuation.

In OPTIC-X, 5 (10.9%) patients have reported a total of 6 diarrhea events and no patients have reported new-onset IBD or IBD exacerbation. All events have been mild in severity and 2 were ongoing as of the data cutoff (study is currently ongoing).

Additional information regarding diarrhea and exacerbation of IBD is provided in [Section 6.7.3](#).

Hearing Impairment

In the Double-Masked Population, 8 (9.5%) patients in the teprotumumab group experienced an event of hearing impairment (captured under a broad range of terms e.g. eustachian tube dysfunction, tinnitus, deafness) compared to no patients in the placebo group. In the OPTIC-X Population, 5 (10.9%) patients experienced 6 events of hearing impairment. Thus, a total of 13 patients have experienced 15 events of hearing impairment in the TED clinical program. All events were reported as non-serious and mild or moderate in severity.

Seven patients have recovered from their event of hearing impairment and 6 others have ongoing events. Among the 6 patients with ongoing events, 2 patients had events that were ongoing at the time Study 1 ended, 1 of whom was noted as improved based on audiology testing. The remaining 4 patients are all enrolled in the ongoing OPTIC-X study, and 2 have been noted as improving.

All patients continued in the study without reporting worsening of their event. No patients discontinued treatment.

Additional information regarding hearing impairment is provided in [Section 6.7.4](#).

Muscle Spasms

Muscle spasms were reported in 21 (25%) patients in the teprotumumab group of the Double-Masked Population and 19 (41%) teprotumumab-treated patients in OPTIC-X. Body areas affected primarily involved the lower limbs, and to a lesser extent, upper limbs and the trunk. No events involved the maxillofacial area. The events were non-serious with no associated laboratory abnormalities, and the majority were mild in intensity. General comfort measures, magnesium, calcium and vitamin B supplements were used for cramping events, and two patients were treated with muscle relaxants (cyclobenzaprine, metaxolone). At the time of the 120-day safety update, *Muscle spasms* were ongoing for 21 of the 39 teprotumumab-treated patients, including mild events in 20 patients and a moderate event in 1 patient. With the exception of a single patient in OPTIC-X, no *Muscle spasms* events led to discontinuation of study drug.

Additional information regarding muscle spasm is provided in [Section 6.7.5](#).

1.6 Safety Experience in Oncology Populations

Teprotumumab is one of several antibodies to IGF-1R that have been investigated in the oncology setting as a noncytotoxic, targeted therapy premised on the role of IGF-1 in tissue growth and differentiation. Hyperglycemia has emerged as a manageable side effect across the class of IGF-1R monoclonal antibodies investigated for oncology indications; most cases have been reported as mild to moderate and reversible ([King ER and Wong KK 2012](#); [Ma HH 2013](#)).

The oncology development program for teprotumumab consisted of 9 clinical trials in mostly late stage cancers, of which one was a randomized placebo-controlled study in combination with erlotinib. Others were open-label, single-arm or multiple-arm studies of mono- or combination therapies. Across all studies, 727 patients received at least one dose of teprotumumab. The safety data was reviewed in its entirety for potential safety signals. Single-armed studies were reviewed for frequency of adverse events in the context of background disease and comorbidities. The single placebo-controlled study offered the opportunity to review differences across treatment arms. There was no compelling evidence of safety signals beyond what has been described for the TED program. Across the oncology program, teprotumumab was found to be well tolerated with no dose-limiting toxicities identified ([Kurzrock 2010](#), [Pappo AS 2014](#)).

1.7 Benefit-Risk Summary

TED is a debilitating, vision threatening and disfiguring autoimmune disease with no FDA-approved treatment options. Patients need a well-tolerated treatment that reduces proptosis, diplopia and inflammation and improves quality of life.

Teprotumumab was effective in patients with TED, the majority of whom achieved substantial improvements in proptosis, CAS, diplopia and overall quality of life with 24 weeks of therapy. The safety data accumulated throughout the teprotumumab development program provide evidence of the overall safety and tolerability of teprotumumab for the treatment of TED. The safety profile of teprotumumab has been characterized, allowing patients and physicians to make informed decisions regarding treatment and medical management during therapy. The totality of evidence shows that teprotumumab offers patients and healthcare professionals the first effective and generally well-tolerated treatment for TED.

2 THYROID EYE DISEASE AND CURRENT TREATMENT OPTIONS

Summary

- Thyroid eye disease (TED) is a debilitating, vision-threatening autoimmune disease.
- Patients who have active/inflammatory disease may present with orbital pain, conjunctival redness, swelling and erythema of the eyelids, proptosis, eyelid retraction, diplopia and optic neuropathy. Sight can be threatened by compressive optic neuropathy or corneal ulceration in roughly 6% of patients with TED (Bartley 1996), but threats to functional vision are more common.
- There can be profound changes in facial appearance due to tissue expansion.
- TED can have a significant psychosocial impact.
- Active TED typically lasts approximately 2-3 years. Although the active inflammation subsides over time, significant remodeling and scarring of orbital tissue remains along with persistent proptosis, diplopia and disfigurement. There may be a limited window during which the disease may respond to pharmacologic intervention before damage becomes fibrotic and permanent.
- Currently, there are no medical treatments approved by the FDA for the treatment of TED.
 - Current management of TED includes use of corticosteroids and other immunosuppressive medications aimed at minimizing inflammatory symptoms. No pharmacological treatments to date have been shown to be effective at addressing the underlying disease processes nor reversing the lasting consequences of TED such as proptosis and diplopia.
 - When inflammation is no longer evident, surgery can be performed to reduce the permanent consequences of tissue remodeling (e.g., proptosis, diplopia); however, multiple sequential surgeries are often required and patients rarely return to baseline.
- There is a significant unmet need for a well-tolerated pharmacologic treatment that reduces proptosis, diplopia and inflammation in patients with TED.

2.1 Overview of Thyroid Eye Disease

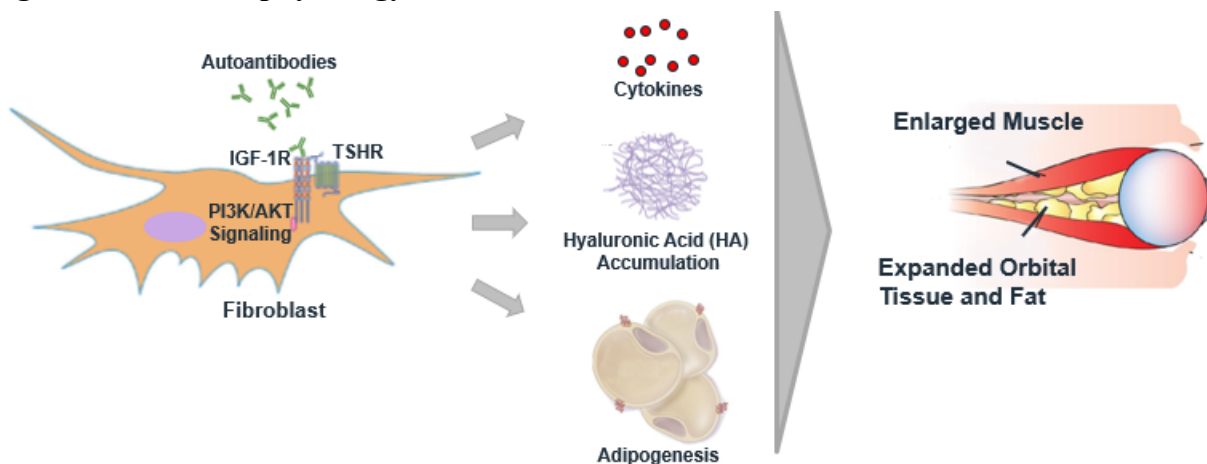
TED (also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy, or Graves' orbitopathy) is a progressive, vision-threatening autoimmune disease that leads to extensive retro-orbital fibrosis and long-term damage to the orbit.

Although most commonly associated with Graves' hyperthyroidism/disease, TED also occurs rarely in patients with other autoimmune thyroid diseases, including Hashimoto's thyroiditis, as well as euthyroid states (Hiromatsu 2014). Risk factors for TED include female sex, middle age and smoking (Sikder 2010); the risk of TED increases 7 to 8 times in smokers (Perros 2009).

The median age at diagnosis is 43 years. In addition, a positive family history of TED is observed in 61% of TED patients (Bartley 1996). There is no significant ethnic predisposition for TED (Lazarus 2012). There is a paucity of literature to inform the incidence of TED. Based on limited published literature and using current U.S. population numbers, the prevalence of active TED is estimated at approximately 75,000 patients (Bartley 1994; Bartley 1996 Perros 2015; Ponto 2015).

As seen with other autoimmune conditions, autoantibodies play a major role in driving TED (Smith 2017; Wang 2014; Smith 2018). In Graves' disease, it is well established that hyperthyroidism is driven by autoantibodies to the thyroid stimulating hormone receptor (TSHR), but TED can occur in the absence of Graves' disease and also without detectable TSHR autoantibodies (Bartley 1994; Tabasum 2016). Insulin-like growth factor-1 receptor (IGF-1R) is overexpressed in TED and plays a central role in the disease pathogenesis due to autoantibody signaling through IGF-1R and TSHR complex (Smith 2004; Tsui 2008; Bahn 2010; Smith 2010; Iyer 2012; Kumar 2012). In the orbital fibroblasts of TED patients, this signaling cascade that results in the production of inflammatory cytokines and chemokines, accumulation of hyaluronic acid, extracellular matrix deposition and adipogenesis. These processes result in inflammation, enlargement of extraocular muscles and expansion of orbital tissue and fat, which in turn cause forward displacement of the eye, resulting in proptosis and inflammation (Figure 4).

Figure 4: Pathophysiology of TED



Iyer 2012; Smith 2018; Douglas 2019

AKT = Protein kinase B; IGF-1R = insulin-like growth factor-1 receptor; PI3K = phosphoinositide 3-kinase; TSHR = thyroid stimulating hormone receptor

TED involves an initial progressive worsening of signs and symptoms during what is referred to as active TED (Rundle 1945; Bartalena 2016; Ross 2016).¹ This phase is characterized by

¹ Activity refers to the inflammatory status of the disease, while severity refers to the level of soft tissue and muscular involvement (effects on optic nerve function, proptosis, ocular motility, and eyelid position). In clinical practice, the activity of the disease is often estimated using the Clinical Activity Score (CAS). Severity is defined by functional impairment and disfigurement and can be assessed using a scale like NOSPECS (No signs or symptoms / Only signs, no symptoms / Soft tissue involvement / Proptosis / Extraocular muscle involvement / Corneal involvement / Sight loss) or the European Group on Graves' Orbitopathy (EUGOGO) severity scale.

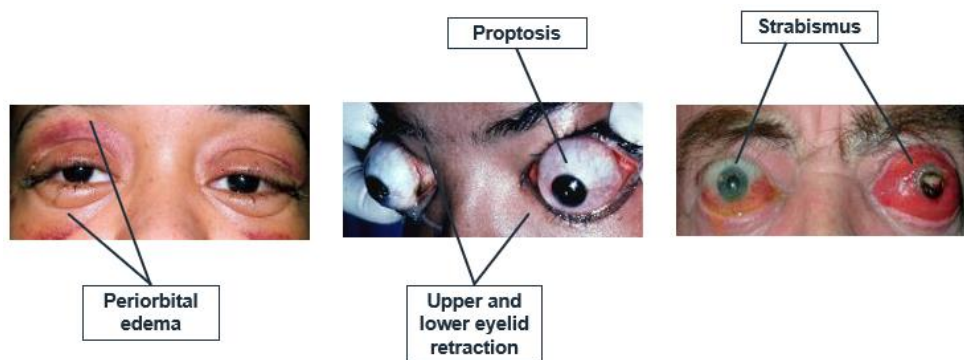
visible signs of inflammation as well as the effects of tissue expansion and remodeling which worsen over time. In a patient population with moderate to severe disease, much of this expansion and remodeling may have already occurred. For the large majority of patients, active TED lasts up to 3 years. After this, inflammatory signs and symptoms generally resolve but the proptosis, diplopia and disfigurement can persist based on the remodeled orbital structures. Eventually, remodeled tissues can become fibrotic, leaving patients with significant residual structural damage (Stan 2012). Patients left with diplopia, proptosis and lid retraction from tissue scarring may need to undergo corrective surgery, which can entail multiple procedures including orbital decompression, strabismus surgery and eyelid surgery. A limited window of opportunity may exist to treat TED before it results in irreversible damage, and a therapeutic agent that reverses the tissue expansion and stops remodeling before fibrosis and scarring set in may help to prevent or minimize the potential for permanent damage and the likelihood of multiple surgeries.

TED is heterogeneous and variable in presentation. However, clinical manifestations include:

- Inflammation of orbital soft tissues causing pain, erythema, swelling and foreign object sensation in the eyes
- Eyelid retraction with increased eyelid aperture
- Proptosis (eye bulging), due to expansion of the soft tissues of the orbit forcing eyes out of their sockets
- Strabismus (misalignment of the eyes) with compromised eye motility
- Diplopia (double vision), due to incorrect orientation of the eyes
- Corneal ulceration because patients cannot fully close their eyelids
- Optic neuropathy, due to the rigid orbital walls and tissue enlargement putting undue pressure on the optic nerve

Over time, there is a progressive worsening of symptoms. Sight can be threatened from optic nerve compression or severe corneal exposure, affecting 6% of patients with TED (Bartley 1996). However, threats to functional vision are more common, as patients often have diplopia.

Figure 5: Potential Presentations / Signs of TED



Proptosis and diplopia, which have been resistant to pharmacotherapy, are particularly devastating for patients with TED. Proptosis, one of the most widely known signs of TED, (Wiersinga 1989; Strianese 2013), impairs patients' ability to close their eyes, resulting in dry eyes, pain, inability to sleep and even corneal ulceration. It also results in profound changes in facial appearance, which can negatively influence facial expression, communication, self-perception and social interactions. Diplopia is a common symptom of TED in which more than one image of a single object is seen as a result of misalignment of the eyes. Patients with diplopia often experience headaches and nausea and have difficulty performing activities of daily living.

The clinical manifestations of TED can lead to marked reductions in quality of life, comparable to diabetes and other chronic diseases, and significant socioeconomic consequences (Wiersinga 2012; Ponto 2013). A study examining quality of life and occupational disability in 192 patients with TED showed an association between diplopia and occupational disability (Ponto 2009). Among the study patients, 28% were disabled, 5% retired early and 3% had lost their jobs. Furthermore, patients with TED are at increased risk of anxiety and depression (Farid 2005; Kahaly 2005) and have a significantly higher risk of death by suicide compared to matched controls (Ferlov-Schwensen 2017).

In short, TED has the potential to have a profound and long-lasting impact on the physical, functional, psychological and economic well-being of affected patients.

2.2 Current Treatment Options

The ideal treatment for TED could reduce the activity and severity early in its progression. This would limit morbidity, loss in function and quality of life and minimize the potential for irreversible damage, thereby obviating the need for rehabilitative surgeries. There are however currently no FDA-approved pharmacotherapies for TED and no current consensus in the U.S. on how to treat this disease. Local measures, such as artificial tears, ointments, sunglasses and selenium supplementation, are used to manage mild symptoms of TED.

Current management of more severe TED symptoms may include the following exploratory pharmacologic interventions used off label:

Pharmacologic

- Corticosteroids, the most commonly used treatment for inflammatory signs and symptoms, are typically administered at high intravenous pulse dosages. Corticosteroids may reduce soft-tissue manifestations, such as edema and erythema of eyelids and conjunctiva; however, they have a minimal effect on proptosis (van Geest 2008; Zang 2011). Furthermore, corticosteroids have significant dose- and duration-dependent systemic adverse effects, such as hyperglycemia, hypertension, osteoporosis, dyslipidemia, weight gain, Cushingoid features, glaucoma, and in rare cases, severe hepatotoxicity (Zang 2011; Bartalena 2012; Marcocci 2012; Wichary 2012; Miśkiewicz 2014; Moleti 2016).

