Teprotumumab for Treatment of Thyroid Eye Disease

December 13, 2019

Horizon Therapeutics

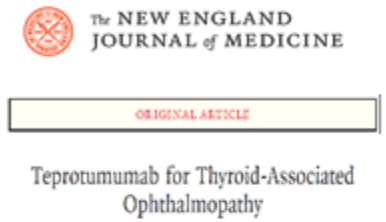
Dermatologic and Ophthalmic Drugs Advisory Committee

Introduction

Timothy P. Walbert
Chairman, President and Chief Executive Officer
Horizon Therapeutics

More Than 7,000 Known Rare Diseases: Only 5% with Treatments

Teprotumumab History in Thyroid Eye Disease



IND submission	Orphan drug designation granted	Fast Track designation granted	Breakthrough designation granted	Horizon acquired teprotumumab	BLA submitted
2011	2013	2015	2016	2017	2019
	First patient enrolled in Study 1	Last patient completed Week 24 in Study 1	Study 2 design discussed (EOP2)	First patient enrolled in Study 2	Last patient completed Week 24 in Study 2

Teprotumumab Clinical Program Overview

- Positive benefit / risk profile across 2 trials
- Provided clinically meaningful improvements across multiple facets of Thyroid Eye Disease

Agenda

Unmet Medical Need	**Raymond S. Douglas, M.D., Ph.D.** Director of Orbital and Thyroid Eye Disease Program Cedars-Sinai Medical Center
Teprotumumab Mechanism and Program Overview	**Shao-Lee Lin, M.D., Ph.D.** Executive Vice President, Head of Research and Development, Chief Scientific Officer, Horizon Therapeutics
Efficacy and Safety	**Elizabeth H.Z. Thompson, Ph.D.** Vice President, Clinical Development, Rare Disease Horizon Therapeutics
Clinical Perspective	**Raymond S. Douglas, M.D., Ph.D.** Director of Orbital and Thyroid Eye Disease Program Cedars-Sinai Medical Center

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Thyroid Eye Disease
Unmet Medical Need

Raymond S. Douglas, M.D., Ph.D.
Director of Orbital and Thyroid Eye Disease Program
Cedars-Sinai Medical Center

Thyroid Eye Disease – Commonly Associated with Graves' Disease but Distinct

- Treatment of Graves' Disease does not treat Thyroid Eye Disease
  - Radioactive iodine treatment of Graves' Disease can induce or exacerbate Thyroid Eye Disease[1]
- Also occurs in patients with euthyroidism or hypothyroidism[2]

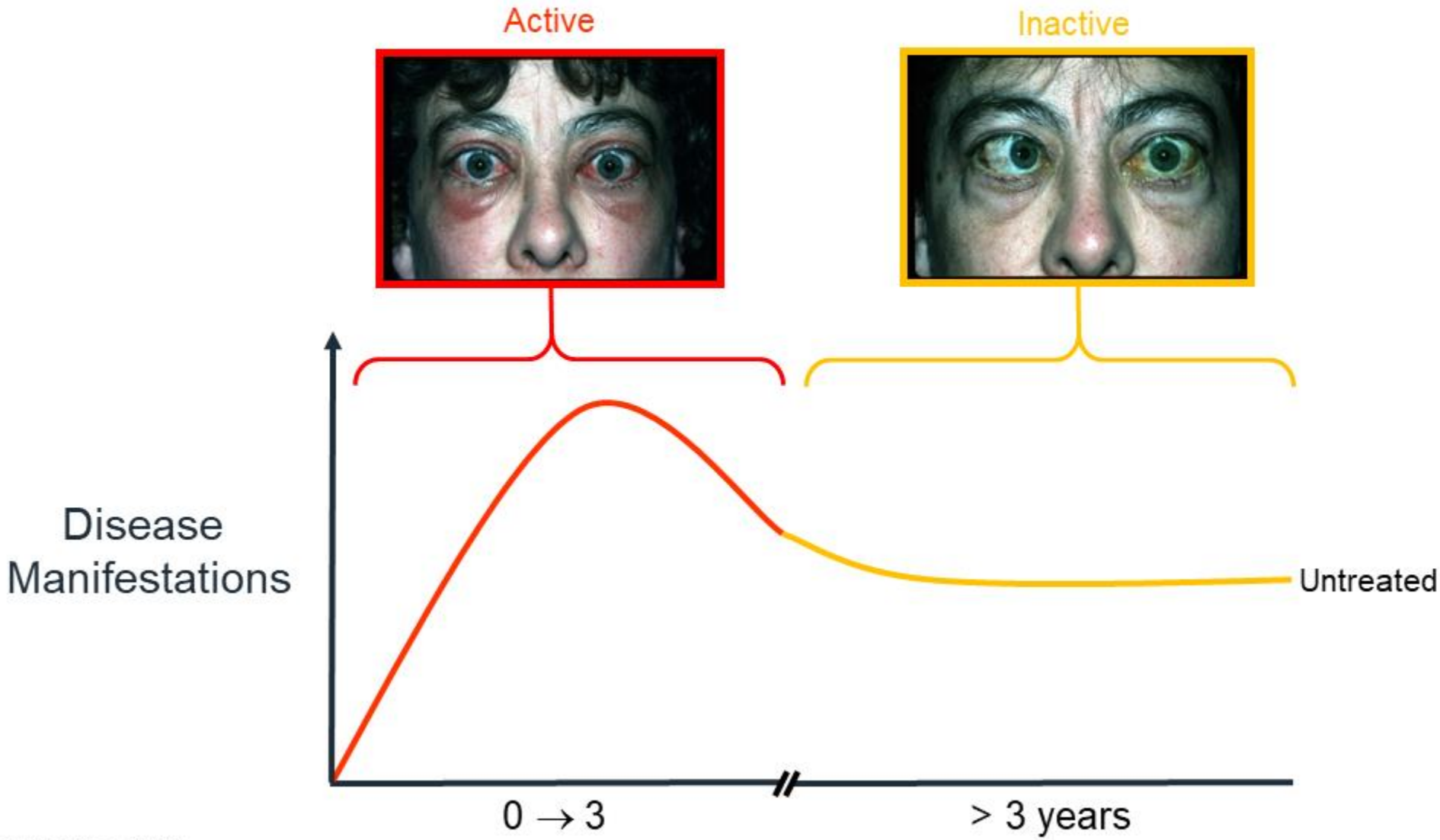
1. Ponto, 2010; 2. Ponto, 2015

Thyroid Eye Disease – Progressive, Vision Threatening, Autoimmune Disease

- Potential for visual impairment
- Impairment can become permanent due to fibrosis over time
- Impacts more women than men[1]
- Generally two peaks of incidence with Thyroid Eye Disease[1]
- Limited published epidemiologic data
- No known significant ethnic predisposition
- Smoking worsens severity[1]

1. Wiersinga, 2002

Natural History of Thyroid Eye Disease



Smith and Douglas, 2011

Signs and Symptoms of Thyroid Eye Disease

Periorbital edema

Proptosis (bulging eye)

Upper and lower eyelid retraction

Strabismus (eye misalignment)

1

1. Reprinted from *Eye (Lond)*, vol. 27, Verity DH, Rose GE. Acute Thyroid Eye Disease (TED): principles of medical and surgical management. pp. 308-319. 2013. Reproduced with permission from copyright holder.

Proptosis – Most Disfiguring Sign of Thyroid Eye Disease

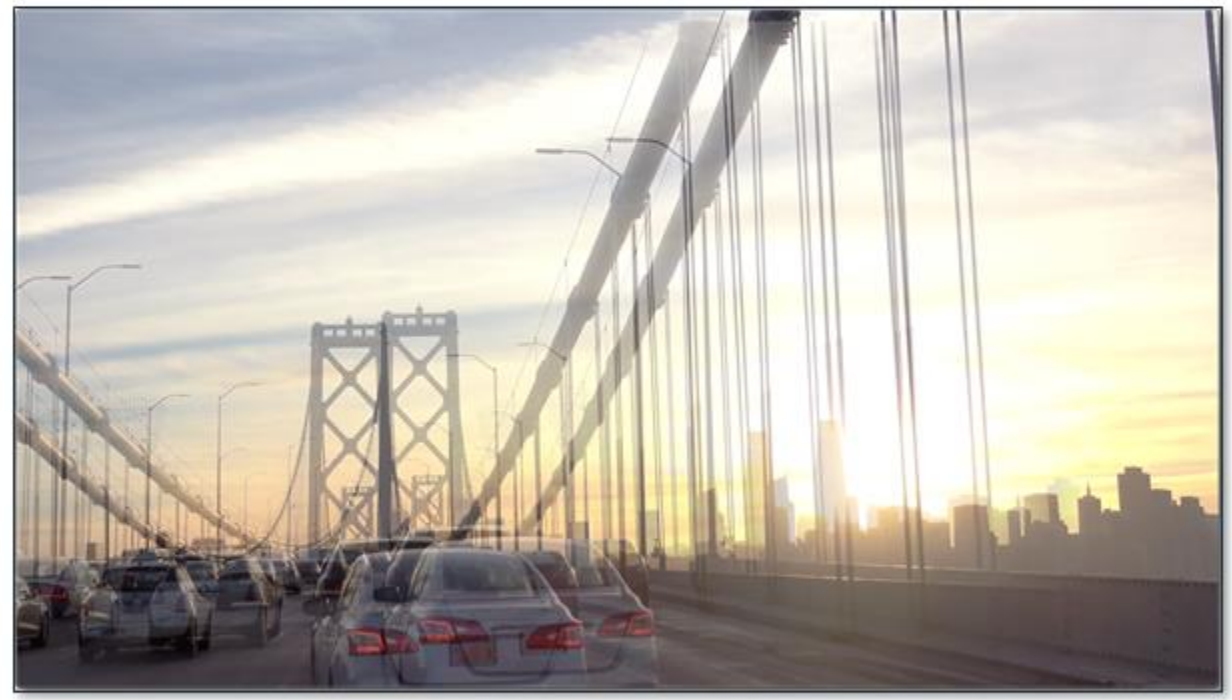
- Bulging eye
- Results from inflammation and expansion of soft tissue and muscle tissue posterior to eye[1]
- Excessive proptosis impairs patient's ability to blink or close eyes[2]
  - Pain, corneal ulceration and inability to sleep
- Profound changes in facial appearance

3

1. Barrio-Barrio, 2015; 2. Rose et al, 2017; 3. Reprinted from Emergencies of the Orbit and Adnexa Rose GE, Verity DH. Management of fulminant Thyroid Eye Disease. pp. 171-178, 2017 Springer India. Reproduced with permission from copyright holder.

Diplopia (Double Vision) – Common Symptom That Impairs Daily Living

- See more than one image of single object
  - Result of misalignment of eyes
- Associated with headaches and nausea
- Difficulty working, driving and conducting daily activities



Clinical Manifestations of Thyroid Eye Disease Negatively Impact Quality of Life

- Impaired functional vision and activities of daily living
  - Difficulties driving, reading, moving around the house
- Facial disfigurement leading to social isolation

Terwee, 1998

Current "Standard" of Care in Thyroid Eye Disease

- Glucocorticoids at high intravenous pulse dosages not effective at reducing proptosis[1]

Drug Treatment Methylprednisolone IV	Response[1] Low Dose (2.25g) n=53	High Dose (7.47g) n=52	p-value
Proptosis mean baseline (mm)	23.3	22.5	
Proptosis Δ 12 weeks (mm)	−0.8	−0.6	NS
CAS median baseline	4	5	
CAS Δ 12 weeks	−1.8	−2.7	0.01

  - Hyperglycemia (32%), new onset diabetes (19%) associated with high-dose corticosteroids[2]
  - Liver toxicity[3] and in rare cases sudden death
  - 20-40% of patients who have improvements in inflammatory signs and symptoms relapse within 12 weeks[2]
- Watch and wait for stabilization of disease prior to surgery

CAS: Clinical Activity Score

1. Bartalena, 2012; 2. Liu, 2014; Wiersinga, 2017; 3. National Library of Medicine, 2014; Bartalena, 2016

Other Approaches Used in Thyroid Eye Disease

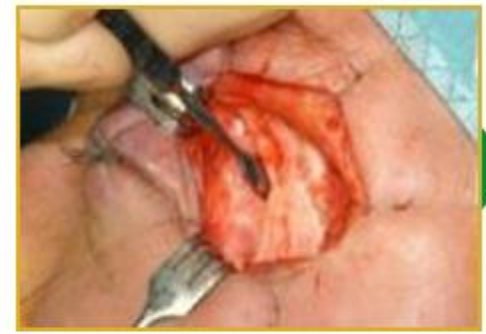
- Other exploratory, off-label treatments not effective at reducing proptosis
  - Mycophenolate mofetil, cyclosporine, tocilizumab, azathioprine and rituximab[1]
- Present treatments may impact inflammatory signs but not proptosis or diplopia and have substantial side effects
- Orbital radiation commonly used non-pharmacological method

1. Kotwal, 2018; Xu, 2018

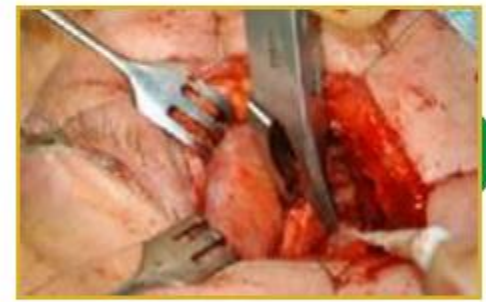
Currently Surgery Only Option for Inactive Thyroid Eye Disease

- Typically wait until inflammation has abated
- Often requires multiple surgeries per eye
  - Orbital decompression, strabismus surgery, eyelid surgery
- Can result in permanent eye misalignment, diplopia (double vision), sight impairment
  - Sinusitis, orbital hemorrhage, cerebral spinal fluid leak and meningitis

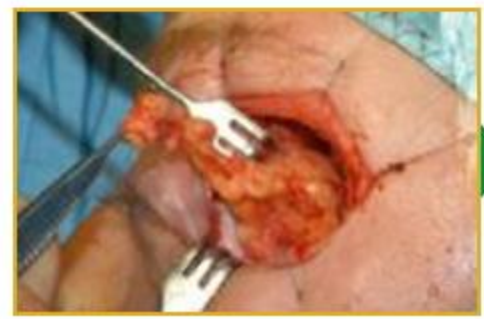
1



Exposing Orbit



Removing Bone

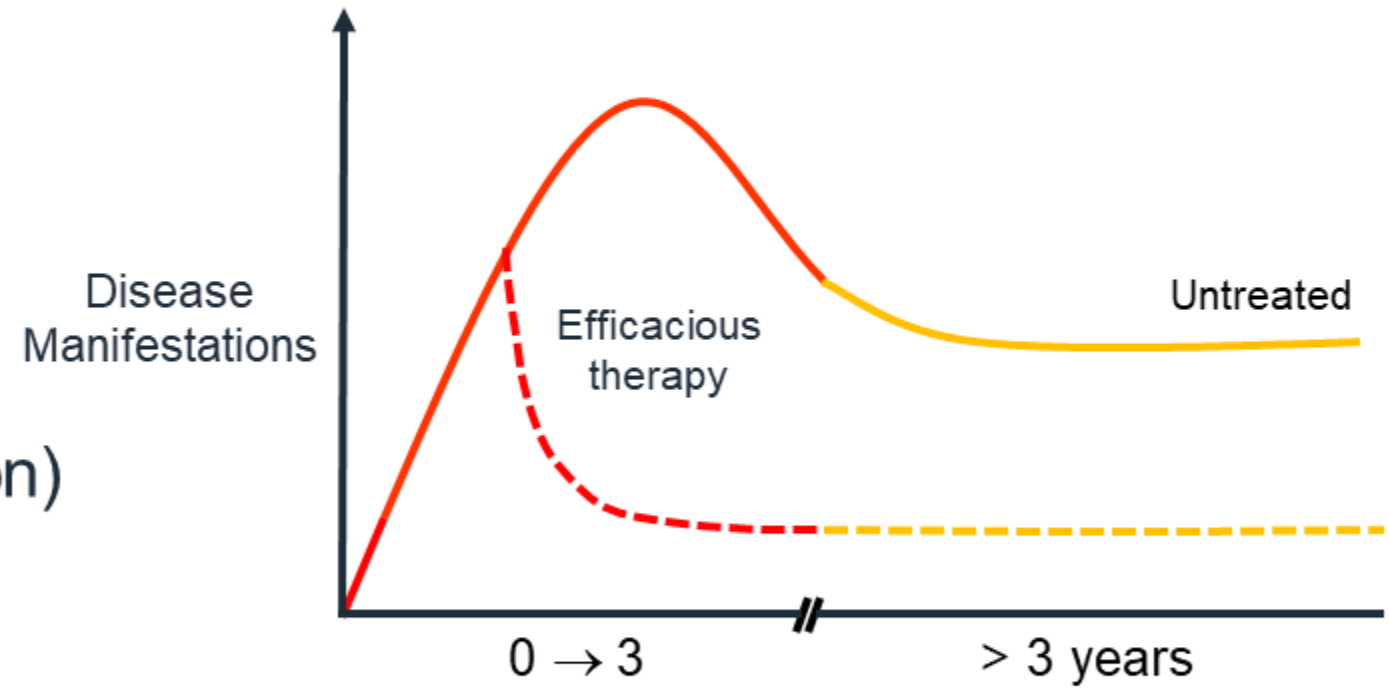


Removing Tissue and Fat

1. Reprinted from *ISRN Ophthalmology*, vol. 2012, Fichter N et al. Orbital decompression in Thyroid Eye Disease. pp. 1-12, 2012. Reproduced with permission from copyright holder.

Target Profile for an Efficacious Thyroid Eye Disease Treatment

- Decrease inflammatory signs
- Reduce proptosis (major driver of morbidity)
  - ≥ 2 mm reduction is clinically relevant[1]
- Reduce diplopia (double vision)
- Improve quality of life
- Manageable side effects



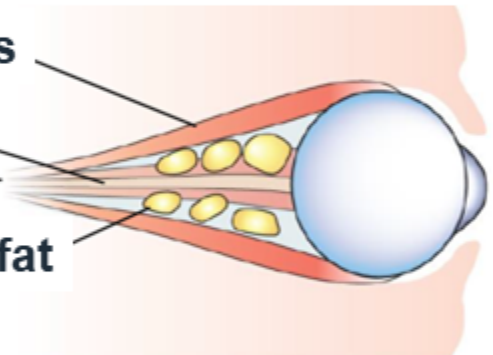
1. The European Group on Graves' Orbitopathy, 2006

Pathophysiology of Thyroid Eye Disease and Mechanism of Action of Teprotumumab

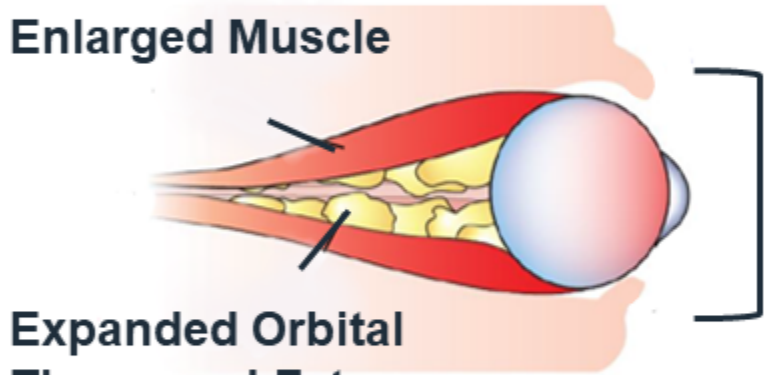
Shao-Lee Lin, M.D., Ph.D.
Executive Vice President, Head of Research and Development and
Chief Scientific Officer
Horizon Therapeutics

Pathology of Thyroid Eye Disease Occurs in Tissues Behind Eye

Healthy Eye and Orbital Tissue



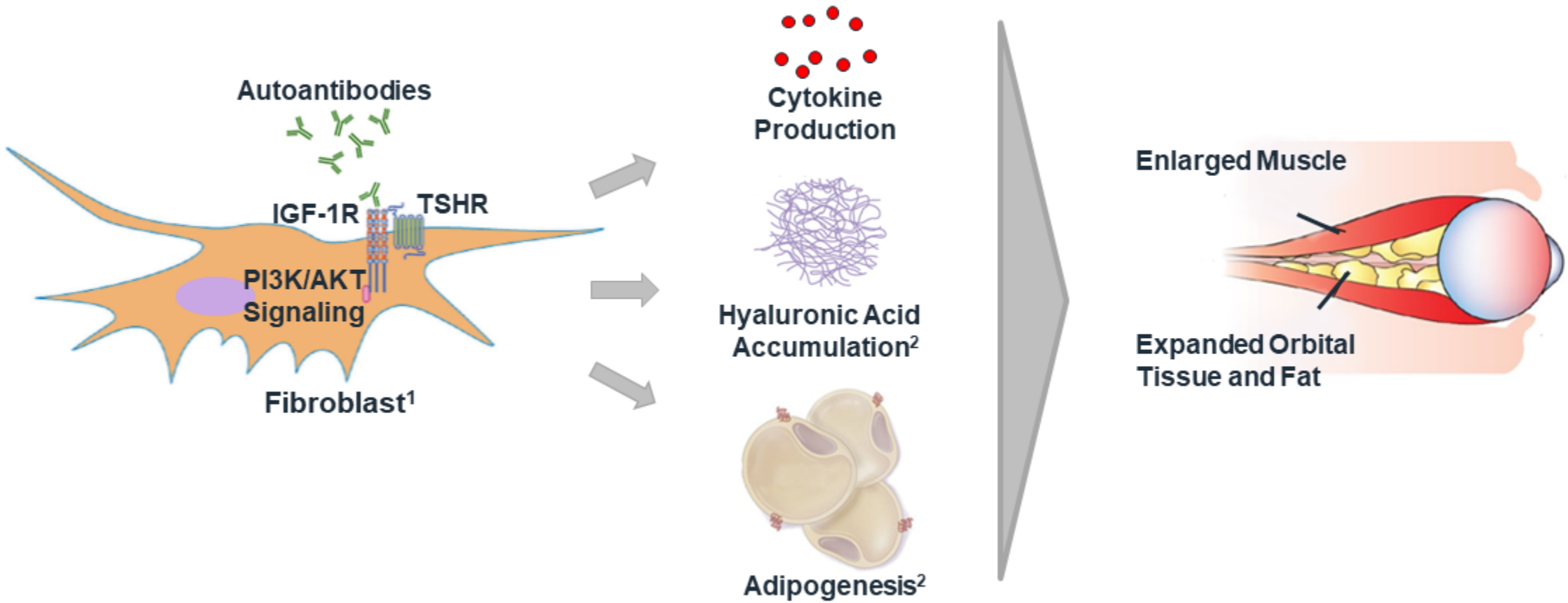
Thyroid Eye Disease



- Inflammation subsides over time but significant remodeling and scarring remains, along with persistent proptosis, diplopia and disfigurement
- Autoantibodies play central role in pathogenesis of Thyroid Eye Disease

Smith et al, 2016; Wang et al, 2014; Smith et al, 2018

IGF-1R – Central to Pathogenesis of Thyroid Eye Disease[1]