- Rituximab has been investigated in active TED because of its B-cell-depleting action. Two studies have been reported. In a randomized trial comparing rituximab to intravenous corticosteroids in 32 patients with active TED, treatment with rituximab showed symptomatic improvement assessed by Clinical Activity Score (CAS) compared to corticosteroids. Mean proptosis values did not significantly decrease in either treatment group. At Week 24, a reduction in proptosis of 2 mm or greater was observed in 0 of the 16 patients treated with rituximab and 1 of the 16 patients treated with intravenous corticosteroids (Salvi 2015). In the second trial, which was placebo-controlled, there was no evidence of efficacy (Stan 2015). Both trials showed higher rates of adverse events with rituximab including optic neuropathy, vasculitis and infections. The therapeutic effect and the benefit-risk ratio of rituximab in active TED remains unclear.
- Other immunosuppressive therapies (mycophenolate mofetil, cyclosporine, tocilizumab and azathioprine) are exploratory and lack clinical data demonstrating benefit in active TED (Kotwal 2018; Xu 2018). The known adverse events differ across the agents, though all can lead to increased susceptibility to infections.

Additional Management

- Orbital radiation therapy is considered as a second-line therapy in moderate to severe active TED (Bartalena 2016); however, literature on orbital radiation therapy report mixed efficacy results and its use is not standardized (Bartalena 2000; Mourits 2000; Gorman 2001; Prummel 2004; Stiebel-Kalish 2009; Hahn 2014). Potential adverse effects include cataracts. In addition, retinopathy has been reported in patients with diabetes and hypertension (Marcocci 2003).
- Sequential orbital surgeries (orbital decompression, strabismus surgery and eyelid surgery) are a mainstay of TED treatment. However, these procedures are normally withheld until the inactive stage due to the potential to exacerbate ongoing inflammatory processes (Baldeschi 2017). During active TED, orbital decompression or eyelid surgery are generally reserved for emergencies, to treat immediate threats to sight from dysthyroid optic neuropathy and corneal ulceration (Baril 2014). While surgery can be effective, especially in addressing proptosis, multiple sequential surgeries are often required and patients rarely return to their pre-TED state.

To date, no controlled clinical study, other than the studies of teprotumumab, has shown that proptosis or diplopia responds to pharmacotherapy (Chang 2006; Stan 2006; Bartalena 2012; Strianese 2014; Salvi 2015); proptosis is also not responsive to orbital radiotherapy. Potential new therapies for TED continue to be explored, which underscores the need for an efficacious and safe therapy, particularly for proptosis and diplopia.

3 OVERVIEW OF TEPROTUMUMAB DEVELOPMENT

3.1 Regulatory Milestones in TED

The development of teprotumumab for TED was discussed with the FDA throughout the clinical program. Agreement with the Agency was reached on study design, endpoints and statistical analyses. Teprotumumab was acquired by Horizon through the acquisition of River Vision in May 2017 after the completion of Study 1.

3.2 Clinical Development Program

The efficacy and safety of teprotumumab for the treatment of TED was evaluated in two randomized, double-masked, placebo-controlled studies, each conducted at sites in the U.S. and Europe:

- Study TED01RV (NCT01868997), referred to as “Study 1,” enrolled and randomized 88 patients (43 to teprotumumab [42 of whom were treated] and 45 to placebo)
- Study HZNP-TEP-301 (NCT03298867), referred to as “Study 2,” enrolled and randomized 83 patients (41 to teprotumumab and 42 to placebo)

Both randomized controlled studies comprise a 24-week Double-Masked Treatment Period and an off-treatment Follow-up Period. In both studies, patients randomized to teprotumumab were to receive 8 infusions of teprotumumab Q3W (10 mg/kg for the first infusion and 20 mg/kg thereafter).

The evidence of efficacy for teprotumumab is provided by the Treatment Periods of Study 1 and Study 2. Study 1 has completed and data from the 48-week Follow-up Period are discussed in [Section 5.5](#) with respect to persistence of efficacy. The Treatment Period of Study 2 has been completed, and the Follow-up Period is currently ongoing.

A third study in TED (Study HZNP-TEP-302 [NCT03461211], hereafter referred to as “OPTIC-X”) is ongoing. In this study, patients from Study 2 who were Week 24 non-responders (had < 2 mm decrease in proptosis in the study eye) or who were Week 24 responders and subsequently lost response will receive open-label treatment with a course of teprotumumab (8 infusions Q3W at a dose of 10 mg/kg for the first infusion and 20 mg/kg thereafter). To date, 46 patients from the Study 2 have been enrolled (37 from the placebo group and 9 from the teprotumumab group).

The evidence of safety for teprotumumab is based primarily on the Treatment Periods of Study 1 and Study 2. Additional safety data as of the 120-day safety update from the ongoing OPTIC-X study also contributes to the safety assessment.

Prior to teprotumumab being developed for TED, it was developed for a variety of oncology indications by Roche. All oncology trials were either completed or terminated. There are no ongoing oncology studies. Development for oncology indications was discontinued by Roche due to insufficient efficacy. The efficacy data from the oncology studies are not applicable in

TED and therefore will not be discussed further. A high-level summary of safety from the oncology studies is provided in [Section 1.6](#).

4 MECHANISM OF ACTION, NONCLINICAL SAFETY AND CLINICAL PHARMACOLOGY

Summary

- Toxicology studies in cynomolgus monkeys demonstrated developmental malformations with the administration of teprotumumab; therefore, there is the potential for embryo-fetal toxicity.
- Pharmacokinetics of teprotumumab in TED patients was linear.
- Drug-drug interactions are not anticipated with teprotumumab and the thyroid medications commonly used by patients with TED, as these do not share common or overlapping clearance pathways (Zhou 2011).
- Dosing of teprotumumab with an initial infusion of 10 mg/kg followed by subsequent infusions of 20 mg/kg Q3W for a total of 8 infusions was an effective and well tolerated treatment regimen.

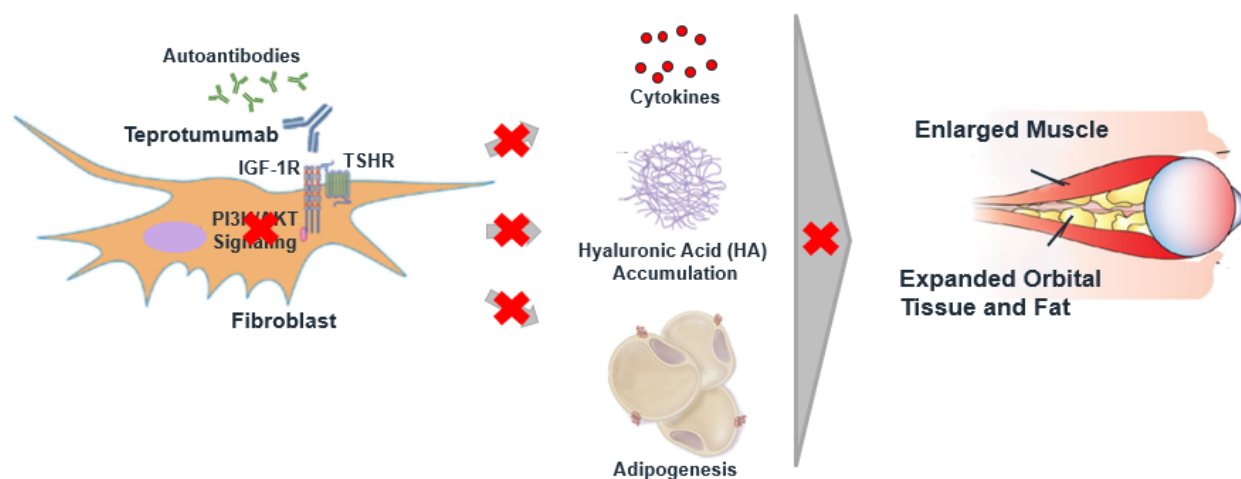
4.1 Mechanism of Action

Teprotumumab is a fully human IgG1 monoclonal antibody that binds to IGF-1R. It inhibits autophosphorylation (half maximal inhibitory concentration [IC₅₀] of 1 nM), displaces binding of IGF-1R ligands IGF-1 and IGF-2 (IC₅₀ of 0.40 nM and 0.28 nM, respectively), blocks IGF-1R-mediated downstream signaling and downregulates cell-surface levels of the receptor.

As noted in Section 2.1, autoantibody signaling through IGF-1R plays a key role in cytokine production, hyaluronic acid accumulation, cellular differentiation and orbital muscle and tissue remodeling, the processes that underlie TED. Inhibition of these disease-driving processes through IGF-1R inhibition supports biological plausibility of disease modification with this targeted intervention.

Published nonclinical data have demonstrated these effects of IGF-1R inhibition. In orbital fibroblasts and circulating fibrocytes from TED patients, IGF-1R inhibition has been shown to block autoantibody-mediated increases in inflammatory cytokines (RANTES, IL-16, IL-6 and TNF- α) and hyaluronic acid accumulation (Pritchard 2003; Smith 2004; Kumar 2012; Chen 2014; Chen 2015; Smith 2018; Douglas 2019). IGF-1R inhibition has also been shown to prevent proliferation of orbital adipose-derived stromal cells and their differentiation into adipocytes, indicating the ability to inhibit adipogenesis (Zhao 2013).

As an IGF-1R inhibitor, teprotumumab was hypothesized to inhibit the disease driving processes of systemic inflammatory cytokine production as well as localized immune cell infiltration, hyaluronic acid accumulation, adipogenesis and the resultant muscle expansion and remodeling of orbital tissue (Figure 6). Teprotumumab was therefore evaluated in the clinical setting as a targeted therapy with the potential for disease modification in TED.

Figure 6: Mechanism of Action of Teprotumumab

Iyer 2012; Smith 2018; Douglas 2019

AKT = Protein kinase B; IGF-1R = insulin-like growth factor-1 receptor; PI3K = phosphoinositide 3-kinase; TSHR = thyroid stimulating hormone receptor

4.2 Key Nonclinical Findings – Pregnancy

In cynomolgus monkeys dosed intravenously with teprotumumab throughout pregnancy and at a pharmacologically active dose 8.8-fold higher than the recommended clinical dose of teprotumumab based on exposure, there was decreased placental weights, decreased primary disk measurements, decreased amniotic fluid volume and decreased fetal body weights reflected in both decreased organ weights and fetal measurements. External and skeletal abnormalities included misshapen cranium, closely set eyes, open fontanelles, micrognathia, pointing and narrowing of the nose, thinning of the cranial bones and ossification abnormalities of multiple bones and teeth. The higher fetal loss with exposure to teprotumumab could not definitively be attributed to teprotumumab; however, a teprotumumab-related effect could not be completely discounted due to effects observed in fetuses at C-section.

To date, no pregnancy has been reported in the clinical development program for teprotumumab. However, based on these findings in animals and its mechanism of action, teprotumumab may cause fetal harm when administered to women who are pregnant.

4.3 Clinical Pharmacokinetics

The pharmacokinetics of teprotumumab were linear in patients with TED. Overall, the pharmacokinetic characteristics of teprotumumab were consistent with other immunoglobulin G1 monoclonal antibodies, with low systemic clearance (0.334 L/day), low volume of distribution (3.9 L for central compartment and 4.2 L for peripheral compartment) and long elimination half-life (geometric mean of 19.9 days) (Dirks 2010; Ryman 2017).

Population pharmacokinetic analysis indicated that demographic covariates, such as age, sex, race and weight had no significant effect on teprotumumab exposures. Female patients had 15% higher C_{max} but similar AUC compared to male patients, which is not considered clinically

relevant. Covariates including smoking status, mild or moderate renal impairment and hepatic function (total bilirubin, aspartate aminotransferase and alanine aminotransferase) did not have any impact on teprotumumab pharmacokinetics.

Drug-drug interactions between teprotumumab and thyroid medications (e.g., levothyroxine, propylthiouracil) commonly used by TED patients are not expected, as teprotumumab and small molecule drugs do not share common or overlapping clearance pathways (Zhou 2011).

4.4 Rationale for Dose Selection

Pharmacokinetic analyses of data from a dose-ranging (range: 1 to 16 mg/kg) Phase 1 oncology study suggested the contribution of target-mediated clearance on teprotumumab pharmacokinetics. Based on these data, serum concentrations of teprotumumab that would provide greater than 90% saturation of target-mediated clearance were considered. The recommended teprotumumab regimen, including an initial dose of 10 mg/kg followed by 20 mg/kg Q3W, was initially selected for evaluation in Study 1 to maintain exposures at a population level that were pharmacologically active and provided greater than 90% saturation of IGF-1R throughout the three-week dosing intervals. The initial 10 mg/kg dose was selected to assess tolerability of a new biologic entity before escalating to the target dose of 20 mg/kg for all subsequent infusions.

The results of Study 1 demonstrated that this regimen was effective and well tolerated and therefore provided justification for continued evaluation in Study 2. Population pharmacokinetic analyses from Study 1 and Study 2 in patients with TED demonstrated that the selected regimen maintained a C_{trough} above the target saturation threshold.

No relationship was observed between teprotumumab exposures (AUC , C_{max}) and safety variables.

The overall findings from the development program in TED support the recommended teprotumumab dosing described above and a regimen totaling 8 infusions.

5 CLINICAL EFFICACY

Summary

- Two independent, randomized, double-masked, placebo-controlled, multicenter studies (Study 1 and Study 2) were conducted to assess the efficacy of a 24-week course of teprotumumab.
- Teprotumumab was superior to placebo for the primary efficacy endpoints of overall responder rate (Study 1) and proptosis responder rate (Study 2).
 - A clinically meaningful improvement in both proptosis and CAS was achieved by the majority of patients in the teprotumumab group and by a statistically significantly higher proportion of patients on teprotumumab compared to placebo.
 - Treatment differences in proptosis responder rates between teprotumumab and placebo were consistent across subgroups defined by tobacco use status, region, age and sex.
- Teprotumumab was superior to placebo for 4 out of 5 secondary efficacy endpoints in Study 1 and all 5 secondary endpoints in Study 2.
 - Teprotumumab resulted in a greater proportion of patients with no or minimal inflammation on the CAS, a larger reduction in proptosis, improved diplopia responder rate and a larger improvement in the Graves' Ophthalmopathy Quality of Life (GO-QoL) overall score.
- In integrated analyses of both studies combined, teprotumumab provided meaningful improvement in patients' assessments of quality of life with respect to visual functioning and appearance.
- Across endpoints, the onset of therapeutic effect of teprotumumab was evident at the first post-Baseline assessment (Week 6) and increased over time from Week 6 to Week 24.
- Results were durable as assessed seven weeks following the last dose of study drug, suggesting little evidence for acute recurrence of disease activity after treatment was completed.
- Over half (53%) of the teprotumumab patients who were proptosis responders at the end of treatment (Week 24) maintained response (≥ 2 mm improvement in proptosis) approximately a year off treatment. Moreover, approximately three-quarters still showed reduced proptosis from Baseline without any additional treatment for TED, and 69% were still diplopia responders.
- Teprotumumab was effective in patients with TED with a large majority of patients achieving substantial improvements in proptosis, CAS, diplopia and overall quality of life with a 24-week course of therapy.

5.1 Study Design (Study 1 and Study 2)

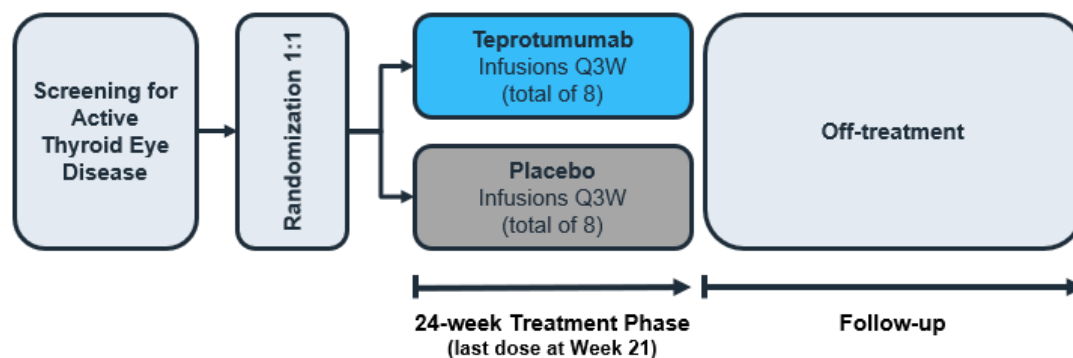
Study 1 and Study 2 were conducted at sites in the U.S. and Europe with Investigators who specialized in oculoplastic surgery, endocrinology, neuro-ophthalmology, or ophthalmology.