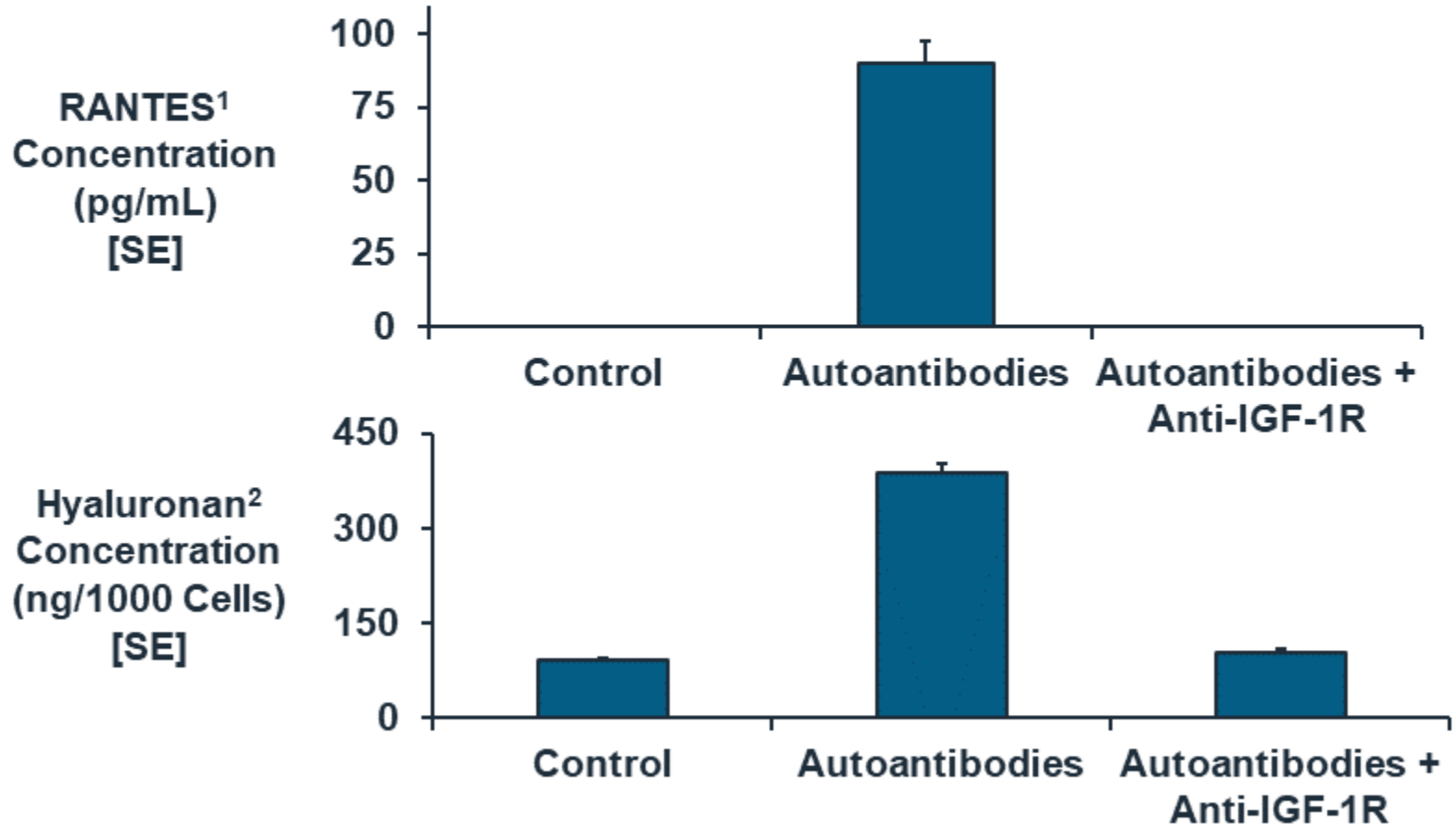


- IGF-1R necessary for downstream signaling and structural changes driving disease

1. Reprinted from Best Practice & Research Clinical Endocrinology & Metabolism, 26, Iyer et al, Immunopathogenesis of Graves' Ophthalmopathy: The role of the TSH receptor, p286, 2012. *Reproduced with permission from the copyright holder.*
2. Reprinted from Eye, 33, Douglas, Teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in the treatment of active Thyroid Eye Disease: a focus on proptosis, p185, 2019. *Reproduced with permission from the copyright holder.*

IGF-1R Blockade Inhibits Cytokine Production and Hyaluronic Acid Accumulation

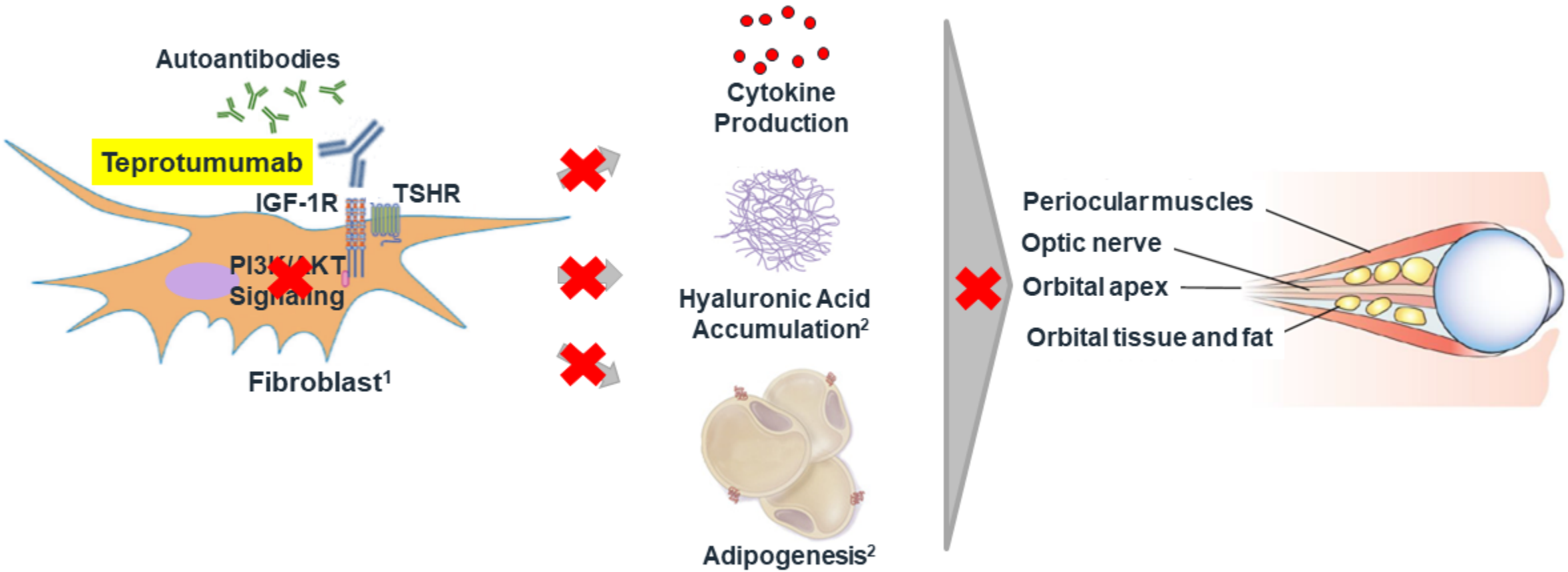
- Anti-IGF1R treatment blocks autoantibody-mediated disease drivers in orbital fibroblasts



1. Reprinted from The Journal of Immunology, 170, Pritchard et al , Immunoglobulin Activation of T Cell Chemoattractant Expression in Fibroblasts from Patients with Graves' Disease Is Mediated Through the Insulin-Like Growth Factor I Receptor Pathway, p6349, 2003. *Reproduced with permission from the copyright holder.*

2. Reprinted from The Journal of Clinical Endocrinology & Metabolism, 89, Smith and Hao , Immunoglobulins from Patients with Graves' Disease Induce Hyaluronan Synthesis in Their Orbital Fibroblasts through the Self-Antigen, Insulin-Like Growth Factor-I Receptor, p5078, 2004. *Reproduced with permission from the copyright holder.*

Teprotumumab Blocks Key Components of Thyroid Eye Disease



- Teprotumumab binds to IGF1-R, blocks downstream signaling and subsequent disease activity

1. Reprinted from Best Practice & Research Clinical Endocrinology & Metabolism, 26, Iyer et al, Immunopathogenesis of Graves' ophthalmopathy: The role of the TSH receptor, p286, 2012. *Reproduced with permission from the copyright holder.*
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Teprotumumab Clinical Program Overview

Shao-Lee Lin, M.D., Ph.D.
Executive Vice President, Head of Research and Development and Chief Scientific Officer
Horizon Therapeutics

Teprotumumab Clinical History

- One of several antibodies to IGF-1R investigated in oncology
  - Developed as non-cytotoxic, targeted therapy
  - Most – including teprotumumab – discontinued for lack of efficacy
- Hyperglycemia emerged as manageable side effect across IGF-1R class
  - Most cases reported as mild to moderate and reversible[1,2]
- Across oncology program, teprotumumab found to be well tolerated with no dose-limiting toxicities identified[3,4]

1. King ER and Wong KK 2012; 2. Ma HH, 2013; 3. Kurzrock 2010; 4. Pappo AS 2014

Teprotumumab Oncology Program: 727 Patients Treated Across 9 Studies

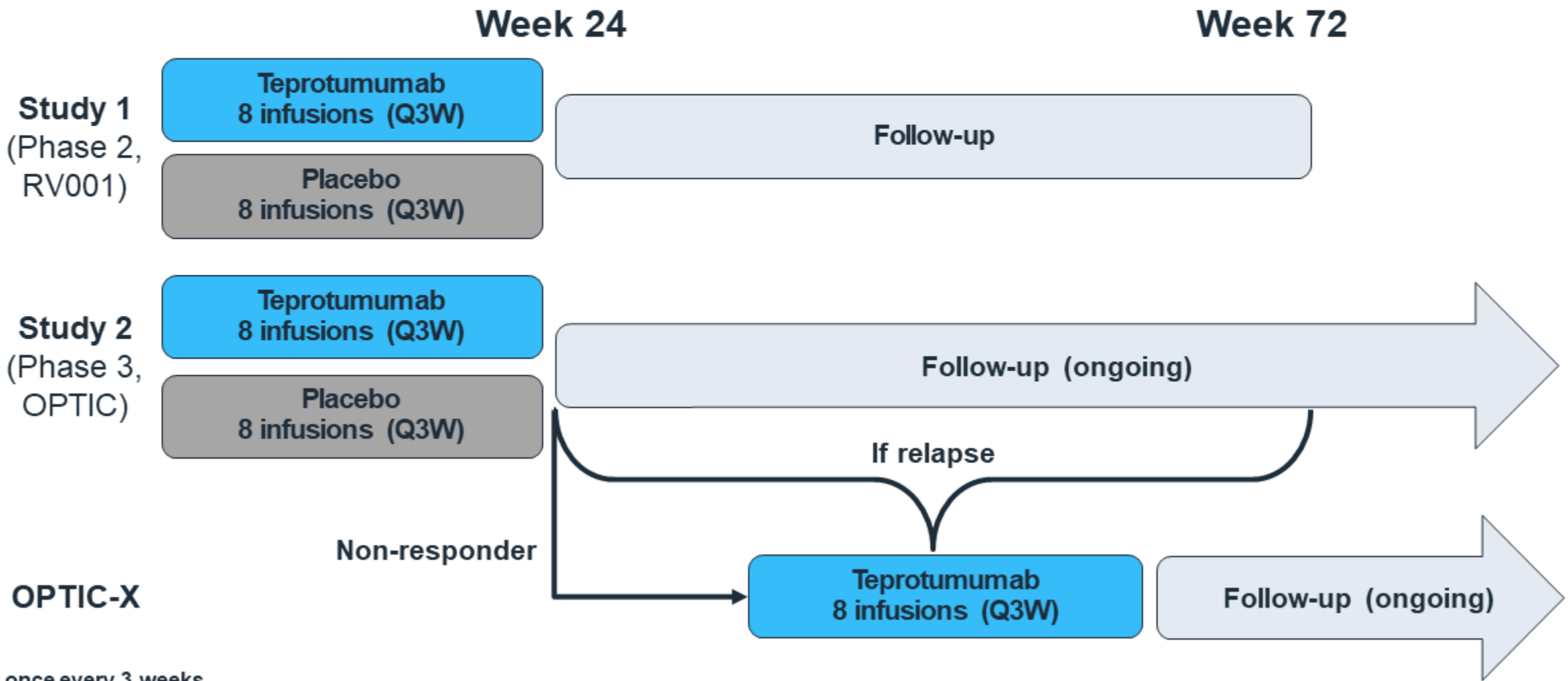
Study Number	N = 727	Population	Design	Regimen(s) Tested (mg/kg)
BO19373	97	Advanced solid tumors, non-Hodgkin's and Hodgkin's lymphomas	Open-label MAD	1, 3, 6 and 9 QW; 1, 3, 9 and 16 Q3W
NO21200	34	Age 2-17 years; advanced solid tumors	Open-label MAD	3 and 9 QW; 16 Q3W
NP22002	8	Early breast cancer prior to surgery	Open-label, single dose	16 Q3W
NO22068	104	Advanced malignancies	Open-label in combo with different standard chemo	3 and 9 QW; 5 and 10 Q2W; 9 and 16 Q3W
NO21161	6	Post-menopausal women with ER+ HER2-advanced breast cancer	Open-label in combo with letrozole	16 Q3W
NO21884	11	Advanced solid tumors	Open-label in combo with everolimus	16 Q3W
NO21160	116	Stage 3b/4 non-small cell lung cancer	Placebo-controlled in combo with erlotinib	9 QW; 16 Q3W
NO21746	34	Stage 3b/4 non-small cell lung cancer	Open-label in combo with erlotinib	9 QW
NO21157/ SARCO11	317	Age ≥ 2 years; recurrent or refractory sarcomas	Open-label	9 QW; 27 Q3W