Both Study 1 and Study 2 comprised a 24-week Double-Masked Treatment Period followed by an off-treatment Follow-up Period (Figure 7). Patients who met eligibility criteria were randomized in a 1:1 ratio to receive 8 infusions of teprotumumab or placebo Q3W. The teprotumumab group received 10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions. As tobacco use has been associated with an increased risk of TED, the development of more severe forms of TED (particularly those associated with proptosis and diplopia) and delayed responses to immunosuppressive therapies (Bartalena 2016; Czarnywojtek 2016; Sadeghi-Tari 2016), randomization in both studies was stratified by tobacco use status.

Safety and efficacy assessments were conducted at follow-up visits at Weeks 6, 12, 18 and 24 during the Double-Masked Treatment Period; follow-up visits were also conducted at Weeks 28, 36, 48, 60 and 72 (Months 7, 9, 12, 15 and 18) during the Follow-up Period. The Follow-up Period has been completed for Study 1 and is currently ongoing for Study 2.

Patients from Study 2 who completed the Double-Masked Treatment Period and met the criteria for enrollment were eligible to enroll in the ongoing, open-label extension study, OPTIC-X (Section 3.2).

Figure 7: Schematic of Study Design (Study 1 and Study 2)



Q3W = every 3 weeks

Local supportive measures for TED, simple analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory therapies) and medications/supplements for conditions other than TED were permitted during the study. Steroids for the treatment of TED were prohibited, but topical steroids and inhaled steroids were allowed for non-TED conditions. Oral corticosteroid use was restricted to patients who experienced infusion related adverse events. Lastly, selenium and biotin were not allowed although taking a multivitamin that included selenium and/or biotin was allowed.

Both groups were to receive treatment to correct mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial.

5.1.1 Key Enrollment Criteria (Study 1 and Study 2)

The full list of inclusion and exclusion criteria for Study 1 and Study 2 are provided in [Appendix 9.1](#). Key enrollment criteria are below:

- Patients were 18 to 75 (Study 1) or 18 to 80 (Study 2) years of age with a clinical diagnosis of Graves' disease associated with active TED.
 - Patients had a CAS ≥ 4 for the more severely affected eye.
 - Patients had moderate-to-severe active TED (not sight-threatening but had an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, proptosis ≥ 3 mm above normal for race and sex and/or inconstant or constant diplopia (Study 2).
- Fewer than 9 months must have elapsed since the onset of active TED (as determined by patient records) as treatment for active TED should begin as early as possible.
- Patients could not have received prior orbital radiation or surgical therapy for the treatment of TED, excluding local supportive measures and oral steroids if the maximum cumulative dose was < 1000 mg methylprednisolone or equivalent.
- There must have been at least 6 weeks (Study 1) or 4 weeks (Study 2) between last administration of steroids and study randomization, in order to prevent any potential impact on outcome measures.
- Patients were to be euthyroid or have mild hypo- or hyperthyroidism (defined as free thyroxine and free triiodothyronine levels $< 50\%$ above or below the normal limits). Every effort was made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the study, as thyroid dysfunction is associated with more severe TED ([Gillespie 2012](#)).
- Patients with diabetes must have had well-controlled, stable disease.

The key difference in enrollment criteria for the two studies was the exclusion of patients with inflammatory bowel disease (IBD) in Study 2, an entry criterion that was added as a precaution because of two cases of potential IBD exacerbation in Study 1 (see [Section 6.7.3](#) for additional information).

5.1.2 Efficacy Endpoints

The primary and secondary endpoints selected for Study 1 and Study 2 (proptosis, CAS, diplopia and GO-QoL questionnaire) are established and well-defined measures used in the assessment of patients with TED, both in clinical practice and clinical study ([Bartalena 2016](#)).

5.1.2.1 Primary Endpoint

The primary efficacy endpoint was as follows:

- Study 1: overall responder rate (percentage of patients with ≥ 2 mm reduction in proptosis AND ≥ 2 -point reduction in CAS from Baseline in the study eye, provided there was no corresponding deterioration [≥ 2 mm/point increase] in proptosis or CAS in the non-study eye) at Week 24.
- Study 2: the proptosis responder rate (percentage of patients with a ≥ 2 mm reduction from Baseline in proptosis in the study eye, without deterioration [≥ 2 mm increase] of proptosis in the non-study eye) at Week 24.

The change in endpoint from Study 1 to Study 2 was done to focus on an objective measure (proptosis) that was less influenced by the time course of the disease (i.e., proptosis is expected to remain relatively constant while CAS is expected to improve as the disease transitions from active to inactive). Horizon and the FDA were in agreement that a change of at least 2 mm in proptosis was clinically meaningful and an appropriate primary endpoint measure.

5.1.2.2 Secondary Endpoints

The rank-ordered secondary endpoints in Study 1 and Study 2 are listed in sequential order in [Table 1](#).

5.1.2.3 Description of Endpoint Measures

Proptosis

Proptosis assessments for both eyes were performed with a Hertel exophthalmometer. Exophthalmometry has been found to be a valid and reproducible method across sites for measuring axial globe position in a multicenter study as compared with computed tomography (CT) ([Bingham 2016](#)). Extensive observer training, using the same intercanthal distance and requiring the same observer (except when strictly unavoidable) to evaluate a patient at each visit for the duration of the study ensured that data were collected consistently across different sites and observers. A change of at least 2 mm is considered to constitute a response to therapy ([Wiersinga 2006](#)).

Clinical Activity Score

TED activity was assessed by the Investigator using the 7-item EUGOGO amended CAS ([Mourits 1989](#)), which measures spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis and inflammation of caruncle or plica. One point is given for each item present for a possible total score ranging from 0 (none of these symptoms present) to 7 (all of these symptoms present). The CAS has been widely used to assess inflammatory signs with the aim of identifying patients in the active phase who are most likely to respond to immunosuppressive therapies. EUGOGO guidelines indicate a CAS ≥ 3 represents active TED ([Bartalena 2008](#)). A change of at least 2 points is considered a response ([Wiersinga 2006](#)) and a score of 0 or 1 represents no or minimal inflammation.

Diplopia

Subjective Diplopia was assessed using the Gorman scoring system ([Terwee 1998](#)), with the following possible grades:

0 = no diplopia

1 = intermittent (diplopia in primary position of gaze, when tired or when first awakening)

2 = inconstant (diplopia at extremes of gaze)

3 = constant (continuous diplopia in primary or reading position)

A decrease ≥ 1 grade represents a clinically meaningful improvement ([Wiersinga 2006](#)).

Graves' Ophthalmopathy Quality of Life

The GO-QoL is a disease-specific, 16-item patient self-administered questionnaire. It is divided into 2 subscales, one assessing the perceived effects of TED on daily physical activity as it relates to functional vision and the other assessing the effects of TED on appearance ([Table 6](#)). A score on each subscale and an overall score is derived, with each ranging from a minimum of 0 (marked limitation) to 100 (no limitation). A score change of 6 points is considered clinically meaningful for the GO-QoL instrument ([Terwee 2001](#)). Both scales have good reliability and high face validity. Correlations with other measures support construct validity ([Terwee 1998](#)).

Table 6: Graves' Ophthalmopathy Quality of Life Questionnaire¹

Subscale	Item	Response
Visual functioning	During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?	
	1. Bicycling	<i>Yes – seriously limited;</i> <i>Yes – a little limited;</i> <i>No – not at all limited</i>
	2. Driving	
	3. Moving around the house	
	4. Walking outdoors	
	5. Reading	
	6. Watching TV	
	7. Hobby or pastime	
	8. During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	<i>Yes – severely hindered;</i> <i>Yes – a little hindered;</i> <i>No – not at all hindered</i>
Appearance	9. Do you feel that your appearance has changed because of your thyroid eye disease?	<i>Yes – very much so;</i> <i>Yes – a little;</i> <i>No – not at all</i>
	10. Do you feel that you are stared at in the streets because of your thyroid eye disease?	
	11. Do you feel that people react unpleasantly because of your thyroid eye disease?	
	12. Do you feel that your thyroid eye disease has an influence on your self-confidence?	
	13. Do you feel socially isolated because of your thyroid eye disease?	
	14. Do you feel that your thyroid eye disease has an influence on making friends?	
	15. Do you feel that you appear less often on photos than before you had thyroid eye disease?	
	16. Do you try to mask changes in appearance caused by your thyroid eye disease?	

1. A dossier describing instrument validation in accordance with FDA guidance was submitted as part of the teprotumumab Biologics License Application.

5.1.3 Statistical Analyses and Sample Size Calculations

Because the primary analysis of dichotomous data in Study 1 used logistic regression (which is parameterized by the odds ratio) and the primary analysis of dichotomous data in Study 2 used weighted differences in proportions, the point estimates are in different scales. For any summaries of dichotomous data from both studies combined, analyses will match analyses of Study 2 data (weighted differences in proportions).

In both Study 1 and Study 2, the intent-to-treat (ITT) principle was followed, but the ITT populations were defined slightly differently. The ITT population in Study 1 comprised all patients who were randomized and received at least one dose of study drug (N=42, teprotumumab [1 patient randomized to teprotumumab was never treated]; N=45, placebo). In Study 2, the ITT population comprised all patients who were randomized (N=41, teprotumumab; N=42, placebo). Both are consistent with ICH E-9 guidance. For summaries of the two studies combined, the ITT population was defined as in Study 2.

5.1.3.1 Primary Endpoint

The prespecified analysis of the primary endpoint in each individual study was as follows:

- Study 1: The primary analysis used a logistic regression model with treatment group as the model effect with tobacco use as a covariate and was performed on the ITT population.

Patients missing the Week 24 evaluation were considered treatment failures (non-responders).

- Study 2: The primary analysis assessed the stratified difference in the proportions of proptosis responders between the treatment groups using the ITT population. The stratified difference was the weighted average of the difference within each stratum (tobacco user vs non-user) combined using Cochran-Mantel-Haenszel weights. A 2-sided p-value was calculated assuming that the test statistic was distributed as a standard normal random variable under the null hypothesis.

Patients missing the Week 24 evaluation were considered treatment failures (non-responders).

5.1.3.2 Secondary Endpoints

Within each study, the primary and secondary endpoints were tested sequentially, comparing teprotumumab versus placebo, to control for type 1 error. If the primary efficacy endpoint achieved significance at the 0.05 alpha level, then the secondary endpoints were evaluated for significance. As long as all endpoints earlier in the prespecified sequence ([Table 1](#)) achieved $p < 0.05$, testing of the next endpoint proceeded at the same level.

Analysis of dichotomous secondary endpoints followed the method of analysis of the primary efficacy endpoint within each study. Analysis of continuous endpoints in both studies used longitudinal analysis methods to assess the effect over 24 weeks.

5.1.3.3 Sample Size Calculations

Study 1 was powered at 80% if 42 evaluable patients per treatment group were included, assuming a response rate of 30% in placebo patients and 60% in teprotumumab patients. Based on the results of Study 1, the sample size of 38 patients per group for Study 2 was calculated to provide 90% power at the 2-sided alpha 0.05 level to detect a difference of 39% between teprotumumab and placebo.

5.2 Patient Population

5.2.1 Patient Disposition

In Study 1, 88 patients (43 teprotumumab and 45 placebo) were randomized and all but 1 patient received at least one dose of study drug, leaving the ITT population with a total of 42 teprotumumab patients and 45 placebo patients.

In Study 2, 83 patients (41 teprotumumab and 42 placebo) were randomized and comprised the ITT population. All randomized patients in Study 2 received at least one dose of study drug.

In summaries of both studies combined, the Sponsor used the ITT definition from Study 2 (all randomized). Thus, in analyses of both studies combined, there are 171 patients (84 teprotumumab and 87 placebo).

The rate of early study discontinuation was similar for teprotumumab and placebo within each study and was higher overall in Study 1, with adverse events and lack of efficacy being the most common reasons for discontinuation in the teprotumumab and placebo groups, respectively. Approximately 86% and 95% of patients completed the 24-week assessment in Study 1 and Study 2, respectively.

Table 7: Patient Disposition (Study 1 and Study 2)

Disposition, n (%) ¹	Study 1		Study 2	
	Teprotumumab	Placebo	Teprotumumab	Placebo
Randomized	43	45	41	42
Received ≥ 1 dose study drug	42	45	41	42
ITT population	42	45	41	42
Completed 24-week assessment	37 (86.0)	39 (86.7)	39 (95.1)	40 (95.2)
Withdrew early	6 (14.0)	6 (13.3)	2 (4.9)	2 (4.8)
Reason for withdrawal				
Adverse event	5 (11.6)	1 (2.2)	1 (2.4)	1 (2.4)
Lack of efficacy	0	2 (4.4)	0	0
Withdrawal by patient	0	0	1 (2.4)	1 (2.4)
Other ²	1 (2.3)	3 (6.7)	0	0

1. Percentages based on number of patients randomized.

2. Voluntary withdrawal before receiving study drug (teprotumumab), scheduled for back surgery (placebo), dispensed incorrect treatment at Week 3 in error and Sponsor decided to discontinue the patient (placebo) and optic disc edema left eye (placebo).

ITT = intent-to-treat

5.2.2 Demographics and Baseline Characteristics

The demographic and baseline characteristics were generally similar between the teprotumumab and placebo groups in each individual study (Table 8 and Table 9).

The mean age was 53 years (range: 20 to 77) in Study 1 and 50 years (20 to 79) in Study 2. The majority of patients in both studies were female, with a higher percentage of females in the placebo group compared to the teprotumumab group in Study 1; a large majority of patients were White.

Table 8: Patient Demographics (Study 1 and Study 2)

Characteristic	Study 1		Study 2	
	Teprotumumab (N = 42)	Placebo (N = 45)	Teprotumumab (N = 41)	Placebo (N = 42)
Age (years)				
Mean (SD)	51.7 (10.8)	54.1 (12.9)	51.6 (12.6)	48.9 (13.0)
Median	51.1	55.1	53.0	51.5
Min, max	22.3, 72.6	20.4, 77.0	31, 79	20, 73
Sex, n (%)				
Male	14 (33.3)	9 (20.0)	12 (29.3)	11 (26.2)
Female	28 (66.7)	36 (80.0)	29 (70.7)	31 (73.8)
Race, n (%)				
Asian	1 (2.4)	2 (4.4)	2 (4.9)	1 (2.4)
Black/AA	4 (9.5)	4 (8.9)	4 (9.8)	2 (4.8)
NH/PI	1 (2.4)	0	0	0
White	36 (85.7)	39 (86.7)	35 (85.4)	37 (88.1)
Other ¹	0	0	0	2 (4.8)
Ethnicity, n (%)				
Hispanic/Latino	2 (4.8)	4 (8.9)	2 (4.9)	1 (2.4)
Not Hispanic/Latino	40 (95.2)	41 (91.1)	39 (95.1)	41 (97.6)
Weight (kg)				
Mean (SD)	80.4 (19.8)	80.8 (21.4)	75.0 (16.5)	75.8 (18.5)
Median	74.9	73.5	73.9	74.5
Min, max	47.6, 138.0	53.6, 168.7	49.4, 110.0	45.0, 122.9

1. Patients with more than 1 race indicated appear in the "Other" category.

AA = African American; max = maximum; min = minimum; NH/PI = Native Hawaiian or Other Pacific Islander; SD = standard deviation

The time since diagnosis of active TED was approximately 6 months on average across treatment groups in both studies. Tobacco use is a risk factor for TED, and a minority of patients were tobacco users at Baseline with a higher proportion in the placebo group of Study 1 (40.0% vs 26.2% in the teprotumumab group). Approximately two-thirds of patients had diplopia at Baseline across treatment groups in both studies, with the exception of the teprotumumab group of Study 1, which had a diplopia rate of 90.5%. The Baseline GO-QoL scores were comparable between the teprotumumab and placebo groups in both studies.