MAD: multiple ascending dose; QW: once every week; Q2W: once every 2 weeks; Q3W: once every 3 weeks

Oncology Dose-Ranging Led to Teprotumumab Dose Selection in Thyroid Eye Disease

- Teprotumumab pharmacokinetics from oncology dose ranging informed dose selection in Thyroid Eye Disease
  - Systemic levels of teprotumumab providing > 90% target coverage considered
- Study 1 evaluated initial dose of 10 mg/kg followed by 20 mg/kg for remaining infusions
- Similar approach used in Study 2 to allow replicate studies with similar design and dose regimen

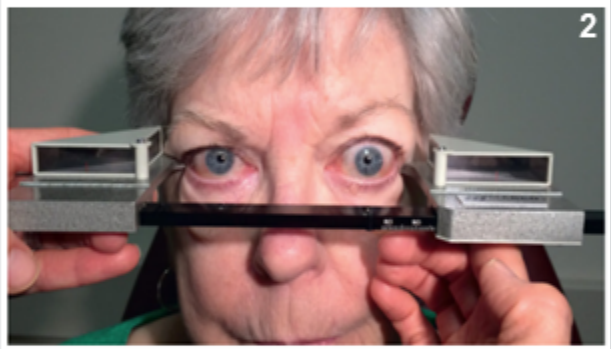
Teprotumumab Clinical Program – Largest in Thyroid Eye Disease



Q3W: once every 3 weeks

Commonly Used Assessment Tools Measure What Is Important to Patients

Proptosis Exophthalmometer[1]



- Valid and reproducible across sites[3]
- Measures taken to reduce variability
- ≥ 2 mm change clinically meaningful[4]

Diplopia Score[5]

0 - No diplopia

1 - Intermittent

2 - Inconstant

3 - Constant

Clinical Activity Score (CAS)[6]

1 - Spontaneous orbital pain

2 - Gaze evoked orbital pain

3 - Eyelid swelling

4 - Eyelid erythema

5 - Conjunctival redness

6 - Chemosis

7 - Inflammation of caruncle OR plica

Graves' Ophthalmopathy Quality of Life (GO-QoL)[7]

- 16 items
- Patient self-administered
- Literature supporting validation
- Assesses:
  - Functional vision (e.g., ability to drive, read)
  - Appearance / psychosocial functioning

1. Riordan et al, 2018; 2. Reprinted from Liu, Volpe, and Galetta's Neuro-Ophthalmology (3rd ed.). Liu GT, Volpe NJ, Galetta SL. The neuro-ophthalmic examination. pp.7-36, 2019 Elsevier. Reproduced with permission from copyright holder; 3. Ophthal Plast Reconstr Surg 2016; 4. Wiersinga, 2006; 5. Bahn et al, 1987; 6. Mourits et al, 1989; 7. Terwee, 1998

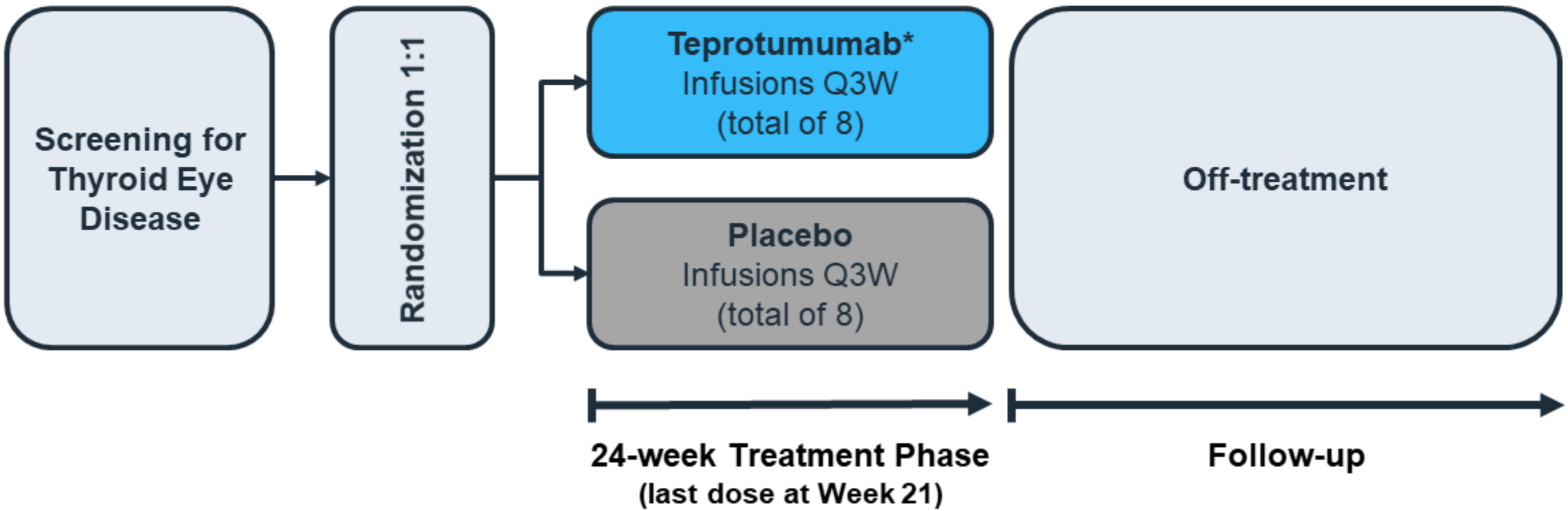
Teprotumumab Efficacy

Elizabeth H.Z. Thompson, Ph.D.
Vice President, Clinical Development, Rare Diseases
Horizon Therapeutics

Overview of Teprotumumab Efficacy in Patients with Thyroid Eye Disease

- Majority of patients achieved substantial improvements with 24 weeks of therapy
  - Proptosis (eye bulging)
  - Diplopia (double vision)
  - Inflammation as assessed by Clinical Activity Score (CAS)
  - Patient assessment of functional vision and appearance

Replicate Randomized, Double-Masked, Placebo-Controlled Trials



*10 mg/kg for 1st infusion, 20 mg/kg for all subsequent infusions

Primary Endpoints

- Study 1
  - Overall Response: ≥ 2 mm improvement in proptosis AND ≥ 2 points improvement in CAS at Week 24
    - FDA accepted single component – proptosis – as primary endpoint
- Study 2
  - Proptosis response: ≥ 2 mm improvement in proptosis at Week 24

CAS: Clinical Activity Score

Powering of Study 1 and 2

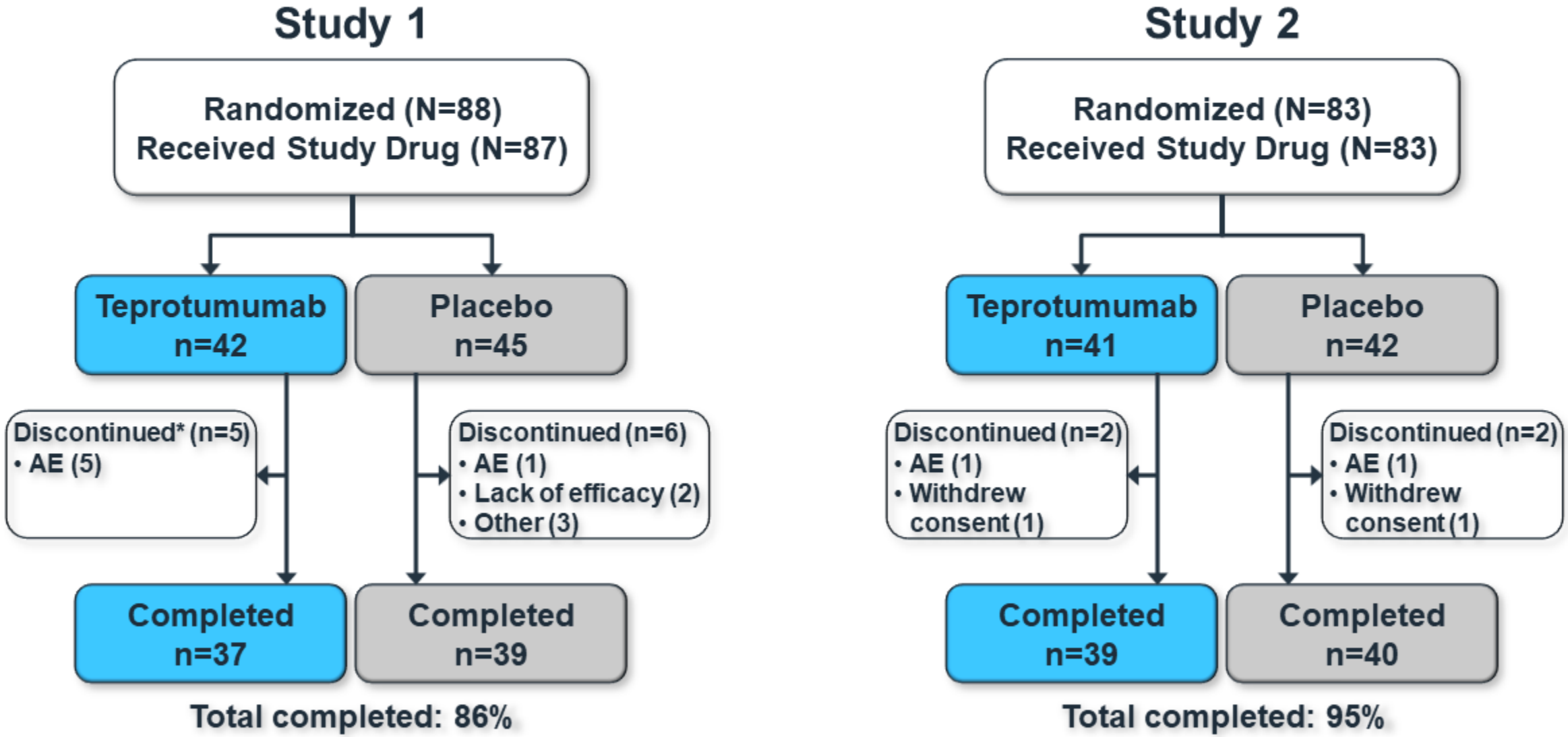
- Study 1: powered at 80%
  - 42 patients per group
  - 2-sided alpha 0.05 level
  - Success rate of 30% in placebo patients and expected 60% in teprotumumab patients
- Study 2: powered at 90%
  - 38 patients per group
  - 2-sided alpha 0.05 level
  - Detect difference of 39% between teprotumumab and placebo

Secondary Endpoints in Studies 1 and 2 in Hierarchical Order

Study 1		Study 2	
Secondary Endpoint	**p-value**	**Secondary Endpoint**	**p-value**
Mean CFB through Week 24 in GO-QoL overall score	**0.001**	Overall responder rate at Week 24	**< 0.001**
Mean CFB through Week 24 in proptosis measurement in study eye	**< 0.001**	Percentage of patients with CAS value of 0 or 1 in study eye at Week 24	**< 0.001**
Mean CFB through Week 24 in CAS in study eye	**< 0.001**	Mean CFB through Week 24 in proptosis measurement in study eye	**< 0.001**
Mean CFB through Week 24 in GO-QoL functional vision subscale score	**< 0.001**	Diplopia responder rate at Week 24	**0.001**
Mean CFB through Week 24 in GO-QoL appearance subscale score	**0.101**	Mean CFB through Week 24 in GO-QoL overall score	**< 0.001**