Table 9: Patient Baseline Characteristics (Study 1 and Study 2)

Characteristic	Study 1		Study 2	
	Teprotumumab (N = 42)	Placebo (N = 45)	Teprotumumab (N = 41)	Placebo (N = 42)
Study eye, n (%)				
Right	26 (61.9)	21 (46.7)	22 (53.7)	20 (47.6)
Left	16 (38.1)	24 (53.3)	19 (46.3)	22 (52.4)
Tobacco use status, n (%)				
Non-user	31 (73.8)	27 (60.0)	32 (78.0)	34 (81.0)
User	11 (26.2)	18 (40.0)	9 (22.0)	8 (19.0)
Time since diagnosis of Graves' Disease (years)				
Mean (SD)	2.8 (4.2)	3.5 (5.5)	3.5 (6.1)	2.2 (3.2)
Median	0.9	1.0	1.0	0.9
Min, max	0.2, 19.1	0.2, 25.0	0.3, 28.2	0.1, 14.8
Time since diagnosis of active TED (months)				
Mean (SD)	5.6 (2.0)	6.1 (2.5)	6.2 (2.3)	6.4 (2.4)
Median	5.3	6.6	6.3	6.8
Min, max	2.3, 10.1	1.2, 11.0	0.9, 9.7	1.1, 10.3
CAS, n (%)				
0-3	1 (2.4)	0	0	0
4	10 (23.8)	6 (13.3)	10 (24.4)	19 (23.8)
5	17 (40.5)	24 (53.3)	18 (43.9)	14 (33.3)
6	12 (28.6)	13 (28.9)	10 (24.4)	13 (31.0)
7	2 (4.8)	2 (4.4)	3 (7.3)	5 (11.9)
Proptosis measurement, mm				
Mean (SD)	23.4 (3.2)	23.1 (2.9)	22.6 (3.3)	23.2 (3.2)
Diplopia, n (%)				
Present	38 (90.5)	31 (68.9)	28 (68.3)	28 (66.7)
Not present	4 (9.5)	14 (31.1)	13 (31.7)	14 (33.3)
GO-QoL				
Mean (SD)	58.7 (26.1)	63.9 (26.2)	63.3 (22.1)	60.9 (19.4)

CAS = clinical activity score; GO-QoL = Graves' Ophthalmopathy Quality of Life; max = maximum; min = minimum; SD = standard deviation; TED = thyroid eye disease

No clinically meaningful differences were observed between the treatment groups for medications used prior to entering either Study 1 or Study 2.

In Study 1 and Study 2, no patient in the teprotumumab group received intravenous glucocorticoids prior to the study. The most commonly used concomitant medications included sulfur-containing imidazole derivatives for treatment of Graves' disease (53.5% placebo and 44.0% teprotumumab) and thyroid hormones for treatment of hypothyroidism (43.0% placebo and 54.8% teprotumumab).

5.3 Study Results

Results from the Treatment Periods of Study 1 and Study 2 consistently demonstrated the effectiveness of teprotumumab across the primary and secondary endpoints. For Study 1, teprotumumab was superior to placebo for the primary endpoint (overall responder rate) and the first 4 of the 5 ranked secondary endpoints (change in GO-QoL overall score, proptosis measurements, CAS and GO-QoL visual functioning subscale score); for the last rank-ordered secondary endpoint, a numerically greater improvement in the GO-QoL appearance subscale score was observed in the teprotumumab group compared with placebo (Table 10). For Study 2, teprotumumab was superior to placebo for the primary endpoint (proptosis responder rate) and all 5 secondary endpoints (overall responder rate, CAS categorical responder rate, change in proptosis, diplopia responder rate and change in GO-QoL overall score) (Table 11).

Table 10: Primary and Secondary Efficacy Endpoints (Study 1, ITT Population)

	Teprotumumab (N = 42)	Placebo (N = 45)			
Primary Endpoint¹			Odds Ratio	95% CI	p-value
Overall responder rate at Week 24, n (%)	29 (69.0)	9 (20.0)	8.96	3.29, 23.8	< 0.001
Secondary Endpoints²			Difference	95% CI	p-value
CFB in GO-QoL overall score through Week 24, LS mean (SE)	17.3 (2.4)	6.4 (2.2)	10.9 (3.2)	4.5, 17.2	0.001
CFB in proptosis (mm) through Week 24, LS mean (SE)	-2.5 (0.2)	-0.2 (0.2)	-2.3 (0.3)	-2.8, -1.8	< 0.001
CFB in CAS (points) through Week 24, LS mean (SE)	-3.4 (0.2)	-1.9 (0.2)	-1.6 (0.2)	-2.1, -1.1	< 0.001
CFB in GO-QoL visual functioning through Week 24, LS mean (SE)	21.1 (2.9)	6.8 (2.7)	14.3 (3.8)	6.7, 21.9	< 0.001
CFB Baseline in GO-QoL appearance through Week 24, LS mean (SE)	12.9 (2.8)	6.6 (2.7)	6.3 (3.8)	-1.3, 13.9	0.101

1. Odds ratio, 95% CI and p-value were from a logistic regression with treatment and tobacco use status (non-user vs user) as covariates.

2. Results from a MMRM analysis with an unstructured covariance matrix using treatment, tobacco use, Baseline value, visit, treatment-by-visit and visit-by-Baseline value interaction as fixed effects. CAS = Clinical Activity Score; CI = confidence interval; CFB = change from Baseline; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = least squares; MMRM = mixed model repeated-measures; SE = standard error

Table 11: Primary and Secondary Efficacy Endpoints (Study 2, ITT Population)

	Teprotumumab (N = 41)	Placebo (N = 42)	Difference	95% CI	p-value
Primary Endpoint¹					
Proptosis responder rate at Week 24, n (%)	34 (82.9)	4 (9.5)	73.5 (7.4)	58.9, 88.0	< 0.001
Secondary Endpoints					
Overall responder rate at Week 24 ¹ , n (%)	32 (78.0)	3 (7.1)	70.8 (7.6)	55.9, 85.8	< 0.001
CAS responder rate at Week 24 ¹ , n (%)	24 (58.5)	9 (21.4)	36.0 (9.5)	17.4, 54.7	< 0.001
CFB in proptosis (mm) through Week 24 ² , LS mean (SE)	-2.8 (0.2)	-0.5 (0.2)	-2.3 (0.2)	-2.8, -1.8	< 0.001
Diplopia responder rate at Week 24 ^{1,3} , n/N (%)	19/28 (67.9)	8/28 (28.6)	39.3 (12.1)	15.6, 63.0	0.001
CFB in GO-QoL overall score through Week 24 ² , LS mean (SE)	13.8 (2.074)	4.4 (2.1)	9.4 (2.7)	4.1, 14.6	< 0.001

1. Stratified difference is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights. Test statistic calculated by dividing the stratified difference by the SE. Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

2. Results from an MMRM with an unstructured covariance matrix including the following terms: Baseline value, tobacco use status, treatment group, visit, visit-by-treatment interaction and visit-by-Baseline value interaction. A change from Baseline of 0 was imputed at the first post-Baseline visit for any patient without a post-Baseline value.

3. Denominator is number of patients who had diplopia at Baseline.

CAS = Clinical Activity Score; CI = confidence interval; CFB = change from Baseline; CMH = Cochran-Mantel-Haenszel; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = least squares; MMRM = mixed model repeated-measures; SE = standard error

In the remainder of this section, efficacy results from the individual studies are presented side-by-side by endpoint measure (as opposed to sequential order of statistical testing, which varied by individual study) in order to show the consistency of the results across both Study 1 and Study 2 (Table 12). Results of the study eye are presented as applicable; results of the non-study eye generally followed the same pattern of improvement as the study eye and are briefly summarized in Section 5.3.8.

Additionally, results from efficacy analyses based on data pooled from Study 1 and Study 2 are presented in Section 5.4 and results from the off-treatment Follow-up Period of Study 1 are summarized in Section 5.5.

Table 12: Guide to Presentation of Efficacy Endpoints in Section 5.3

Endpoint	Prespecified in Study 1	Prespecified in Study 2
Clinical Measures		
Proptosis responder rate	-	Primary
Overall responder rate	Primary	Secondary #1
CFB in proptosis	Secondary #2	Secondary #3
CFB in CAS value	Secondary #3	Exploratory
CAS responder rate	-	Secondary #2
Diplopia responder rate	-	Secondary #4
Quality of Life Measures		
CFB in in GO-QoL – Overall	Secondary #1	Secondary #5
CFB in GO-QoL – Visual Function (Section 5.4.1) ¹	Secondary #4	Exploratory
CFB in GO-QoL – Appearance (Section 5.4.1) ¹	Secondary #5	Exploratory

1. Prespecified as secondary endpoint for sequential statistical testing in integrated analyses of Study 1 and Study 2.

CAS = Clinical Activity Score; CFB = change from Baseline; GO-QoL = Graves' Ophthalmopathy Quality of Life

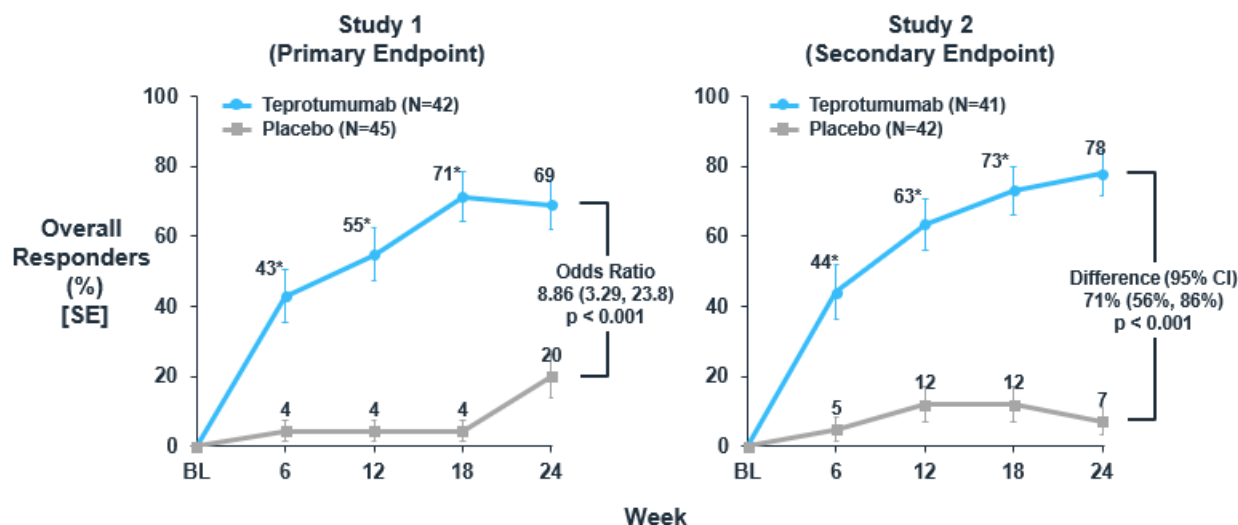
5.3.1 Proptosis Responder Rate (Study 2 Primary Endpoint)

In Study 2, in which the proptosis responder rate was the primary efficacy endpoint, a statistically significantly greater proportion of patients treated with teprotumumab were proptosis responders compared with patients who received placebo (82.9% vs 9.5%, $p < 0.001$; difference: 73.4%; 95% confidence interval [CI]: 58.9%, 88.0%). In Study 1, a greater percentage of patients treated with teprotumumab were proptosis responders compared with patients who received placebo (71.4% vs 20.0%, $p < 0.001$; odds ratio: 9.84; 95% CI: 3.63, 28.7).

The percentage of proptosis responders among teprotumumab patients increased through Week 24 in each study, and a greater proportion of responders was observed at all study visits (Figure 1). The median time to proptosis response was 45.5 days in Study 1 and 45.0 days in Study 2.

5.3.2 Overall Responder Rate (Study 1 Primary Endpoint)

Figure 8 shows the results for the overall responder rate. A greater proportion of patients treated with teprotumumab were overall responders compared with patients who received placebo at all study visits for each individual study. In Study 1, in which the overall responder rate at Week 24 was the primary efficacy endpoint, a statistically significantly greater proportion of patients treated with teprotumumab were overall responders compared with patients treated with placebo (69.0% vs 20.0%, $p < 0.001$; odds ratio: 8.86; 95% CI: 3.29, 23.8). A sensitivity analysis using all randomized subjects (rather than the prespecified primary analysis set of all randomized and treated subjects) showed identical conclusions on overall response rate (67.4% vs 20.0%, $p < 0.001$; odds ratio: 8.28; 95% CI: 3.10, 22.09). In Study 2, a statistically significantly greater proportion of patients treated with teprotumumab were overall responders compared with patients who received placebo (78.0% vs 7.1%, $p < 0.001$; difference: 70.8%; 95% CI: 55.9%, 85.8%).

Figure 8: Overall Responder Rate over Time (Study 1 and Study 2)

*Nominal p-value: $p < 0.001$

BL = Baseline; CI = confidence interval; SE = standard error

5.3.3 Change from Baseline in Proptosis

Over the course of the 24-week Treatment Period, a larger reduction in proptosis was observed for patients treated with teprotumumab compared with patients treated with placebo for each individual study (least squares [LS] mean [standard error (SE)] treatment difference: -2.3 [0.3] for Study 1 and -2.3 [0.2] for Study 2; [Figure 2](#)). Reductions in proptosis occurred early with teprotumumab, with improvements seen at the first post-Baseline efficacy assessment (Week 6) in each individual study. The level of proptosis reduction observed at Week 24 in patients treated with teprotumumab (-3.0 mm and -3.3 mm in Study 1 and Study 2, respectively) approached the mean levels attained with decompression surgery (-3.8 mm; [Rootman 2017](#); [Wu 2017](#)).

5.3.4 Change from Baseline in CAS

When CAS values were averaged in each individual study, a significant difference in change from Baseline was observed through Week 24, favoring the teprotumumab group ([Table 13](#)). At Baseline, the mean CAS was almost identical in both groups in each study. At Week 24, a greater decrease (improvement) from Baseline in CAS was observed in the teprotumumab group; the LS mean (SE) difference between treatment groups was -1.6 (0.2) in Study 1 and -1.4 (0.3) in Study 2.

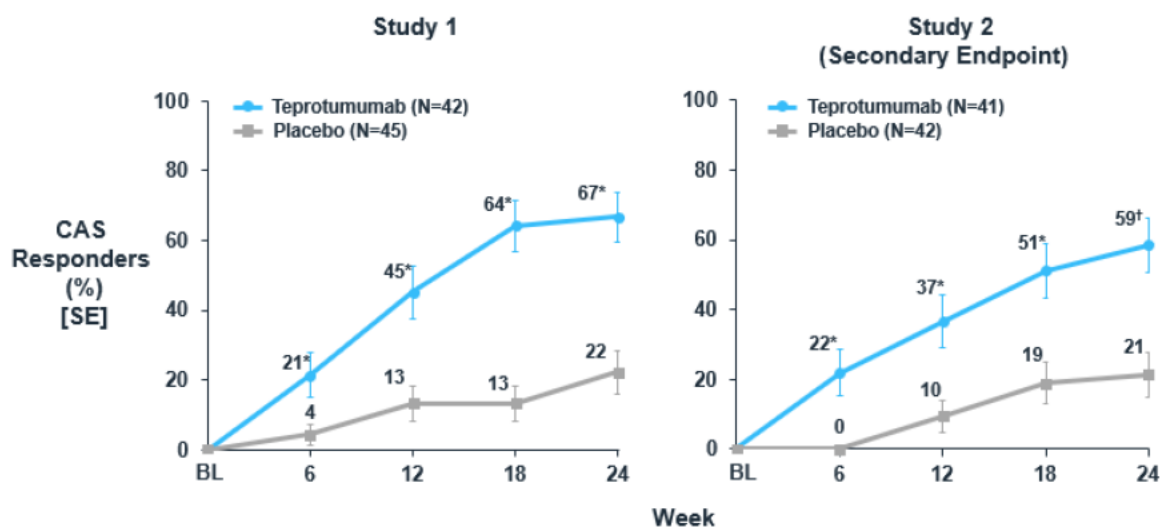
Table 13: Change from Baseline in CAS Value Through Week 24 (Study 1 and Study 2)

CAS Value	Study 1		Study 2	
	Teprotumumab (N = 42)	Placebo (N = 45)	Teprotumumab (N = 41)	Placebo (N = 42)
Baseline				
Mean (SD)	5.1 (1.0)	5.2 (0.7)	5.1 (0.9)	5.3 (1.0)
Min, max	2, 7	4, 7	4, 7	4, 7
Week 24				
Mean (SD)	1.0 (1.1)	2.6 (1.6)	1.4 (1.4)	3.3 (1.9)
Min, max	0, 4	0, 7	0, 5	0, 7
Change from Baseline through Week 24				
LS mean (SE)	-3.4 (0.2)	-1.9 (0.2)	-3.5 (0.2)	-2.1 (0.2)
Difference in LS mean (SE)		-1.6 (0.2)		-1.4 (0.3)
95% CI		-2.0, -1.1		-2.0, -0.8
p-value		< 0.001		< 0.001

CAS = Clinical Activity Score; CI = confidence interval; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error

5.3.5 CAS Responder Rate

A greater proportion of patients treated with teprotumumab had a CAS of 0 or 1 (no or minimal inflammation) compared with patients who received placebo in each individual study at all post-Baseline time points through Week 24 (Figure 9). These results show that treatment with teprotumumab led to improvements in the inflammatory effects of TED.