CFB = change from baseline; CAS: Clinical Activity Score

Patient Disposition in 24-Week Double-Masked Period

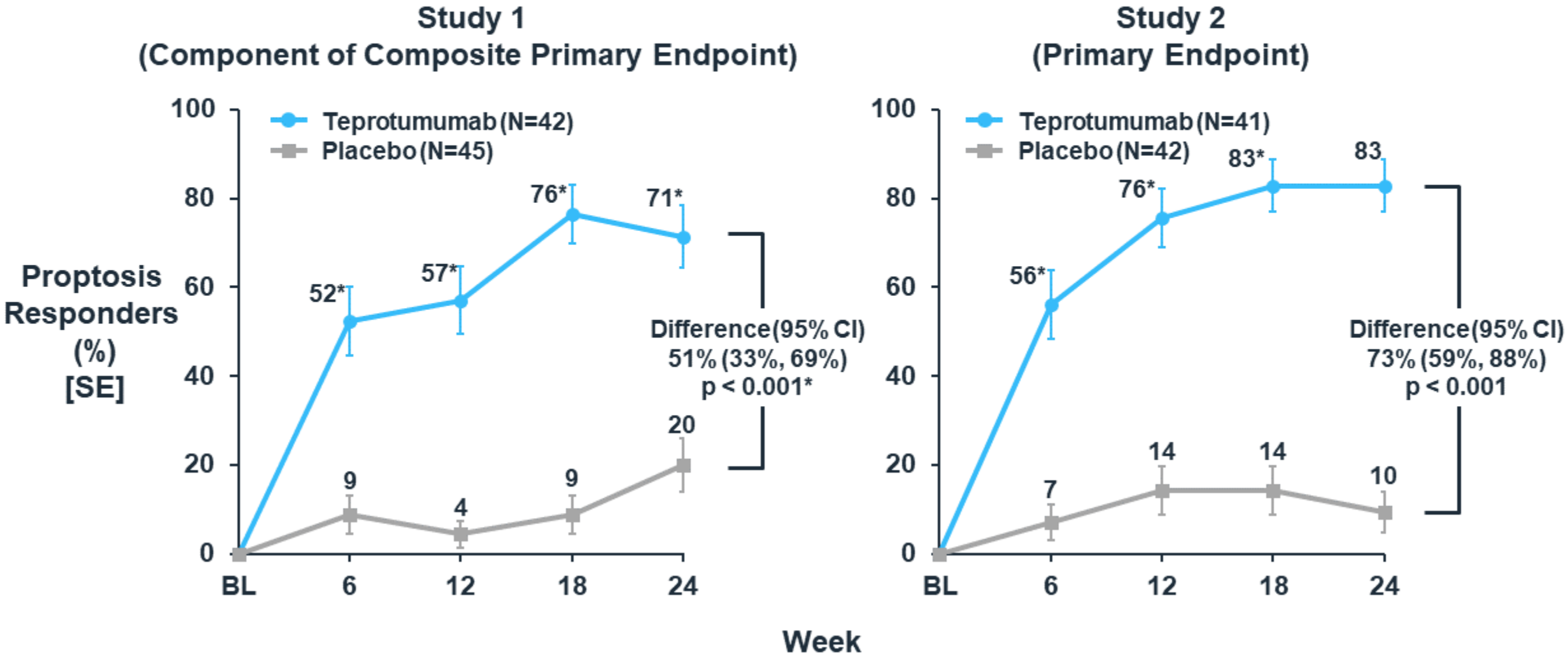


*1 patient had Week 24 data included in the analyses; all other discontinued patients were imputed as non-responders for the primary efficacy endpoint

Baseline and Demographic Characteristics

	Study 1		Study 2	
	Teprotumumab N=43	Placebo N=45	Teprotumumab N=41	Placebo N=42
Age (years), mean (SD)	51.3 (10.7)	53.7 (12.9)	51.6 (12.6)	48.9 (13.0)
Female	67%	80%	71%	74%
Race				
White	84%	87%	85%	88%
Black	12%	9%	10%	5%
Asian	2%	4%	5%	2%
Other	2%	0	0	5%
Years since diagnosis of Graves' Disease, median (range)	0.9 (0.2-19.1)	1.0 (0.2-25.0)	1.0 (0.3-28.2)	0.9 (0.1-14.8)
Months since diagnosis of Thyroid Eye Disease, median (range)	5.3 (2.3-10.1)	6.6 (1.2-11.0)	6.3 (0.9-9.7)	6.8 (1.1-10.3)
Smoker	26%	40%	22%	19%
Proptosis (mm), mean (SD)	23.4 (3.1)	23.1 (2.9)	22.6 (3.3)	23.2 (3.2)

Teprotumumab Produced More Proptosis Responders



Nominal p-value: *p < 0.05

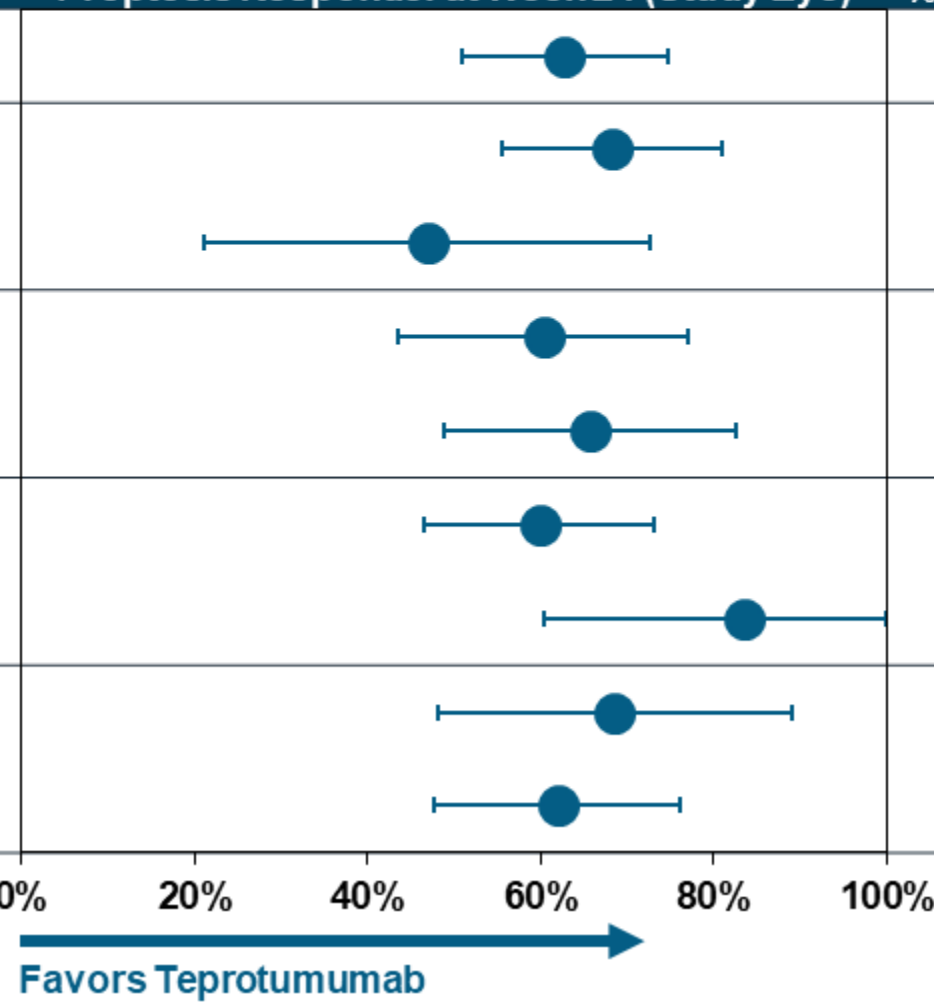
Improvements in Proptosis Seen in Fellow Eye

Week 24 Data	Teprotumumab	Placebo	Difference	p-value
Study 1	N=42	N=45		
Study Eye	30 (71%)	9 (20%)	51%	< 0.001
Fellow Eye	26 (62%)	6 (13%)	49%	< 0.001
Study 2	N=41	N=42		
Study Eye	34 (83%)	4 (10%)	73%	< 0.001
Fellow Eye	27 (66%)	1 (2%)	64%	< 0.001

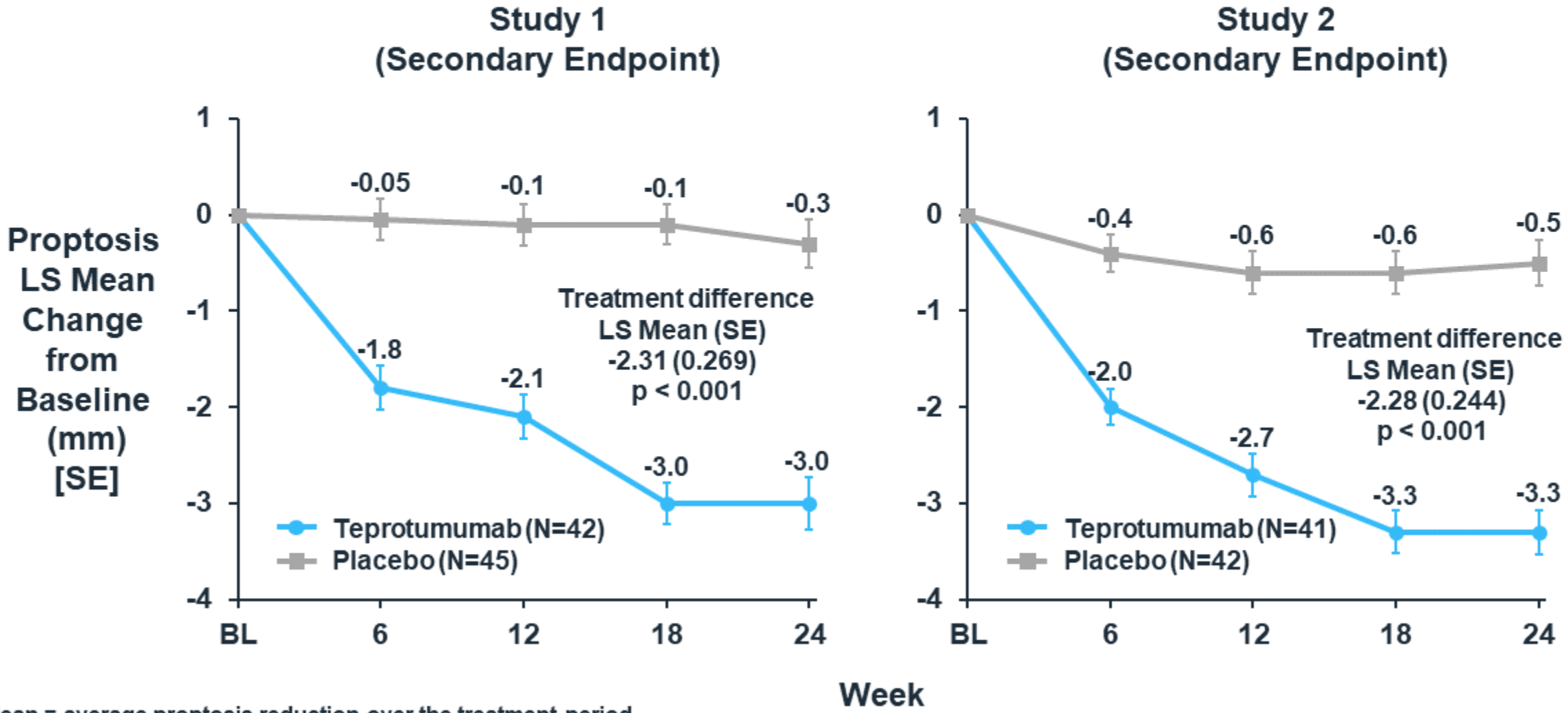
Fellow Eye = Non-study Eye

Teprotumumab Provided Improvements in Proptosis Across All Subgroups

Population	Teprotumumab N	Placebo N	% Difference (95% CI)	p-value
Overall	84	87	**63** (51, 75)	< 0.001
Tobacco non-user	64	61	**68** (56, 81)	< 0.001
Tobacco user	20	26	**47** (21, 73)	0.001
U.S.	49	48	**60** (44, 77)	< 0.001
EU	35	39	**66** (49, 83)	< 0.001
< 65 years	71	74	**60** (47, 73)	< 0.001
≥ 65 years	13	13	**83** (60, 100)	< 0.001
Male	26	20	**69** (48, 89)	< 0.001
Female	58	67	**62** (48, 76)	< 0.001

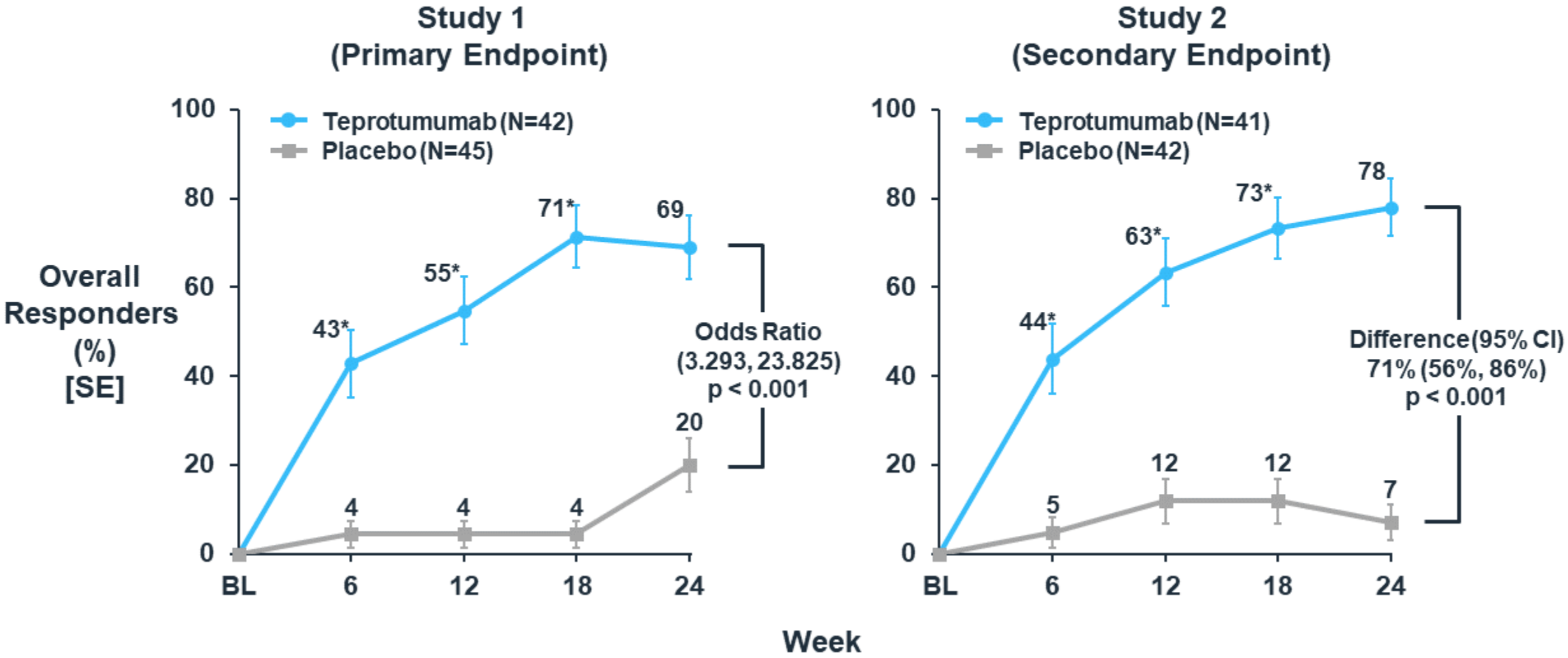


Greater Decrease in Proptosis in Patients Treated with Teprotumumab



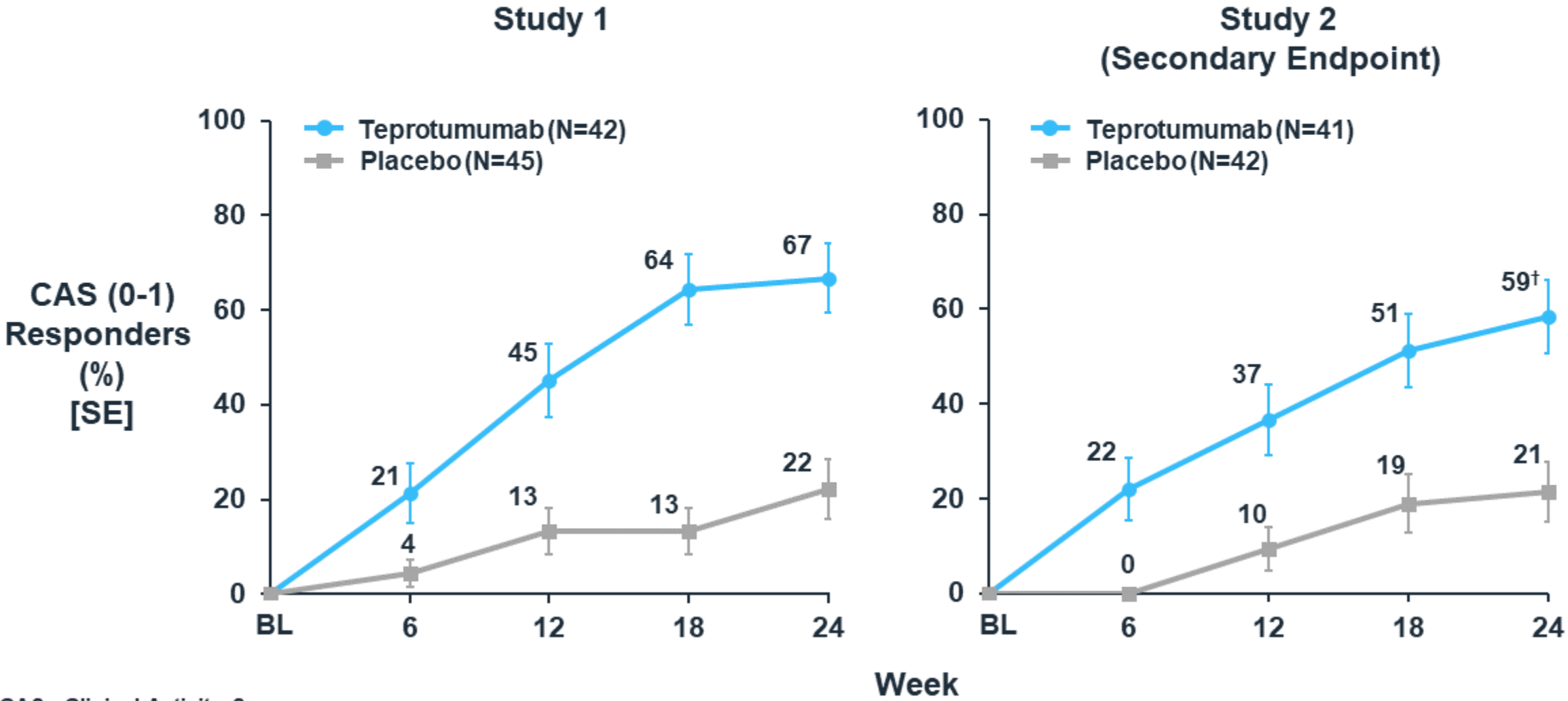
Mean = average proptosis reduction over the treatment period
Nominal p-value at all visits: $p < 0.05$

More Overall Responders with Teprotumumab



Nominal p-values: *p < 0.05

Fewer Inflammatory Signs and Symptoms (CAS 0-1) with Teprotumumab



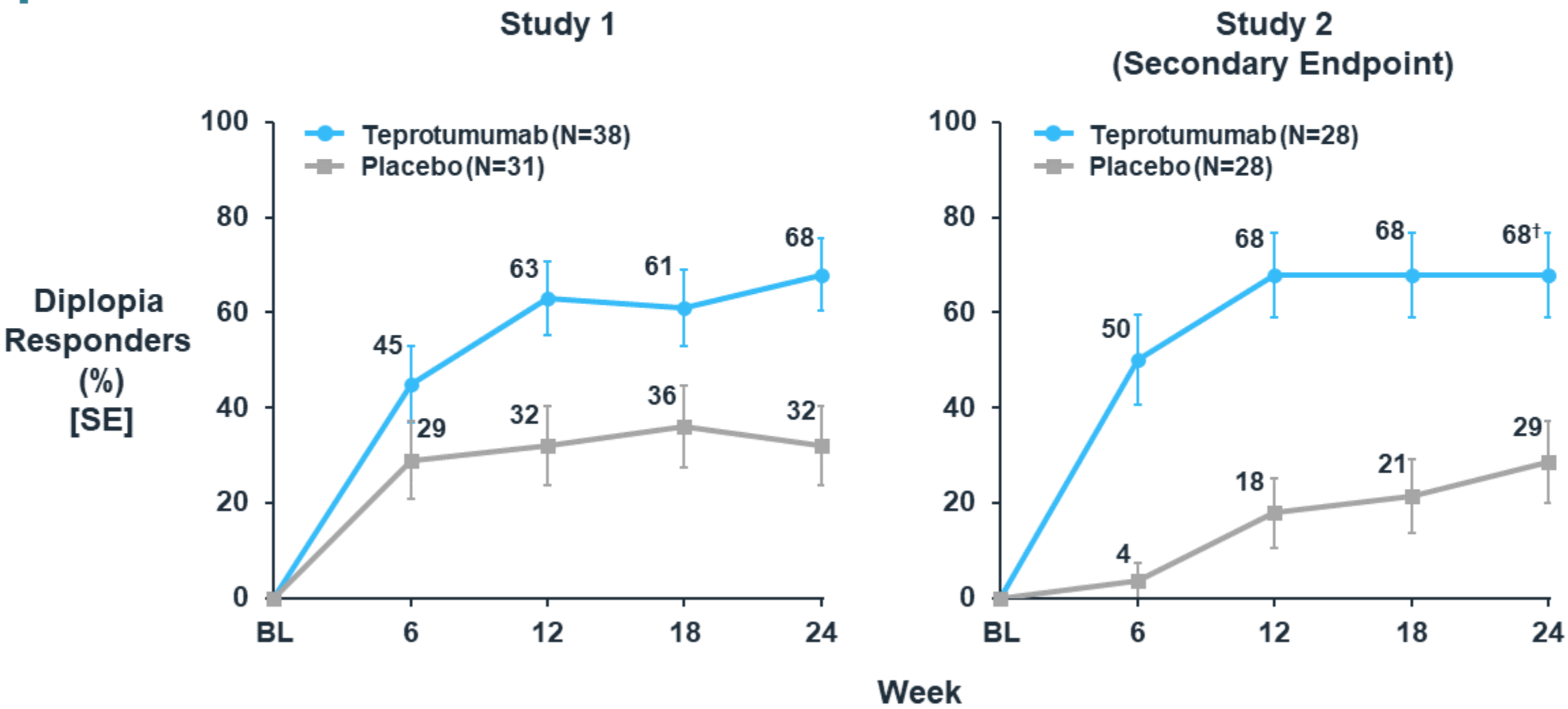
CAS: Clinical Activity Score
Nominal p-values at all visits: $p < 0.05$; †Study 2 visit Week 24, ranked endpoint $p < 0.001$

Complete Resolution (CAS 0) of Inflammatory Signs and Symptoms

Week 24 Data	Teprotumumab	Placebo	Difference
Study 1	N=42	N=45	
CAS 0-1	28 (67%)	10 (22%)	45%
CAS 0	14 (33%)	3 (7%)	26%
CAS 1	14 (33%)	7 (16%)	17%
Study 2	N=41	N=42	
CAS 0-1	24 (59%)	9 (21%)	38%
CAS 0	13 (32%)	4 (10%)	22%
CAS 1	11 (27%)	5 (12%)	15%