Figure 9: CAS Responder Rate over Time (Study 1 and Study 2)

*Nominal p-value: $p < 0.05$

†Ranked endpoint: $p < 0.001$

BL = Baseline; CAS = Clinical Activity Score

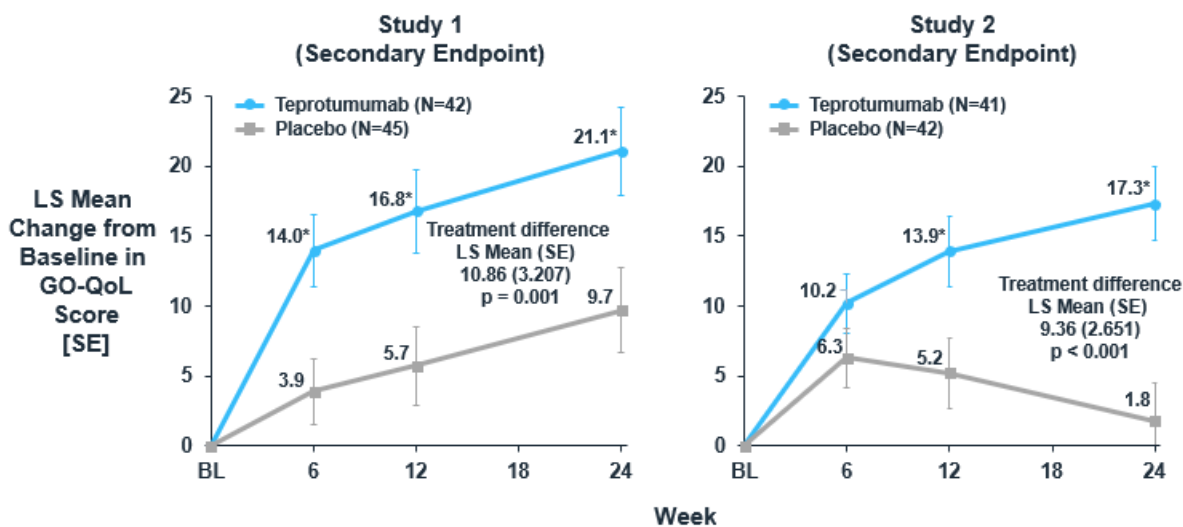
5.3.6 Diplopia Responder Rate

Among patients who were experiencing diplopia at Baseline (grade > 0 in the study eye), a greater proportion of those treated with teprotumumab had an improvement of ≥ 1 grade compared with those who received placebo. The diplopia responder rate in the teprotumumab group increased throughout the Treatment Period in Study 1 and was stable starting at Week 12 in Study 2 (Figure 3).

5.3.7 Change from Baseline in GO-QoL – Analysis from Individual Studies

Teprotumumab resulted in a greater improvement in the disease-specific quality of life questionnaire, GO-QoL, compared with placebo (Figure 10). The range of the GO-QoL overall transformed scores is 0 to 100, where higher values correspond to better quality of life. In each individual study, a greater increase in the overall transformed score through Week 24 was observed for patients treated with teprotumumab compared with patients treated with placebo. The change observed with teprotumumab exceeded the 6-point minimal clinically important difference for the GO-QoL instrument (Terwee 2001).

Figure 10: Change from Baseline in GO-QoL Overall Score over Time (Study 1 and Study 2)



*Nominal p-value: $p < 0.05$

BL = Baseline; GO-QoL = Graves' Ophthalmopathy Quality of Life; LS = least squares; SE = standard error

5.3.8 Results in Non-Study Eye

Similar efficacy results were observed for the non-study eye in both Study 1 and Study 2 when the primary efficacy endpoints were analyzed using patients' non-study eye (Table 4). In addition, the non-study eye showed larger reductions in proptosis and CAS for teprotumumab compared to placebo and a substantial proportion of CAS responders and diplopia responders.

5.4 Analyses of Pooled Data (Study 1 and Study 2 Combined)

As Study 1 and Study 2 enrolled similar patient populations and assessed efficacy using similar assessments, a prespecified analysis combining the pooled efficacy data from the two studies was performed. This pooled analysis allows for more precise estimation of treatment effects for smaller subsets of the study population and higher power to find small but clinically relevant treatment effects. In addition to including the primary and secondary endpoints of Study 2, the GO-QoL visual functioning and appearance subscale scores were prespecified as secondary endpoints in the integrated analyses. The pooling of analysis populations and statistical methods were prospectively defined and discussed with the FDA.

The integrated analyses for all prespecified primary and secondary endpoints were similar to what was seen in the individual studies. Changes in GO-QoL scores are presented below.

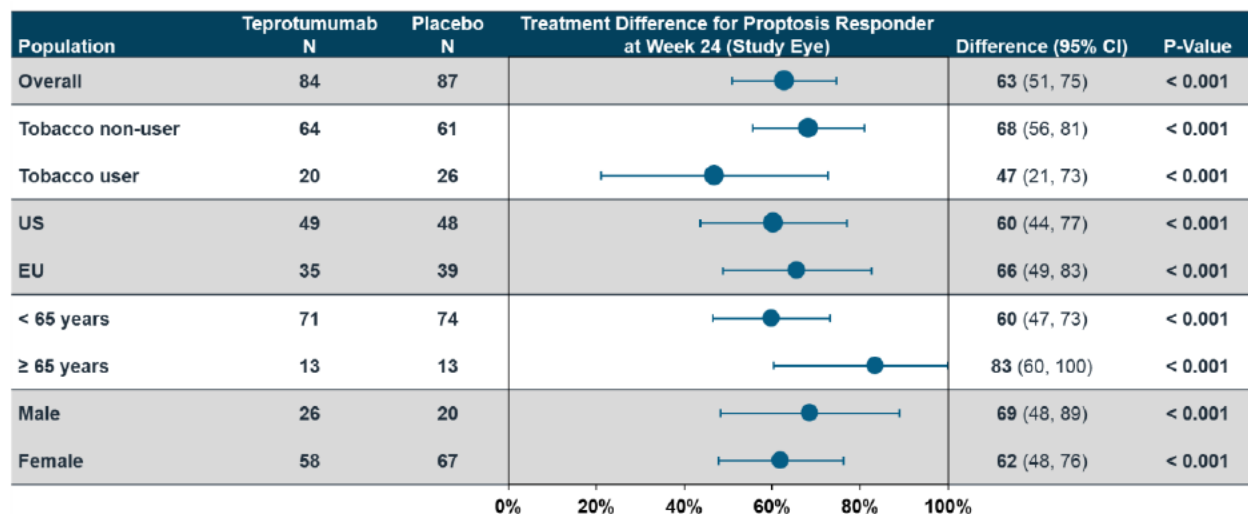
5.4.1 *Change from Baseline in GO-QoL*

In the combined analysis, larger improvements from Baseline through Week 24 were observed in patients treated with teprotumumab than patients treated with placebo for the GO-QoL overall score as well as the GO-QoL visual functioning and appearance subscales (Table 3). These results are consistent with those from the individual studies except that the treatment difference for GO-QoL appearance did not achieve $p < 0.05$ in Study 1.

The improvements observed with teprotumumab in the combined analysis of overall score, visual functioning, and appearance were statistically significant and clinically meaningful, as the magnitude of change (15.6, 16.8 and 13.5 points, respectively) was larger than 6 points, the minimum clinically important difference in GO-QoL scores (Terwee 2001).

5.4.2 *Efficacy in Subgroups*

The treatment benefit of teprotumumab was consistent across tobacco users and non-users as well as patient subgroups by geographic region, age and sex (Figure 11). There were too few Black or African-American and Asian patients to adequately assess differences in effects in those populations.

Figure 11: Proptosis Responder Rate at Week 24 by Subgroups (Placebo adjusted for Study 1 and Study 2 Combined)

CI = confidence interval; EU = Europe; US = United States

5.5 Persistence of Efficacy (Study 1)

Following completion of the 24-week Double-Masked Treatment Period in Study 1, patients entered a Follow-up Period of 48 weeks with no additional treatment for TED during at least the first 12 weeks, unless medically indicated. Efficacy assessments were performed at Weeks 28 and 72. For responder analyses, patients who received additional treatment for TED were counted as non-responders, as were any patients who did not have Week 28 or Week 72 data.

5.5.1 Assessment of Acute Rebound in Overall Response and Proptosis Response at Week 28

Cessation of steroids has been known to lead to an acute rebound of inflammatory symptoms in TED. To ensure this was not the case with teprotumumab, overall response (≥ 2 mm proptosis improvement AND ≥ 2 -point CAS improvement) and proptosis response were assessed at Week 28, seven weeks after the last dose of study drug. At Week 28, the proportions of teprotumumab responders were comparable to those observed at Week 24 (Table 14), suggesting little evidence for acute recurrence of disease activity.

Table 14: Overall Response and Proptosis Response at Week 24 and Week 28 (Study 1)

Efficacy Endpoint	Teprotumumab	
	Week 24 (N=42)	Week 28 (N=42)
Overall responders, n (%)	29 (69.0)	31 (73.8)
Proptosis responders, n (%)	30 (71.4)	31 (73.8)

5.5.2 Maintenance of Response at Week 72

To evaluate persistence of effect post-treatment, patients who were proptosis responders at Week 24 were evaluated for loss of proptosis response following the completion of treatment.

At Week 72 (51 weeks following the last dose of study drug), 16 (53%) of the 30 teprotumumab responders assessed still maintained at least a 2 mm improvement. Furthermore, 22 (73%) of the 30 teprotumumab responders still showed reduced proptosis from Baseline without any additional treatment for TED.

Similarly, of patients who were diplopia responders at Week 24, 69% (18 of 26) were still responders at Week 72, nearly a year after the last dose of teprotumumab.

5.6 Efficacy Conclusions

Teprotumumab delivered statistically significant and clinically meaningful improvements across a range of relevant TED endpoints in two independent, well-designed randomized controlled studies that showed consistent treatment effects. Greater proportions of patients treated with teprotumumab were proptosis responders compared with patients who received placebo and the level of proptosis reduction observed with teprotumumab approached the levels attained with decompression surgery. In addition, greater proportions of patients treated with teprotumumab were overall responders, CAS responders and diplopia responders compared with patients who received placebo. These changes were associated with meaningful improvements favoring teprotumumab in patients' assessments of quality of life with respect to visual functioning and appearance.

6 CLINICAL SAFETY

Summary

- The safety of teprotumumab has been assessed in a total of 121 patients with TED who received treatment with teprotumumab for an average of 157.2 days, as of the 120-day safety update. Of these, 84 were in the Double-Masked Population. The Double-Masked Population allows for an assessment of drug-related events by comparison to placebo and interpretation of event rates.
- Teprotumumab was generally well-tolerated. Most adverse events were mild or moderate, were manageable and resolved with few treatment discontinuations.
- Treatment-emergent adverse events (TEAEs) in the Double-Masked Treatment Period, were greater among teprotumumab patients (80%) compared with placebo patients (70%).
 - *Muscle spasms* (25.0%), *Nausea* (16.7%), *Alopecia* (13.1%), *Diarrhoea* (11.9%) *Fatigue* (9.5%), *Dysgeusia*, *Headache*, *Dry skin* (each 8.3%), *Hyperglycaemia* (7.1%) and *Rash* (6.0%) were the most commonly reported TEAEs in the teprotumumab group – all occurring at a higher rate than in the placebo group, except *Rash*.
 - In the teprotumumab group, few patients experienced TEAEs that were serious (8.3%), severe or higher in intensity (4.8%) or led to discontinuation of study drug (6.0%). Such TEAEs pertained to exacerbation of IBD and infusion related reactions or were either consistent with patient comorbid conditions or unrelated to study treatment. No deaths occurred.
 - In the placebo group, 1 patient experienced a TEAE that was severe and serious – *Visual field defect* requiring emergent optic nerve decompression surgery as a result of TED – and another patient discontinued due to a TEAE of *Presyncope*.
- Adverse Events of Special Interest (AESI) in the Double-Masked Treatment Period:
 - More hyperglycemia adverse events were observed in teprotumumab-treated patients compared to placebo (9.5% vs 1.2%), and more commonly reported in patients with pre-existing diabetes mellitus or impaired glucose tolerance. All events were non-serious and mild or moderate in severity; none led to discontinuation of study drug.
 - Infusion reactions were reported as mild or moderate in 3 teprotumumab-treated patients, were managed with symptomatic treatment and resolved the same day without complications; 2 patients discontinued without re-challenge and 1 continued study treatment with premedication and a slower infusion rate.
 - Two teprotumumab-treated patients experienced serious TEAEs (SAEs) consistent with exacerbation of pre-existing IBD, requiring discontinuation of study drug. No events suggestive of new-onset IBD have been observed.

- Hearing impairment was reported among 9.5% of patients treated with teprotumumab compared to no patients treated with placebo. These events were mild or moderate in severity with no patients discontinuing therapy due to hearing impairment.
- There were 2 teprotumumab subjects with anti-drug (ADA) antibodies which were low titer and transient. There was no correlation between ADA development and clinical response or adverse reactions.

6.1 Overview of Safety Analyses and Populations

The safety evaluation of teprotumumab is based on data from the 24-week Treatment Periods of the placebo-controlled studies (Study 1 and Study 2) in what is referred to as the Double-Masked Population. The Double-Masked Population allows for an assessment of drug-related events and interpretation of event rates. It includes any patient who received at least one dose of study drug in Study 1 or Study 2 (N=84 teprotumumab patients and N=86 placebo patients). Additional data collected from the ongoing open-label extension study (OPTIC-X, as of the 120-day safety update) are presented for TEAEs, SAEs and adverse events of special interest (AESI) to ensure a comprehensive assessment. Follow-up information for serious adverse events or adverse events of special interest after the 120-day safety update is also included where available as of October 29, 2019. The OPTIC-X Population (N=46) comprises patients who received at least one dose of teprotumumab in OPTIC-X.

Analyses of TEAEs, SAEs and AESI include adverse events occurring or worsening after the first dose on Study Day 1 through 3 weeks following the last dose of study drug.

Each study was monitored by a Data Safety Monitoring Board (DSMB), independent from the Sponsor. The DSMB reviewed safety data on an ongoing basis and upon each review, has recommended continuation of the study without modifications.

6.2 Treatment Exposure

A total of 121 patients have received treatment with teprotumumab for an average of 157.2 days.

In the Double-Masked Population, most patients in both the teprotumumab and placebo groups received all 8 infusions of study drug (75 [89.3%] and 80 [93.0%], respectively). The mean number of days on study drug were similar between the teprotumumab and placebo groups (141 and 143, respectively). In the OPTIC-X Population, the median number of teprotumumab doses received at the time of the data cutoff was 8 infusions. As of the data cutoff, 33 patients had completed all 8 infusions in OPTIC-X, bringing the total number of patients to complete a full course of teprotumumab to 106.

Table 15: Teprotumumab Exposure in Patients with TED (Safety Population)

	Number of Patients	
	Teprotumumab	Placebo
Double-Masked Population	84	86
Study 1 ¹	43	44
Study 2 ²	41	42
OPTIC-X Population^{2,3}	46	-
Overall	121	-

1. Per the prespecified analysis plan, for safety analyses in Study 1, patients were categorized according to the treatment received at the first dose. One patient was randomized to placebo but received teprotumumab in error for the first dose; this patient was included in the teprotumumab group in the Safety Population.