CAS: Clinical Activity Score

Teprotumumab Improved Diplopia

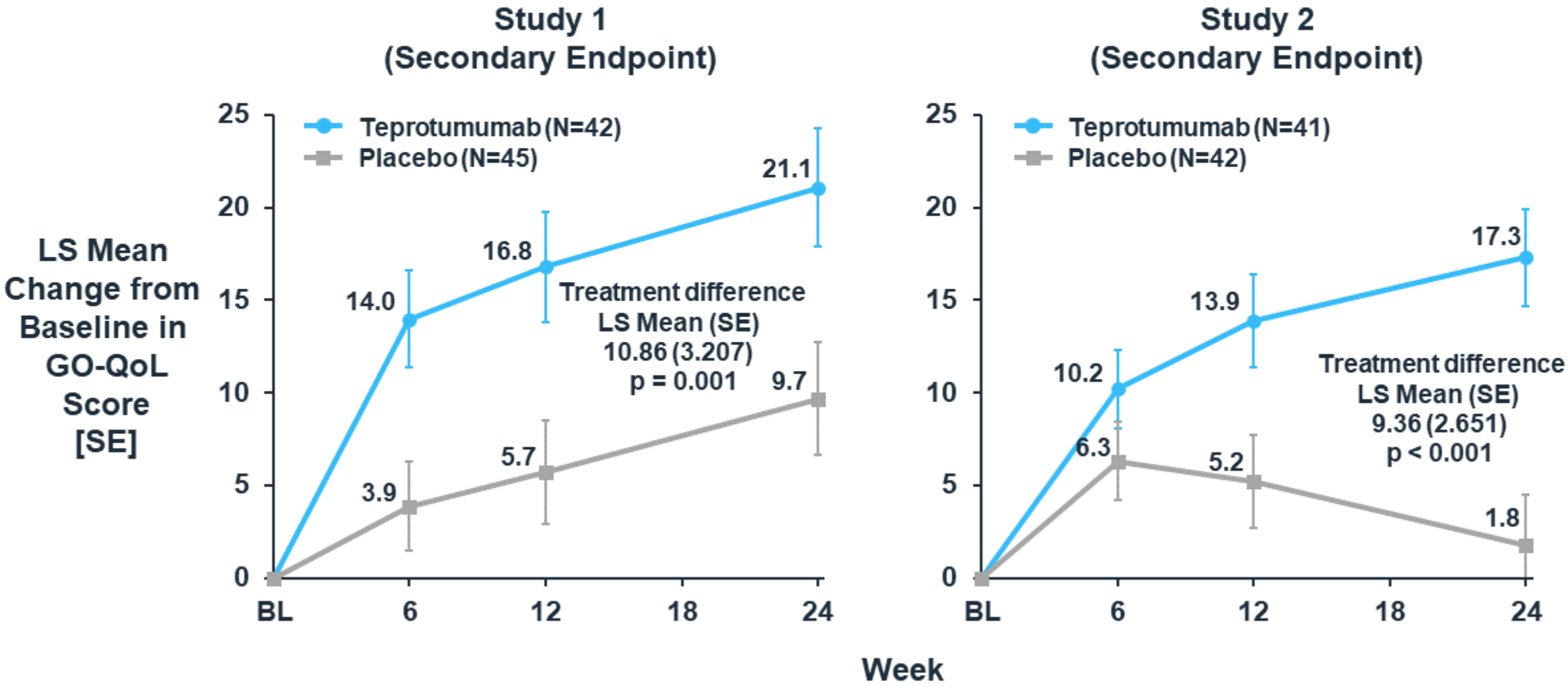


Nominal p-values at all visits: $p < 0.05$, except Study 1 visit Week 6; †Study 2 Visit Week 24, ranked endpoint $p = 0.001$

Teprotumumab Improved Diplopia Complete Responders (Diplopia 0)

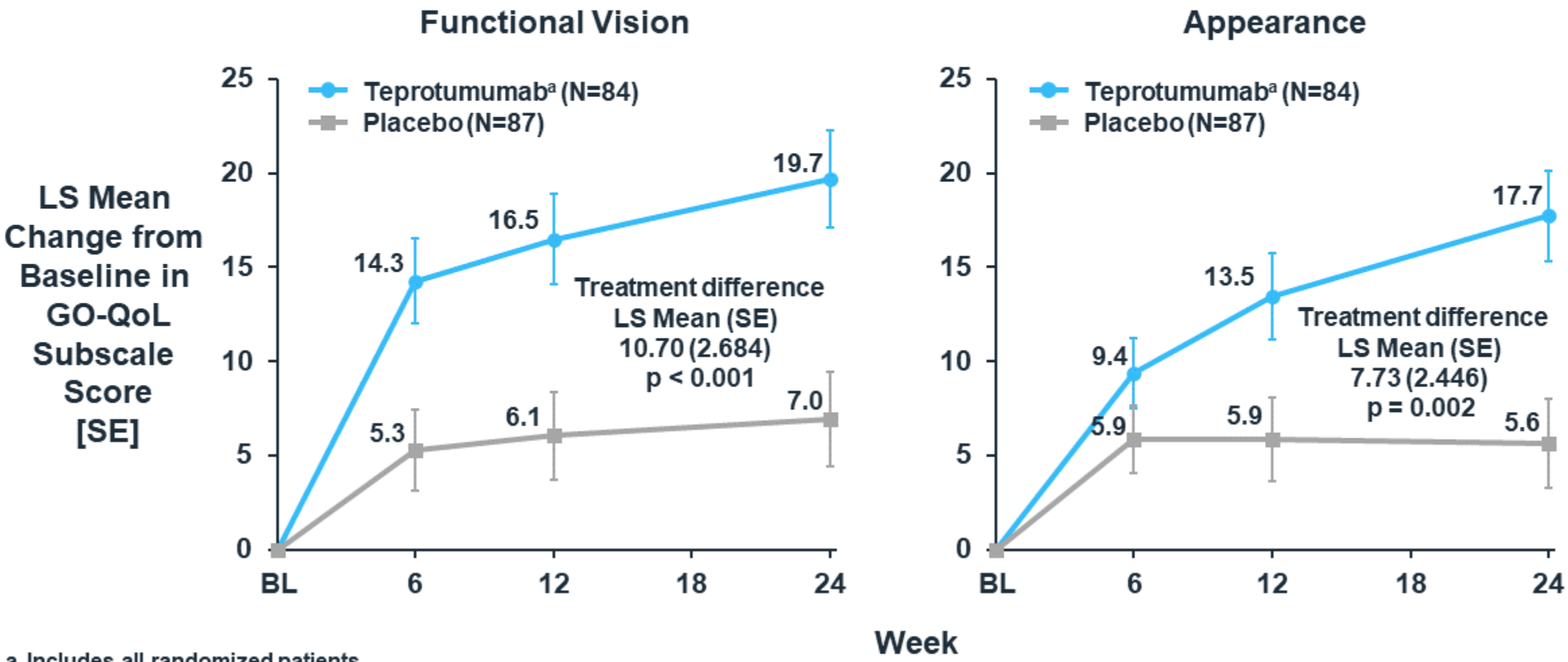
	Teprotumumab N=66	Placebo N=59
Week 24 diplopia complete responders	35 (53%)	15 (25%)

Teprotumumab Improved Quality of Life



Nominal p-values at all visits: $p < 0.05$, except Study 2 visit Week 6

Teprotumumab Improved GO-QoL Subscales Functional Vision and Appearance



a. Includes all randomized patients
Nominal p-values at all visits: $p < 0.05$, except Study 2 visit Week 6

Study 1: Acute Rebound Not Evident

- Overall response assessed at Week 28
  - Similar response to Week 24

Teprotumumab	Week 24 Response Rate	Week 28 Response Rate
Overall responders	69%	74%

  - No evidence of significant acute disease rebound after cessation

Last dose at Week 21

Study 1: Off-Treatment Efficacy Follow-Up

- Week 24 proptosis responders
  - 53% maintained ≥ 2 mm improvement from baseline at Week 72 (~1 year off treatment)
  - 73% had reduced proptosis from baseline and did not receive any additional treatment (e.g., steroids, surgery)
- Week 24 diplopia responders
  - 69% maintained response at Week 72

Ongoing Evaluation of Teprotumumab Therapy – OPTIC X

- Teprotumumab may modify disease course of Thyroid Eye Disease
  - Not chronic or life-long therapy as commonly seen with many disease modification agents
  - Longer-duration or repeat therapy may provide additional benefit
- OPTIC-X specifically designed to provide insight on
  - Longer-duration dosing
  - Retreatment
  - Currently ongoing

Summary of Teprotumumab Efficacy Data

- Teprotumumab effective and provided clinically meaningful improvements across multiple facets of Thyroid Eye Disease
  - Proptosis, diplopia, inflammation and patient assessment of functional vision and appearance
  - Number needed to treat was 1.6 in Studies 1 and 2 combined
- Results consistent across efficacy endpoints and subpopulations
- Majority of responders still benefiting ~1 year off treatment
  - Retreatment evaluation ongoing

Teprotumumab Safety

Elizabeth H.Z. Thompson, Ph.D.
Vice President, Clinical Development, Rare Diseases
Horizon Therapeutics

Safety Exposures: Double-Masked and All Teprotumumab Populations

Thyroid Eye Disease	Double-Masked Population n	OPTIC-X Population n	Total N	Patient Years
Study 1	43	-		
Study 2	41	-		
OPTIC-X	-	46*		
Total Exposure			121	49

Oncology (9 studies)	Total N	Patient Years
Total Exposure	727	164

Exposure	Total N	Patient Years
Total Exposure	848	213

*Includes 37 patients who received placebo in Study 2 and 9 patients who received teprotumumab in Study 2.

Most Patients Received Full Dosing Regimen in Study 1 and Study 2 – Thyroid Eye Disease

	Double-Masked Population	
	Teprotumumab N=84	Placebo N=86
Doses administered		
8 (full regimen), n (%)	75 (89%)	80 (93%)
Days on study drug		
Mean	140.6	142.6

Overall Safety Profile – Thyroid Eye Disease

		Double-Masked Population		OPTIC-X
		Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
AE of any grade		67 (80%)	60 (70%)	39 (85%)
AE leading to study drug discontinuation	Any	5 (6%)	2 (2%)	2 (4%)
	Reported as related	2 (2%)	0	1 (2%)
SAE	Any	7 (8%)	1 (1%)	1 (2%)
	Reported as related	3 (4%)	0	0
AE leading to death		0	0	0

AEs in Double-Masked Period, OPTIC-X – Thyroid Eye Disease

AE Term in ≥ 5% of Teprotumumab Arm	Double-Masked Population		OPTIC-X
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Any AE	67 (80%)	60 (70%)	39 (85%)
Muscle spasms	21 (25%)	6 (7%)	19 (41%)
Nausea	14 (17%)	8 (9%)	1 (2%)
Alopecia	11 (13%)	7 (8%)	5 (11%)
Diarrhea	10 (12%)	7 (8%)	5 (11%)
Fatigue	8 (10%)	6 (7%)	4 (9%)
Headache	7 (8%)	6 (7%)	1 (2%)
Dysgeusia	7 (8%)	0	3 (7%)
Dry skin	7 (8%)	0	5 (11%)
Hyperglycemia	6 (7%)	1 (1%)	0
Rash	5 (6%)	5 (6%)	3 (7%)

SAEs in Double-Masked Period, OPTIC-X – Thyroid Eye Disease

SAE Term	Treatment-Related	Double-Masked Population		OPTIC-X
		Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Any SAE		7 (8%)	1 (1%)	1 (2%)
Hashimoto's encephalopathy	Yes	1 (1%)	0	0
Infusion-related reaction[1]	Yes	1 (1%)	0	0
Diarrhea[1]	Yes	1 (1%)	0	0
Inflammatory Bowel Disease[1]	No	1 (1%)	0	0
E. coli sepsis[1]	No	1 (1%)	0	0
Pneumothorax	No	1 (1%)	0	0
Urinary retention	No	1 (1%)	0	0
Cerebral hemorrhage[1]	No	0	0	1 (2%)
Visual field defect[1]	No	0	1 (1%)	0

1. Discontinued from study drug

AEs Leading to Discontinuation of Study Drug – Thyroid Eye Disease

AE Term (Grouped by Patient)	Double-Masked Population		OPTIC-X
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Any AE leading to discontinuation	5 (6%)	2 (2%)	2 (4%)
Cerebral hemorrhage*	0	0	1 (2%)
Diarrhea*	1 (1%)	0	0
E. coli sepsis*, dehydration	1 (1%)	0	0
Inflammatory bowel disease*	1 (1%)	0	0
Infusion related reaction*	1 (1%)	0	0
Muscle spasms	0	0	1 (2%)
BP increased, flushing, heart rate increased, palpitations	1 (1%)	0	0
Presyncope	0	1 (1%)	0
Visual field defect*	0	1 (1%)	0

*Serious Adverse Event
Additionally, confusional state reported by a single patient, more than 3 weeks after last dose of study drug, led to discontinuation.