2. Includes 9 patients who received teprotumumab in both Study 2 and OPTIC-X. These 9 patients are counted only once in the Overall row.

3. Includes 37 patients who received placebo in Study 2.

6.3 Overview of Adverse Events

TEAEs from the Double-Masked Population and the OPTIC-X Population are summarized in [Table 5](#). TEAEs were reported for the majority of patients in Study 1 and Study 2, with more teprotumumab-treated patients than placebo-treated patients reporting TEAEs. TEAEs were predominantly graded as mild to moderate, with 4 patients in the teprotumumab group and 1 patient in the placebo group experiencing events of severe or higher intensity. Few SAEs and TEAEs leading to study drug discontinuation occurred, with more cases in the teprotumumab group than the placebo group. SAEs are summarized in [Table 17](#).

Among the 46 patients in the OPTIC-X Population, the overall incidence of TEAEs was similar to that observed in Study 1 and Study 2. Two patients discontinued study drug due to TEAEs, including one that was a serious, life-threatening event considered unrelated to teprotumumab by the Investigator and Sponsor. This SAE is described in further detail in [Table 17](#).

6.3.1 Common Adverse Events

[Table 16](#) lists the TEAEs that occurred in $\geq 5.0\%$ of patients in either treatment group in the Double-Masked Population. Each of these TEAEs occurred more frequently in the teprotumumab group compared to the placebo group, with the exception of *Rash*, which occurred at a similar rate in both groups. *Muscle spasms* was the most commonly reported TEAE in the teprotumumab group. TEAEs associated with *Muscle spasms*, *Diarrhoea* and *Hyperglycaemia* were prospectively identified as AESI and are detailed in [Section 6.7](#).

Greater proportions of teprotumumab-treated patients compared to placebo-treated patients had TEAEs in the *Infections and infestations* System Organ Class (SOC) (35.7% vs 22.1%, respectively) and *Ear and labyrinth disorders* SOC (11.9% vs 2.3%); however, none of the individual preferred terms (PTs) within these SOCs occurred at an incidence of $\geq 5.0\%$. Among all TEAEs reported in the *Infections and infestations* SOC, none was recognized as an opportunistic infection. Furthermore, the events were not dominated by any specific type of pathogen. Infectious TEAEs that occurred in 2 or more teprotumumab patients are as follows: *Bronchitis* (4.8% vs 2.3%), *Cystitis* (4.8% vs 1.2%), *Urinary tract infection* (4.8% vs 1.2%),

Nasopharyngitis (3.6% vs 1.2%), *Influenza* (2.4% vs 4.7%), *Localized infection* (2.4% vs 0) and *Sinusitis* (2.4% vs 0). With the exception of *Escherichia sepsis* (discussed in Section 6.5), none of the TEAEs within the *Infections and infestations* SOC was serious, led to discontinuation of study drug or was considered severe or higher in intensity. TEAEs associated with hearing impairment were prospectively identified as events of interest and are detailed in Section 6.7.4.

The TEAE profile in the OPTIC-X Population was similar to that in the Double-Masked Population; *Muscle spasms* was the most commonly reported TEAE, with *Alopecia*, *Diarrhoea*, *Dry skin*, *Fatigue* and *Ear discomfort* also occurring in more than 3 patients each (Table 16).

Table 16: TEAEs Occurring in $\geq 5.0\%$ of Patients in Either Treatment Group of the Double-Masked Population or in $\geq 5.0\%$ of Patients in OPTIC-X Population

Preferred Term	Double-Masked Population		OPTIC-X
	Teprotumumab (N = 84)	Placebo (N = 86)	Teprotumumab (N = 46)
Patients with any TEAE, n (%)	67 (79.8)	60 (69.8)	39 (84.8)
Muscle spasms	21 (25.0)	6 (7.0)	19 (41.3)
Nausea	14 (16.7)	8 (9.3)	1 (2.2)
Alopecia	11 (13.1)	7 (8.1)	5 (10.9)
Diarrhoea	10 (11.9)	7 (8.1)	5 (10.9)
Fatigue	8 (9.5)	6 (7.0)	4 (8.7)
Headache	7 (8.3)	6 (7.0)	1 (2.2)
Dysgeusia	7 (8.3)	0	3 (6.5)
Dry skin	7 (8.3)	0	5 (10.9)
Hyperglycaemia	6 (7.1)	1 (1.2)	0
Rash	5 (6.0)	5 (5.8)	3 (6.5)
Ear discomfort	4 (4.8)	0	4 (8.7)
Pain in extremity	1 (1.2)	1 (1.2)	4 (8.7)
Influenza	2 (2.4)	4 (4.7)	3 (6.5)
Abdominal pain upper	3 (3.6)	4 (4.7)	3 (6.5)
Urinary tract infection	4 (4.8)	1 (1.2)	3 (6.5)
Hypoacusis	2 (2.4)	0	3 (6.5)
Rhinorrhoea	1 (1.2)	1 (1.2)	3 (6.5)
Onychoclasia	2 (2.4%)	0	3 (6.5)

TEAE = treatment-emergent adverse event

6.3.2 Severe or Life-Threatening Adverse Events

In the Double-Masked Population, TEAEs with an intensity of severe or higher occurred in 4 teprotumumab patients (*Chills*, *Dehydration*, *Headache*, *Vomiting* and *Escherichia sepsis* in 1 patient and *Diarrhoea*, *Inflammatory bowel disease* and *Pneumothorax* in 1 patient each) and 1 placebo patient (*Visual field defect*); one additional event was experienced by a patient in OPTIC-X (*Cerebral haemorrhage*). The *Pneumothorax* and the *Cerebral haemorrhage* were both reported by the Investigator as life-threatening and unrelated to study drug; all other events were reported as severe. The patient experiencing *Pneumothorax* was able to complete the

Treatment Period. As at least 1 event for each patient was also serious, these patients are detailed in Section 6.5.

6.3.3 Adverse Events in Subgroups

The TEAE profile observed for the overall Double-Masked Population was generally consistent across demographic and tobacco use subgroups.

6.4 Deaths

There have been no deaths in the teprotumumab clinical program for TED.

6.5 Serious Adverse Events

In the Double-Masked Population, SAEs were reported in 7 (8.3%) teprotumumab patients and 1 (1.2%) placebo patient during the Treatment Period ([Table 17](#)). One additional SAE was reported in the OPTIC-X Population.

Among the SAEs reported in teprotumumab-treated patients, 3 were considered by the Investigator as at least possibly related to study drug (*Infusion related reaction, Diarrhoea and Hashimoto's encephalopathy*) and 5 were considered unrelated (*Escherichia sepsis, Inflammatory bowel disease, Pneumothorax, Urinary retention and Cerebral haemorrhage*). One placebo patient developed *Visual field defect* requiring urgent surgical intervention. Summaries of the SAEs are provided in Table 17.

Table 17: Serious Adverse Events (Double-Masked Population and OPTIC-X Population)

Patient Age/ Sex/ Race	Preferred Term (Severity)	Study Day of Onset ¹	Study Drug Relationship /Action Taken	Comments/Outcome
Study 1 – Teprotumumab Group				
61/M/ W	<i>Hashimoto's encephalopathy</i> (Moderate) <i>Confusional state</i> (Severe, non- serious)	124 129	Possibly related/ Study drug withdrawn	Patient experienced several episodes of transient confusion lasting less than 24 hours between 18 and 32 days following the 6 th infusion of teprotumumab. Head imaging (CT and magnetic resonance imaging) did not show pathological findings; echocardiogram revealed a low ejection fraction of 35% and a laboratory thyroperoxidase antibody titer was elevated. Discharge summary indicated "possible Hashimoto's encephalopathy" based on "intermittent fluctuating nature of the patient's symptoms" and "strong family history of autoimmune thyroid disease."
72/F/W	<i>Diarrhoea</i> (Severe)	143	Possibly related/ Study drug withdrawn	Patient with a medical history of colitis with abdominal cramping and bloody diarrhea in the 7 months preceding randomization experienced severe diarrhea on study. Colonoscopy revealed ulcerative colitis, which was treated with colectomy with small bowel ileostomy with recovery.
43/F/A	<i>Inflammatory bowel disease</i> (Severe)	149	Not related/ Study drug withdrawn	Patient with medical history of loose stools with aphthous ulcers noted on biopsy (colonoscopy) experienced loss of appetite, weight loss, acute diarrhea, abdominal pain and bowel movements 10 to 15 times per day on study. Colonoscopy revealed pancolitis, which was treated with mesalamine and steroid with recovery.
50/M/ B	<i>Escherichia sepsis</i> (Severe) <i>Dehydration</i> (Severe, non- serious)	51 46	Not related/ Study drug withdrawn	Patient with medical history of well-controlled HIV experienced E coli bacteremia complicated by thrombocytopenia and acute tubular necrosis. Patient treated with antibiotic and intravenous fluids with resolution of thrombocytopenia and improved renal function at the time of discharge.
47/M/ W	<i>Urinary retention</i> (Moderate)	146	Not related/ Study drug continued	Patient experienced urinary retention 2 days after outpatient surgery for repair of left inguinal hernia. Patient treated with tamsulosin and an indwelling catheter and recovered 3 days later.

Patient Age/ Sex/ Race	Preferred Term (Severity)	Study Day of Onset ¹	Study Drug Relationship /Action Taken	Comments/Outcome
Study 2 – Teprotumumab Group				
38/M/ W	<i>Infusion related² reaction (Moderate)</i>	1	Related/ Patient withdrew	Patient experienced increased BP, diffuse erythema, flushing and dyspnea 6 minutes into the 1 st teprotumumab infusion, with no hypotension or hypoxemia. Patient treated with antihistamines and intravenous hydrocortisone, but no epinephrine. The event resolved within 2 hours with a normal tryptase level 3.5 hours after the start of the infusion.
65/F/W	<i>Pneumothorax (Life- threatening)</i>	113	Not related/ Study drug continued	Patient with a medical history of scoliosis, throat cancer treated with surgery and radiation therapy and sleep apnea treated with CPAP experienced a pneumothorax in the setting of community acquired pneumonia. Chest x-ray indicated possible underlying emphysema. Patient treated with antibiotics and chest tube placement and recovered.
Study 2 – Placebo Group				
56/F/W	<i>Visual field defect (Severe)</i>	64	Not related/ Study drug withdrawn	Patient experienced visual field defect which was felt to represent progression of underlying TED. Patient discontinued study for orbital decompression surgery.
OPTIC-X				
50/F/W	<i>Cerebral haemorrhage (Life- threatening)³</i>	53	Not related/ Study drug withdrawn	Patient with medical history of tobacco use completed treatment with teprotumumab in Study 2 and relapsed 5 months after final dose. On OPTIC-X Study Day 1, the patient experienced arthralgia and initiated ibuprofen (400 mg TID to BID, Study Day 2) and diclofenac (146.5 mg BID, Study Day 22). Last recorded BP (12 days prior to the event was 134/84 and platelet count was 277K). After the 3 rd infusion, the patient experienced a cerebral hemorrhage and underwent neurosurgery for the bleeding and recovered with sequelae ~3 months later.

1. Study Day is calculated relative to the day of first infusion (Day 1) in each study.

2. Study Investigator noted “not anaphylaxis” for this case, which was coded as infusion reaction.

3. Includes additional information subsequent to 120-day safety update: cerebral hemorrhage (already noted at 120-day safety update as SAE) was changed in severity from moderate to life-threatening and resulted in study discontinuation.

A = Asian; B = Black or African American; BID = twice daily; BP = blood pressure; CPAP = continuous positive airway pressure; F = female; M = male; TED = thyroid eye disease; TID = three times a day; W = white

In summary, the SAEs reported as related to teprotumumab pertained to exacerbation of IBD and infusion reactions. Other serious events are consistent with background disease or patient comorbid conditions or were deemed by the investigators as unrelated to study treatment. The SAEs resolved in six patients and were resolving at last contact for two patients. See [Sections 6.7.2 and 6.7.3](#), respectively, for additional information on infusion reactions and exacerbation of IBD.

6.6 Treatment Emergent Adverse Events Leading to Discontinuation

Five teprotumumab-treated patients and 2 placebo-treated patients discontinued study drug due to TEAEs during the Treatment Period of Study 1 and Study 2, 1 teprotumumab-treated patient discontinued due to an adverse event during the off-treatment Follow-up Period and 2 teprotumumab-treated patients discontinued due to a TEAE in OPTIC-X. Of the 8 discontinuations for teprotumumab, 5 were precipitated by SAEs (*Diarrhoea, Inflammatory bowel disease, Escherichia sepsis, Infusion related reaction and Cerebral haemorrhage*; Section 6.5, Table 17); one was for a patient who experienced *Confusional state* coincident with an SAE (*Hashimoto's encephalopathy*; Section 6.5, Table 17). The other 2 discontinuations were due to non-serious TEAEs (*Flushing, Blood pressure increased, Heart rate increased and Palpitations* in a single patient and *Muscle spasms* in a single patient); these two cases are summarized in Table 18 and Appendix 9.2.

Table 18: Non-Serious TEAEs Leading to Study Drug Discontinuation/Study Discontinuation (Double-Masked Population and OPTIC-X Population)

Study/ Treatment	Patient Age/ Sex/ Race	Preferred Term (Severity)	Study Day of Onset ¹	Study Drug Relationship	Comments/Outcome
Study 1/ Placebo	40/M/W	<i>Presyncope</i> (Moderate)	22	Unrelated	Recovered/Resolved
Study 1/ Tepro	58/F/W	<i>Flushing</i> (Mild)	43	Unrelated	Patient experienced facial flushing with elevated HR and increased BP at end of observation period for 2 nd infusion. Similar reaction experienced upon administration of premedication for 3 rd infusion. Events resolved but patient discontinued study; 3 rd infusion of teprotumumab never received.
		<i>Blood pressure increased</i> (Mild)	43	Unrelated	
		<i>Heart rate increased</i> (Mild)	43	Unrelated	
		<i>Palpitations</i> (Mild)	43	Unrelated	
OPTIC-X	66/F/W	<i>Muscle spasms</i> (Moderate)	84	Related	Ongoing at time of discontinuation

1. Study Day is calculated relative to the day of first infusion (Day 1) in each study.

BP = blood pressure; F = female; HR = heart rate; M = male; Tepro = teprotumumab; W = white

6.7 Adverse Events of Special Interest

AESI were defined for teprotumumab to provide a more comprehensive understanding of its safety profile. Hyperglycemia, infusion related events (including anaphylactic reaction), diarrhea/exacerbation of IBD, hearing impairment and muscle spasms were identified as AESI for teprotumumab. These were defined on the basis of previous clinical experience, mechanism of action and the biologic class of monoclonal antibodies. Mechanism of action and biologic plausibility was considered for all AESI; the only event of interest clearly identified as mechanistically related was hyperglycemia.

6.7.1 *Hyperglycemia*

Hyperglycemia is a known class effect of anti-IGF-1R treatments, generally reported as mild to moderate in severity, adequately controlled by oral antihyperglycemic agents and not otherwise interfering with IGF-1R antibody dosing (Haluska 2007; Chen 2013; Macaulay 2013).

High-dose corticosteroids are commonly used in the treatment of TED. The use of high-dose corticosteroids is associated with a high rate of hyperglycemia (32%) and new onset diabetes (19%) (Liu 2014; Wiersinga 2017).

Teprotumumab binds to IGF-1R and does not bind to insulin receptor. IGF-1R inhibitors are known to act systemically on homeostatic control of growth hormone at the hypothalamic-pituitary axis, causing a loss of feedback inhibition of growth hormone secretion (Gualberto 2009). Elevated growth hormone levels can stimulate liver IGF-1 production, leading to greater liver gluconeogenesis potentially resulting in hyperglycemia. Normoglycemia was observed in the majority of patients treated with teprotumumab, suggesting that increased pancreatic secretion of insulin has the potential to compensate for the increased hepatic glucose production.

During the Double-Masked Treatment Period, a higher incidence of hyperglycemia was seen in patients treated with teprotumumab (8 patients, 9.5%) compared to placebo (1 patient, 1.2%) (Table 19). Patients with pre-existing diabetes mellitus or impaired glucose tolerance were more likely to experience hyperglycemia. Among the 10 patients in the teprotumumab group with pre-existing diabetes or impaired glucose tolerance, 5 patients (50%) reported hyperglycemia compared to 3 patients (4.1%) among the 74 patients without pre-existing diabetes. In OPTIC-X, hyperglycemia was reported in 3 patients, none of whom had pre-existing diabetes or impaired glucose tolerance. Additional events of hyperglycemia occurred in 3 patients during the off-treatment Follow-up Period (one of whom also experienced hyperglycemia during the Treatment Period).

The highest blood glucose value observed in any patient was 303 mg/dL and occurred at the Week 4 visit (Day 29) in a Study 1 patient with a medical history of glucose intolerance (HbA1c at baseline was 7.2%). This patient was managed with metformin and glipizide without further complication. The highest glycosylated hemoglobin (HbA1c) value observed in any patient was 7.9% at the Week 24 visit (Day 168) in a patient without a medical history of glucose intolerance (HbA1c was 5.8% at baseline). This patient was managed with metformin and the TEAE was reported as resolved at the Week 72 visit (now off metformin).

In total, six patients received either new or additional treatment for glycemic control (metformin, glipizide, liraglutide, exenatide, linagliptin) and another patient was managed with sliding scale insulin. Treatment with teprotumumab was temporarily interrupted for one patient. Of the 12 hyperglycemia events in 11 teprotumumab-treated patients, 7 resolved during the Treatment Period, 2 resolved after the last dose (1 after 3 weeks, the other after 6.3 months) and 3 were ongoing as of the data cutoff; the ongoing events are in patients who are currently in an ongoing study (OPTIC-X or Study 2 Follow-up Period). Hyperglycemia events in all 5 patients with pre-existing diabetes mellitus or impaired glucose tolerance at baseline have resolved.

Table 19: Hyperglycemia Events

Preferred Term	Double-Masked Population		OPTIC-X
	Teprotumumab (N = 84)	Placebo (N = 86)	Teprotumumab (N = 46)
Patients with any hyperglycemia ¹ , n (%)	8 (9.5)	1 (1.2)	3 (6.5)
Hyperglycaemia	6 (7.1)	1 (1.2)	0
Blood glucose increased	2 (2.4)	0	1 (2.2)
Diabetes mellitus	0	0	1 (2.2)
Type 2 diabetes mellitus	0	0	1 (2.2)
Patients with pre-existing condition ² with any hyperglycemia ¹ , n/N (%)	5/10 (50.0)	0/9	0/3
Patients without pre-existing condition ² with any hyperglycemia ¹ , n/N (%)	3/74 (4.1)	1/77 (1.3)	3/43 (7.0)

1. From MedDRA SMQ for *Hyperglycaemia/new onset diabetes mellitus* (narrow).

2. Diabetes or impaired glucose tolerance.

SMQ = Standardized MedDRA Query

With respect to individual laboratory results, the highest fasting plasma glucose and highest HbA1c have been described earlier. In the Double-Masked Population, higher mean glucose levels were seen in patients treated with teprotumumab and more patients shifted from normal (Grade 0) to Grade 1 or 2 high glucose levels compared to placebo. The mean change from Baseline in blood glucose ranged from 3.6 to 9.2 mg/dL for the teprotumumab group compared to -2.7 to 1.4 mg/dL for the placebo group. For patients with fasting glucose levels at Baseline and during the study, more patients in the teprotumumab group (11 of 34) compared to those who received placebo (8 of 37) had shifts from normal to Grade 1 or Grade 2 elevations. At Week 24, mean HbA1c increased by 0.22% for the teprotumumab group compared to 0.04% for the placebo group.

All events of hyperglycemia for the teprotumumab-treated patients were non-serious, were mild or moderate in severity and did not lead to discontinuation of study drug. There were no hospitalizations for hyperglycemia, and no hyperglycemic complication such as diabetic ketoacidosis or hyperosmolar hyperglycemic state was reported. Patients were managed with diet and/or antihyperglycemic medication. These data are reassuring, given the high expected rates of hyperglycemia and new onset diabetes associated with high dose corticosteroids often used off-label in the treatment of TED (Liu 2014; Wiersinga 2017).

6.7.2 Infusion Reactions

Infusion reactions are expected across the class of therapeutic monoclonal antibodies. In general, reactions may range from mild hypersensitivity to potential anaphylaxis and therefore monitoring is required.

In the Double-Masked Population, potential infusion reactions occurring within 2 hours of infusion were observed more frequently for teprotumumab compared to placebo (Table 20).

Table 20: Infusion Reactions

	Double-Masked Population		OPTIC-X
	Teprotumumab (N = 84)	Placebo (N = 86)	Teprotumumab (N = 46)
Patients with any potential infusion reaction ¹ , n (%)			
All AEs on day of infusion ≤ 2 hours of infusion	6 (7.1)	4 (4.7)	3 (6.5)
All AEs on day of infusion with unknown onset time	3 (3.6)	8 (9.3)	1 (2.2)
Reported as anaphylaxis	0	0	0
Adjudicated as infusion reactions, n (%)	3 (3.6)	0	0

1. From automated search of all treatment-emergent adverse events occurring within 2 hours (or on day, if time was missing) of study drug infusion. Events that were adjudicated as non-infusion reactions were *Muscle spasms, Abdominal cramping, Nausea, Abnormal feces, Dysguesia, Urine odor abnormal* and *Feeling hot*.

After adjudication by the Sponsor (process described in [Appendix 9.3](#)), infusion reactions were confirmed for three patients, all of whom received teprotumumab:

- A 38-year-old male patient experienced an *Infusion related reaction* (previously described in [Section 6.5](#)) which began approximately 6 minutes after initiation of the first teprotumumab infusion. The event was described as an increase in blood pressure (BP) and tachycardia (191/113 mmHg and heart rate [HR]: 104 bpm) (pre-infusion BP: 140/90 with HR of 75 bpm), diffuse erythema with facial flushing, increased glandular secretion, a feeling of obstruction at the epiglottis, dyspnea, headache and muscular pain in the lumbar region and calf muscles. The infusion was stopped, and the event was treated with intravenous steroids and antihistamines. It was reported that the patient did not experience fever or hypotension. Oxygen saturation was 96%. The event was noted as resolved approximately 2 hours after onset. Approximately 3.5 hours post-dose, serum tryptase level was 5.3 µg/L (normal range: <13.5 µg/L). The event was reported as an SAE, and the patient withdrew from the study drug.
- A 58-year-old female experienced mild *Feeling hot*, mild *Rash*, moderate *Hypertension* and moderate *Tachycardia* at the end of the 90-minute observation period after her second infusion of teprotumumab. She was treated with intravenous diphenhydramine hydrochloride and oral paracetamol and the 4 events resolved the same day. She was discontinued from study drug after experiencing a similar reaction following premedication for her third teprotumumab infusion (not administered) (previously described in [Section 6.6](#)).
- A 37-year-old female patient experienced *Hypertension* of moderate severity on Study Day 85 following her fifth dose of study drug. The patient had a history of hypertension, but was not taking antihypertensive medication at Baseline. Prior to dosing on Study Day 85, the patient's BP was 136/97 mmHg. Approximately 30 minutes after completion of the study drug infusion, the patient experienced an increase in BP that continued to rise

for approximately 1.5 hours, ranging from 160 to 186 mmHg for systolic measurements and from 98 to 112 mmHg for diastolic measurements. The patient was treated with intravenous steroids and antihistamines and the event of *Hypertension* resolved the same day. The patient was started on antihypertensive medication 10 days after the suspected infusion reaction, continued in the study and was premedicated prior to subsequent infusions, which were administered at a slower rate (90 minutes). No recurrence of the event was observed with subsequent infusions of study drug, and the patient completed the Treatment Period.

In summary, infusion reactions were reported with teprotumumab and were managed with antihistamines and/or corticosteroids; premedication and slowing the infusion rate may mitigate the risk of recurrence and enable continued dosing.

6.7.3 Diarrhea/Inflammatory Bowel Disease Exacerbation

In Study 1, SAEs of *Diarrhoea* (n=1) and *Inflammatory bowel disease* (n=1) were reported for 2 patients treated with teprotumumab, both of whom had underlying IBD or signs and symptoms consistent with IBD (previously described in [Section 6.5](#)). In the same study, the only other patient with IBD enrolled in the study was a placebo patient with IBD (Crohn's disease) who did not experience a diarrhea event or exacerbation of IBD. As a result, patients with a history of IBD were excluded from Study 2 and diarrhea was selected as an event of interest to monitor for new onset cases of IBD.

In the Double-Masked Population, diarrhea was reported for 12 (14.3%) patients who received teprotumumab and 7 (8.1%) patients who received placebo; IBD exacerbation was reported for a single patient in the teprotumumab group ([Table 21](#)). All but one of the diarrhea events were non-serious, were mild or moderate in severity and did not require discontinuation of study drug. As described in [Section 6.5](#), the severe SAE of *Diarrhoea* (as a consequence of underlying ulcerative colitis) occurred in a 72-year-old female who had a history of "colitis with several episodes of abdominal cramping with bloody diarrhea in the 7 months preceding randomization" and resulted in discontinuation of study drug; the severe SAE of *Inflammatory bowel disease* occurred in a 43-year-old female who had a history of loose stools and aphthous ulcers noted on colonoscopy and resulted in discontinuation of study drug. Both SAEs were considered exacerbation of IBD and not new-onset IBD because of the patients' underlying condition.

In OPTIC-X, 5 (10.9%) patients have reported a total of 6 diarrhea events and no patients have reported new-onset IBD or IBD exacerbation. All events have been mild in severity and 2 were ongoing as of the data cutoff (study is currently ongoing).

Table 21: Diarrhea/IBD Exacerbation

	Double-Masked Population		OPTIC-X
	Teprotumumab (N = 84)	Placebo (N = 86)	Teprotumumab (N = 46)
Patients with any diarrhea ¹ , n (%)	12 (14.3)	7 (8.1)	5 (10.9)
Patients with any IBD exacerbation ¹ , n (%)	1 (1.2)	0	0

1. From SMQ *Noninfectious diarrhoea* (broad) or HLT *Colitis (excl infective)*, respectively
HLT = MedDRA high-level term; IBD = inflammatory bowel disease; SMQ = standardized MedDRA query

Importantly, no events suggestive of new-onset IBD have been observed in the TED clinical program.

6.7.4 Hearing Impairment

In the Double-Masked Population, 8 (9.5%) patients in the teprotumumab group experienced an event of hearing impairment compared to no patients in the placebo group; 1 of the 8 patients also experienced an event of hearing impairment during the Follow-up Period, 4 months after the last dose. In the OPTIC-X Population, 5 (10.9%) patients experienced 6 events of hearing impairment. Thus, a total of 13 patients have experienced 15 events of hearing impairment in the TED clinical program. Although audiology testing was not performed at Baseline in the clinical studies, testing was performed in all patients reporting moderate hearing impairment events (n=3) and 7 patients overall, with results summarized in [Table 22](#) below.

Table 22: Hearing Impairment Events

Patient Age/ Sex	Preferred Term (Severity)	Study Day of Onset ¹	Study Day of Resolution	Comments/Audiology Test Results
Study 1 – Teprotumumab Group				
59/F	<i>Hyperacusis</i> (Mild)	84 (1 day before 5 th infusion)	251 (~3.5 months after 8 th infusion)	Patient reported during Day 112 exam that her voice echoed when she spoke and that she has occasional bilateral tinnitus with brief episodes of dizziness; denied noise exposure. Audiology: Day 112 – Right ear with mild hearing loss at 6 kHz, left ear with mild conductive to mixed hearing loss at 4-8 kHz, excellent word recognition bilaterally, normal tympanograms; Day 203 – stable from prior evaluation.
43/F	<i>Eustachian tube dysfunction</i> (Moderate)	47	68	Medical history of chronic sinusitis. Treated with prednisone 20 mg BID Days 62-66. Audiology: Day 274 – Speech recognition scores 100% bilaterally, left ear with moderate mixed hearing loss with possible recruitment, right ear normal, normal tympanograms; Day 497 – overall improvement compared to Day 274 evaluation.
	<i>Deafness unilateral</i> (Moderate)	264 (~4 months after 8 th infusion)	Improved at last follow-up	
60/M	<i>Deafness</i> (Mild)	Approximately at the time of the 8 th infusion	Ongoing at last follow-up	Medical history of intermittent tinnitus after exposure to loud noise (prior to study). Audiology: Day 222 – Word recognition 96% on right and 92% on left. Patient suffering from tinnitus with handicapping moderate high frequency sensorineural bilateral hearing loss. Hearing aid evaluation was recommended.
Study 2 – Teprotumumab Group				
32/F	<i>Hypoacusis</i> (Mild)	75 (9 days after 4 th infusion)	76	None
66/M	<i>Hypoacusis</i> (Moderate)	108 (2 days after 6 th infusion)	283	Audiology: Day 167 – Tympanometry was peaked and hearing threshold between 35 and 55 dB pantonal on right and 35 to 70 dB pantonal on left. Moderate hearing impairment right side, mild hearing impairment left side.
79/F	<i>Deafness</i> (Moderate)	134 (1 week after 7 th infusion)	337	Audiology: Day 166 – peaked tympanograms in the normal pressure range and bilateral symmetrical pantonal hearing loss; Day 253 – improvement compared to previous exam, “Patient is satisfied with her hearing so far, doesn't notice any limitations in daily life.”

Patient Age/ Sex	Preferred Term (Severity)	Study Day of Onset ¹	Study Day of Resolution	Comments/Audiology Test Results
60/F	<i>Autophony</i> ² (Mild)	84 (1 day before 5 th infusion)	Recovered ~4 months after 8 th infusion	Events of <i>Ear discomfort</i> on Day 29 (23-Jul-2018) through Aug-2018, <i>Dizziness</i> on Day 29 through Day 51 and <i>Oropharyngeal pain</i> on Day 81 through Day 87. History of allergic rhinitis and concomitant <i>Oropharyngeal pain</i> treated with antihistamine.
39/F	<i>Eustachian tube patulous</i> (Mild)	153 (1 day after 8 th infusion)	304	Events of <i>Rhinorrhoea</i> (Day 151 through Day 152) and <i>Periodontitis</i> (Day 154; ongoing at last follow-up).
OPTIC-X				
66/F	<i>Tinnitus</i> (Mild)	1	20	Audiology: Day 183 – normal hearing sensitivity with the exception of mild sensorineural hearing loss at 500 Hz bilaterally. Tympanometry demonstrated normal middle ear pressure and normal static compliance bilaterally.
	<i>Tinnitus</i> (Mild)	84 (4 days after 5 th infusion)	Ongoing in OPTIC-X	
58/F	<i>Hypoacusis</i> (Mild)	127 (day of 7 th infusion)	Ongoing in OPTIC-X	Event of <i>Sinusitis bacterial</i> (Day 128; ongoing at last follow-up). <i>Hypoacusis</i> has been noted as “markedly improved” per Investigator. ³
74/F	<i>Hypoacusis</i> (Mild)	66 (2 days after 4 th infusion)	Resolved after ~4.5 months ³	None
57/F	<i>Hypoacusis</i> (Mild)	155 (7 days after 8 th infusion)	Ongoing in OPTIC-X	Event of <i>Ear discomfort</i> (Day 130; ongoing at last follow-up). Evaluation with ear, nose and throat physician identified mild-moderate bilateral sensorineural hearing loss. ³
51/F	<i>Tinnitus</i> (Mild)	~69 (after 4 th or 5 th infusion; start date incomplete)	Ongoing in OPTIC-X	Audiology ³ : Borderline hearing at 2 kHz right ear but all other thresholds in both ears deemed normal. “This patient did not show any cochlear damage” and “Her tinnitus is considered mild” per audiologist. <i>Tinnitus</i> has been noted as “resolving” per Investigator. ³

1. Study Day is calculated relative to the day of first infusion (Day 1) in each study.

2.. Event had been noted as tinnitus at time of the 120-day safety update and was subsequently updated by the investigator.

3 Updated after the 120-day safety update.

BID = twice daily

Seven patients have recovered from their event of hearing impairment and 6 others have ongoing events. Among the 6 patients with ongoing events, 2 patients had events that were ongoing at the time Study 1 ended, 1 of whom was noted as improved based on audiology testing. The remaining 4 patients are all enrolled in the ongoing OPTIC-X study, and 2 were noted as improving.

Review of baseline characteristics identified age and female gender as the only potential predisposing factors. Overall, the events were reported as non-serious and mild or moderate in severity. Patients continued in the study without worsening of the event or discontinuation of treatment.

6.7.5 *Muscle Spasm*

Muscle spasms was the most frequently reported TEAE for teprotumumab, occurring at a higher incidence for teprotumumab compared to placebo (25.0% vs 7.0%) in the Double-Masked Population and at a rate of 41.3% in the OPTIC-X Population.

Body areas affected by *Muscle spasms* included the lower limbs primarily, and to a lesser extent, upper limbs and the trunk. No events involved the maxillofacial area. No clinically relevant laboratory abnormalities were observed, although magnesium was not measured.

All events of *Muscle spasms* were non-serious and the majority were mild in severity. Moderate *Muscle spasms* was reported for 6 teprotumumab-treated patients, 5 in the Double-Masked Population and 1 in the OPTIC-X population. Thirteen patients were treated with general comfort measures, magnesium, calcium and vitamin B supplements and two patients were treated with muscle relaxants (cyclobenzaprine, metaxolone). One patient in OPTIC-X discontinued study treatment due to a moderate event of *Muscle spasms*. The patient had received placebo in Study 2 and reported an ongoing event of *Muscle spasms* that worsened after enrollment in OPTIC-X; this patient's creatinine phosphokinase value was within normal limits. No other patient in the TED clinical program discontinued study drug because of *Muscle spasms*.

Among the 39 teprotumumab-treated patients who experienced *Muscle spasms*, 21 had at least 1 event of *Muscle spasms* that was ongoing, including mild events in 20 patients and a moderate event in 1 patient. Resolution of *Muscle spasms* for 5 patients occurred during the Treatment Period and 13 other patients reported resolution of *Muscle spasms* by 0.2 to 6.3 months following their last teprotumumab infusion.

6.8 Anti-Drug Antibodies

Throughout the teprotumumab clinical program in TED, all patients were monitored for the presence of ADAs. Low titer ADAs were detected in 2 (2%) teprotumumab-treated patients, at Week 3 for 1 patient and at Baseline and at 51 weeks after the last teprotumumab infusion for the other patient. No correlation of ADA development to clinical response, adverse reactions or systemic exposures was observed.

7 BENEFIT-RISK CONCLUSIONS

No pharmacotherapies are FDA-approved for the treatment of TED. The most commonly used treatment for active TED is corticosteroids, which can impact inflammatory signs but does not impact the important sequelae of proptosis or diplopia and which is associated with significant dose- and duration-dependent adverse events, including marked hyperglycemia. The most common non-pharmacologic treatment is orbital radiation, which is also ineffective for proptosis.

Currently, after the active stage of TED has passed, surgery is used to attempt to repair residual structural damage (e.g., proptosis, strabismus). A therapeutic that reverses the tissue expansion and remodeling characteristics of the disease might be able to decrease the amount of residual damage and associated proptosis and diplopia.

Thus, there is a significant unmet medical need for a safe and effective therapy for the treatment of TED.

Benefits

In two prospective, randomized, placebo-controlled, multicenter studies, teprotumumab resulted in statistically significant and clinically meaningful improvements in measures that assessed multiple facets of the disease (proptosis, inflammation as measured by CAS, diplopia and quality of life).

In addition, the persistence of effect was demonstrated after approximately one year off treatment. Consistent and reproducible results were shown across all efficacy endpoints and all subpopulations.

Overall benefits of teprotumumab therapy in TED include:

- Significant and clinically meaningful improvement in proptosis, disease activity and diplopia;
- Level of proptosis reduction approached levels obtained with decompression surgery;
- Onset of therapeutic effect evident at the first post-Baseline efficacy assessment (~6 weeks after first infusion), with continued improvement throughout treatment;
- Significant and clinically meaningful improvement in the disease-specific quality of life scale (GO-QoL overall and subscale scores of visual functioning and appearance);
- Treatment benefit in tobacco users and non-users, across subgroups (geographic region, age and sex) and in both the study eye and non-study eye;
- Treatment benefit persisting after approximately one year off treatment in the majority of patients; and

- Significant improvement observed in multiple measures of disease including proptosis and diplopia which have historically not responded to glucocorticoids, the currently recommended first-line therapy.

The totality of the evidence shows that teprotumumab offers clinically meaningful improvement across many facets of this devastating disease for which there is presently no approved treatment. These attributes have the potential to shift the current paradigm of how TED is managed, making teprotumumab a promising new treatment option in the management of TED.

Risks

In the randomized, placebo-controlled studies, 84 patients with TED were exposed to at least one dose of teprotumumab. More than 89% of patients were able to complete the full course of 8 infusions.

Among the 84 patients exposed to teprotumumab in Study 1 and Study 2, 7 (8.3%) experienced SAEs and 5 (6.0%) discontinued study drug due to a TEAE. These events pertained to exacerbation of IBD and infusion related reactions or were either consistent with background disease or considered by the Investigator to be unrelated to study drug. No deaths occurred in the teprotumumab clinical program for TED.

The most commonly reported TEAEs which occurred more frequently among patients treated with teprotumumab than placebo in the Double-Masked Population were *Muscle spasms, Nausea, Alopecia, Diarrhoea, Fatigue, Hyperglycaemia, Dysgeusia, Dry skin* and *Headache*. Most of these reported events were non-serious, were mild or moderate in intensity and did not result in discontinuation of study drug. The safety profile observed in OPTIC-X was generally consistent with that observed in the Double-Masked Population.

AESI defined for teprotumumab in the TED population include:

- **Hyperglycemia:** A higher incidence of hyperglycemia was observed in patients treated with teprotumumab compared to placebo. These events were non-serious, were mild or moderate in severity and were managed as needed with medications used for glycemic control. No patients discontinued treatment for a hyperglycemic event and most hyperglycemic events resolved. Patients with pre-existing diabetes mellitus were more likely to experience hyperglycemia.
- **Infusion reactions:** Infusion reactions were observed in three teprotumumab-treated patients; these events were managed with symptomatic treatment and all resolved the same day without complication. Premedication and slowing of the infusion rate appear to mitigate the risk. No events were reported as anaphylaxis during treatment with teprotumumab.
- **Exacerbation of IBD:** Two cases of exacerbation of pre-existing IBD (*Diarrhoea* and *Inflammatory bowel disease*) reported in Study 1 led to study drug discontinuation. No events suggestive of new-onset IBD have been observed in Study 2 or OPTIC-X up to the data cutoff.

- Hearing impairment: A total of 13 patients have experienced events of hearing impairment in clinical studies in TED. Treatment-emergent events related to hearing impairment were reported as non-serious, mild or moderate in intensity and did not result in discontinuation of study drug. The majority of cases have fully resolved or are noted as improved/improving.
- Muscle spasms: Muscle spasms were the most commonly reported adverse event. Body areas affected primarily involved the lower limbs, and to a lesser extent, upper limbs and the trunk. No events involved the maxillofacial area. The events were non-serious with no associated laboratory abnormalities, and the majority were mild in intensity. With the exception of a single patient in OPTIC-X, no muscle spasm event led to discontinuation of study drug.

Based on findings in animals and its mechanism of action, teprotumumab may cause fetal harm when administered to women who are pregnant.

Adverse events were transient, manageable and resolved while continuing teprotumumab in the majority of cases; other events were able to be managed clinically to prevent significant adverse outcomes.

The totality of the evidence shows that teprotumumab offers patients and healthcare professionals the first effective and generally well-tolerated treatment for TED, a devastating disease for which no FDA-approved therapies exist.

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9 APPENDICES

9.1 Inclusion/Exclusion Criteria in Study 1 and Study 2

Study 1

Inclusion Criteria

1. Aged 18-75 years (inclusive).
2. Clinical diagnosis of Graves' disease associated with active TED with a clinical activity score (CAS) ≥ 4 (on the 7-point version of the scale) for the most severely affected eye (Study Eye).
3. Fewer than 9 months from onset of TED as determined by patient records.
4. No previous medical or surgical therapy for TED, excluding local supportive measures and oral steroids if the maximum cumulative dose was < 1000 mg methylprednisolone or equivalent. There were at least 6 weeks between last administration of steroids and study randomization.
5. Patients were euthyroid or with mild hypo- or hyperthyroidism defined as free thyroxine (FT4) and free triiodothyronine (FT3) levels $< 50\%$ above or below the normal limits. Every effort was made to correct the mild hypo- or hyperthyroidism promptly.
6. Did not require immediate surgical ophthalmological intervention.
7. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) $\leq 3 \times$ the upper limit of normal (ULN) for the reference laboratory; serum creatinine $< 1.5 \times$ ULN according to age.
8. Patients with diabetes were well controlled, demonstrated by no change in diabetes medication (oral or insulin) $> 10\%$ for the previous 60 days.
9. Women of childbearing potential, including those with an onset of menopause within the previous 2 years (women without at least 12 months of nontherapy-induced amenorrhea or not surgically sterile [absence of ovaries and/or uterus]), required a negative pregnancy test at screening and all treatment visits up to follow-up Visit 2 (Week 36) post randomization. They were also willing and able to use two different methods of contraceptive, one of which had to be oral. Male patients had to be surgically sterile or agreed to use a barrier contraceptive method. Contraception had to be continued for 3 months after the last dose of study drug.

Exclusion Criteria

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision within the last 6 months of 2 lines of Snellen chart, new visual field defect or color defect secondary to optic nerve involvement.
2. Corneal decompensation unresponsive to medical management.
3. Improvement in CAS of ≥ 2 points between screening and baseline.

4. Treatment with oral or intravenous steroids within the previous 3 months, except oral steroids for the treatment of TED with a cumulative dose of <1000 mg methylprednisolone or equivalent, provided there was a 6-week washout prior to study randomization. Administration of any other immunosuppressive agent for any indication in the previous 3 months. Topical steroids for dermatological conditions were not excluded.
5. Any treatment with any investigational agent for any condition in the past 60 days or treatment with an investigational agent for any condition during the study.
6. Any previous treatment with rituximab (Rituxan[®] or MabThera[®]).
7. Previous orbital irradiation.
8. Identified pre-existing ophthalmic disease that in the judgment of the Investigator would preclude study participation or complicate interpretation of study results.
9. Platelet count <100 × 10⁹/L at screening or baseline. Patients with platelet count <35 × 10⁹/L following dosing were to be withdrawn.
10. Bleeding diathesis.
11. Hemoglobin concentration >2 g/dL below the lower limit of the local laboratory reference range.
12. Malignant condition in the past 12 months (with the exception of successfully treated basal cell carcinoma of the skin).
13. Pregnant or lactating women.
14. Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the patient.
15. Poorly controlled diabetes.
16. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies.
17. Any other condition that in the opinion of the Investigator would preclude inclusion in the study.
18. Patients who had already been randomized and received treatment under this protocol. Under no circumstances were patients who were enrolled in this study permitted to be re-randomized and enrolled for a second course of treatment.

Study 2

Inclusion Criteria

1. Written informed consent.

2. Male or female patient between the ages of 18 and 80 years, inclusive, at Screening.
3. Clinical diagnosis of Graves' disease associated with active TED with a CAS ≥ 4 (on the 7-item scale) for the most severely affected eye at Screening and Baseline.
4. Moderate-to-severe active TED (not sight-threatening but had an appreciable impact on daily life), usually associated with 1 or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and sex and/or inconstant or constant diplopia.
5. Onset of active TED symptoms (as determined by patient records) within 9 months prior to Baseline.
6. Patients must have been euthyroid with the Baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels $< 50\%$ above or below the normal limits) at Screening. Every effort was made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.
7. Did not require immediate surgical ophthalmological intervention and was not planning corrective surgery/irradiation during the course of the study.
8. Alanine aminotransferase or aspartate aminotransferase ≤ 3 times the upper limit of normal (ULN) or serum creatinine < 1.5 times the ULN according to age at Screening.
9. Diabetic patients must have had well-controlled stable disease (defined as HbA1c $< 9.0\%$ with no new diabetic medication [oral or insulin] or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening).
10. Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have had a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified time points (i.e., prior to each dose and through Week 48 of the Follow-up Period); patients who were sexually active with a non-vasectomized male partner must have agreed to use 2 reliable forms of contraception during the trial, one of which was recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must have started at least 1 full cycle prior to Baseline and continued for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate $< 1\%$ per year), when used consistently and correctly, included implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner.
11. Male patients must have been surgically sterile or, if sexually active with a female partner of childbearing potential, must have agreed to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug.

12. Patient was willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

Exclusion Criteria

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect secondary to optic nerve involvement within the last 6 months.
2. Corneal decompensation unresponsive to medical management.
3. Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline.
4. Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline.
5. Previous orbital irradiation or surgery for TED.
6. Any steroid use (intravenous or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (intravenous or oral) with a cumulative dose of < 1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops was allowed if discontinued at least 4 weeks prior to Screening.
7. Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids were allowed).
8. Selenium and biotin must have been discontinued 3 weeks prior to Screening and must not have been restarted during the clinical trial; however, taking a multivitamin that included selenium and/or biotin was allowed.
9. Any previous treatment with rituximab (Rituxan[®] or MabThera[®]) or tocilizumab (Actemra[®] or Roactemra[®]). Use of any other non-steroid immunosuppressive agent within 3 months prior to Screening.
10. Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial.
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would have precluded study participation or complicated interpretation of study results.
12. Bleeding diathesis that, in the judgment of the Investigator, would have precluded inclusion in the clinical trial.
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin).
14. Pregnant or lactating women.
15. Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the patient.

16. Biopsy-proven or clinically suspected inflammatory bowel disease (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).
17. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies.
18. Any other condition that, in the opinion of the Investigator, would have precluded inclusion in the study.
19. Previous enrollment in this study or participation in a prior teprotumumab clinical trial.
20. Human immunodeficiency virus, hepatitis C or hepatitis B infections.

9.2 Brief Summaries of Non-Serious TEAEs Leading to Discontinuation

See [Table 17](#) for summaries of teprotumumab patients who discontinued following SAEs (*Diarrhoea, Escherichia sepsis, Inflammatory bowel disease, Infusion related reaction, Hashimoto's encephalopathy and Cerebral haemorrhage*).

Two teprotumumab-treated patients discontinued due to non-serious TEAEs:

- A 58-year-old white female experienced mild TEAEs of *Flushing, Blood pressure increased, Heart rate increased and Palpitations* following the administration of premedications prior to her third infusion of teprotumumab. The patient was administered premedications (diphenhydramine hydrochloride, dexamethasone and famotidine) to prevent an infusion related reaction, as she had previously reported face feeling hot, facial rash, hypertension and tachycardia at the end of the observation period following her second infusion. The patient did not receive her third infusion and the study drug was discontinued. The events resolved the same day.
- A 66-year-old white female who had received placebo during the Double-Masked Treatment Period of Study 2 had an event of mild *Muscle spasms* that was ongoing at the time of enrollment in OPTIC-X; the severity of the event increased to moderate 84 days after starting treatment with teprotumumab and resulted in discontinuation from study drug. The event was ongoing at the time of the data cutoff.

9.3 Adjudication Process Used to Identify Non-Anaphylactic Infusion Reaction

The adjudication process was performed before unmasking of study drug and used to identify non-anaphylactic infusion reaction as follows:

1. Search for any adverse event occurring within 2 hours of start of study drug administration or on the day of infusion if adverse event start time is unknown.
2. Adverse events were narrowed down by applying SMQs for *Angioedema, Hypersensitivity, Hypertension* and high-level terms for *Rash*.

The case definition for non-anaphylactic infusion reaction was then applied against this list of adverse events: elevated blood pressure with fever, diffuse erythema/rashes/flushing, chest tightness, myalgia, back pain or dizziness in the absence of anaphylaxis.

3. This process occurred periodically and adjudication was performed by two physicians (a third physician was available to break ties).