Infections – Thyroid Eye Disease

	Double-Masked Population		OPTIC-X
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Infections	30 (36%)	19 (22%)	10 (22%)
Serious and leading to discontinuation (*E.coli* sepsis)	1 (1%)	0	0

- No opportunistic infections

Infections – Thyroid Eye Disease

AE Terms (≥ 2 Patients)	Double-Masked Population		OPTIC-X
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Infections	30 (36%)	19 (22%)	10 (22%)
Urinary tract infection	4 (5%)	1 (1%)	3 (7%)
Bronchitis	4 (5%)	2 (2%)	1 (2%)
Influenza	2 (2%)	4 (5%)	3 (7%)
Cystitis	4 (5%)	1 (1%)	0
Sinusitis	2 (2%)	0	2 (4%)
Nasopharyngitis	3 (4%)	1 (1%)	0
Localized infection	2 (2%)	0	0
Upper respiratory tract infection	0	4 (5%)	0

Immunogenicity of Teprotumumab – Thyroid Eye Disease

Study	False Positive Rate	Anti-Drug Antibody (ADA) Response
Study 1	1%	1 patient positive at baseline and Week 72
		1 patient confirmed positive at Week 3, negative at subsequent visits
Study 2	1%	No confirmed positive ADA samples from teprotumumab patients

- All confirmed positive patients exhibited low titer response
- No impact on pharmacokinetics, efficacy or safety

Adverse Events of Special Interest

Muscle Spasms – Thyroid Eye Disease

- More frequent with teprotumumab
  - 25% vs. 7% in double-masked population
  - 41% in OPTIC-X
- Most mild in intensity
  - 6 patients experienced moderate events
- Lower limbs most often affected
- 1 patient discontinued because of muscle spasms

Hyperglycemia – Thyroid Eye Disease

	Double-Masked Population		OPTIC-X
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Hyperglycemia*	8 (10%)	1 (1%)	3 (7%)
Mild or moderate	8 (10%)	0	3 (7%)
SAE	0	0	0
Leading to discontinuation	0	0	0
Leading to interruption	1 (1%)	0	0

*Includes multiple AE terms related to increased blood glucose

Hyperglycemia Highest Laboratory Values – Thyroid Eye Disease

- Highest values observed
  - Glucose: 303 mg/dL on study day 29 (single patient)
  - HbA1c: 7.9% at Week 24 (single patient)

Infusion Reactions – Thyroid Eye Disease

	Double-Masked Population		All Teprotumumab Population
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	N=121 n (%)
Any AE < 2hr of infusion	6 (7%)	4 (5%)	9 (7%)
Additional AE occurring on day of infusion but with unknown onset time	3 (4%)	8 (9%)	4 (3%)

Infusion Reactions – Detail
Thyroid Eye Disease

Age / Gender	AE Term	Description
58 / F	BP increased, flushing, HR increased, palpitations	↑ BP/HR, rash, "feeling hot," rash after 2nd infusion; similar reaction to pre-medication for 3rd infusion → discontinuation
37 / F	Hypertension	↑ BP after 5th infusion; previously reported as infusion reaction
38 / M	Infusion-related reaction (SAE)	↑ BP/HR, diffuse erythema, feeling of obstruction in epiglottis, dyspnea, headache, muscular pain; oxygen saturation 96%; no hypotension, no fever; normal tryptase; resolved with steroids and antihistamines

- Managed with symptomatic treatment, resolved same day without complication
- 1 patient able to received future infusion with premedication, slower infusion
- No patient received epinephrine

Hearing Impairment – Thyroid Eye Disease

	Double-Masked Population		OPTIC-X
	Teprotumumab N=84 n (%)	Placebo N=86 n (%)	Teprotumumab N=46 n (%)
Hearing impairment	8 (10%)	0	5 (11%)
SAEs	0	0	0
Mild	5 (6%)	0	5 (11%)
Moderate	3 (4%)	0	0

- 10 of 13 patients completely or partially resolved to date
- 8 of 13 patients underwent audiology testing, including all patients with events graded as moderate

Hearing Impairment with Audiogram (n=8)

Age / Gender	MedDRA PTs	Audiology Result (Left Ear)	Audiology Result (Right Ear)	Outcome
59 / F	Hyperacusis	Normal to mild high frequency conductive to mixed hearing loss	Normal to mild high frequency sensorineural hearing loss	Resolved
66 / M	Hypoacusis	Mild in low-mid frequency to severe high frequency sensorineural loss	Mild in low-mid frequency to moderate mixed hearing loss	Resolved
79 / F	Deafness	Sensorineural loss; magnitude not indicated	Sensorineural loss; magnitude not indicated	Resolved
43 / F	Eustachian tube dysfunction	Moderate mixed hearing loss	Normal	Resolved
	Deafness unilateral			Overall improvement; lost to follow-up
51 / F	Tinnitus	Normal	Mild mid frequency sensorineural hearing loss	Resolving
60 / M	Deafness	Normal in low-mid frequency moderate in high frequency sensorineural loss	Normal in low-mid frequency moderate in high frequency sensorineural loss	Ongoing
57 / F	Ear discomfort	Mild to moderate high frequency sensorineural hearing loss	Mild to moderate high frequency sensorineural hearing loss	Ongoing
	Hypoacusis			
66 / F	Tinnitus	Mild low frequency sensorineural hearing loss	Mild low frequency sensorineural hearing loss	2nd event of tinnitus ongoing

Inflammatory Bowel Disease (IBD) – Thyroid Eye Disease

- Study 1: 2 patients had underlying IBD or signs / symptoms consistent with IBD and events consistent with exacerbation
  - Both experienced SAE and withdrew
- Study 2: patients with history of IBD excluded
  - Diarrhea rates balanced (10% teprotumumab, 12% placebo)
  - Other terms representative of potential IBD also balanced
    - Abdominal pain and rectal bleeding

Overall Safety Profile in Thyroid Eye Disease

- AEs greater among teprotumumab vs. placebo
- Most AEs mild or moderate and resolved during or after treatment
- 89% of teprotumumab patients able to receive all 8 infusions in Studies 1 and 2
- Elevated glucose and HbA1c levels in some patients
  - Otherwise no significant shifts in laboratory findings
- No clinically significant changes in vital signs or ECGs
- Only anti-drug antibodies detected were transient, low titer and seen in 2 patients

Teprotumumab Oncology Data

SAEs – Teprotumumab in Combination with Erlotinib in Advanced Non-Small Cell Lung Cancer

System Organ Class	Teprotumumab + Erlotinib N=116 n (%)	Placebo + Erlotinib N=55 n (%)
Any SAE	32 (28%)	8 (15%)
Infections and infestations	9 (8%)	3 (5%)
Respiratory, thoracic and mediastinal disorders	8 (7%)	2 (4%)
Gastrointestinal disorders	5 (4%)	1 (2%)
General disorders and administrative site conditions	5 (4%)	1 (2%)
Cardiac disorders	4 (3%)	0
Nervous system disorders	3 (3%)	1 (2%)
Vascular disorders	3 (3%)	0
Metabolism and nutrition disorders	2 (2%)	0
Musculoskeletal and connective tissue disorders	2 (2%)	0
Skin and subcutaneous disorders	2 (2%)	0

AEs – Teprotumumab Non-Small Cell Lung Cancer (1 of 2)

AE Term (≥ 5%)	Teprotumumab + Erlotinib N=116 n (%)	Placebo + Erlotinib N=55 n (%)
Rash	74 (64%)	30 (55%)
Diarrhea	62 (53%)	23 (42%)
Fatigue	45 (39%)	11 (20%)
Nausea	39 (34%)	10 (18%)
Decreased appetite	35 (30%)	12 (22%)
Weight decreased	24 (21%)	2 (4%)
Stomatitis	24 (21%)	6 (11%)
Epistaxis	22 (19%)	1 (2%)
Vomiting	21 (18%)	11 (20%)
Muscle spasms	20 (17%)	3 (5%)

AE Term (≥ 5%)	Teprotumumab + Erlotinib N=116 n (%)	Placebo + Erlotinib N=55 n (%)
Cough	19 (16%)	9 (16%)
Mucosal inflammation	18 (16%)	4 (7%)
Dyspnea	18 (16%)	11 (20%)
Dysguesia	13 (11%)	4 (7%)
Constipation	13 (11%)	4 (7%)
Dyspepsia	13 (11%)	3 (5%)
Pruritus	12 (10%)	5 (9%)
Asthenia	12 (10%)	9 (15%)
Paronychia	10 (9%)	2 (4%)
Headache	10 (9%)	2 (4%)

AEs – Teprotumumab Non-Small Cell Lung Cancer (2 of 2)

AE Term (≥ 5%)	Teprotumumab + Erlotinib N=116 n (%)	Placebo + Erlotinib N=55 n (%)
Dry skin	9 (8%)	7 (13%)
Haemoptysis	8 (7%)	2 (4%)
Nasopharyngitis	8 (7%)	2 (4%)
Dehydration	8 (7%)	2 (4%)
Arthralgia	8 (7%)	2 (4%)
Blood creatinine increased	8 (7%)	0
Dizziness	7 (6%)	7 (13%)
Anaemia	7 (6%)	7 (13%)
Hyperglycemia	7 (6%)	0

AE Term (≥ 5%)	Teprotumumab + Erlotinib N=116 n (%)	Placebo + Erlotinib N=55 n (%)
Pyrexia	7 (6%)	2 (4%)
Nail disorder	7 (6%)	1 (2%)
Dermatitis acneiform	7 (6%)	0
Abdominal pain	6 (5%)	1 (2%)
Edema peripheral	6 (5%)	1 (2%)
Conjunctivitis	6 (5%)	2 (4%)

SAEs – Teprotumumab in Recurrent or Refractory Sarcoma

Serious Adverse Events (≥ 2 Patients)	Teprotumumab N=317 n (%)
Any SAE	48 (15%)
Somnolence	3 (< 1%)
Infection	3 (< 1%)
Pain	2 (< 1%)
Pneumonia	2 (< 1%)
Constipation	2 (< 1%)
Device-related infection	2 (< 1%)
Pulmonary embolism	2 (< 1%)
Vomiting	2 (< 1%)
Dehydration	2 (< 1%)

NO21157/SARCO11, table from Clinical Study Report

AEs – Teprotumumab in Recurrent or Refractory Sarcoma (1 of 2)

AE Term (≥ 5%)	Teprotumumab N=317 n (%)
Fatigue	101 (32%)
Nausea	71 (22%)
Diarrhea	56 (18%)
Vomiting	56 (18%)
Headache	53 (17%)
Constipation	51 (16%)
Cough	51 (16%)
Hyperglycemia	49 (15%)
Decreased appetite	47 (15%)
Muscle spasms	43 (14%)

AE Term (≥ 5%)	Teprotumumab N=317 n (%)
Pyrexia	47 (15%)
Dyspnea	43 (14%)
Weight decreased	41 (13%)
Back pain	39 (12%)
AST increased	37 (12%)
Anemia	37 (12%)
Chest pain	30 (10%)
Pain	30 (10%)
Asthenia	27 (9%)
Musculoskeletal pain	27 (9%)

AEs – Teprotumumab in Recurrent or Refractory Sarcoma (2 of 2)

AE Term (≥ 5%)	Teprotumumab N=317 n (%)
Pain in extremity	25 (8%)
ALT increased	26 (8%)
Arthralgia	23 (7%)
Blood ALP increased	22 (7%)
Thrombocytopenia	21 (7%)
Epistaxis	21 (7%)
Abdominal pain	21 (7%)
Hyponatremia	22 (7%)
Oropharyngeal pain	20 (6%)
Infusion related reaction	18 (6%)

AE Term (≥ 5%)	Teprotumumab N=317 n (%)
Hypoalbuminemia	18 (6%)
Rash	18 (6%)
Hypophosphatemia	18 (6%)
Hypokalemia	18 (6%)
Blood LDH increased	17 (5%)
Edema peripheral	16 (5%)
Musculoskeletal chest pain	15 (5%)
Hypocalcemia	15 (5%)
Insomnia	15 (5%)

Proposed Post-Marketing Safety Plan

Action	Activities
Enhanced Surveillance	• Registry following ~ 200 patients • Proactive follow-up for AEs of special interest
Labeling (to be finalized with FDA)	• Hyperglycemia • Infusion reaction • Inflammatory bowel disease • Pregnancy prevention • Muscle spasm • Infections • Hearing impairment
Educate and Support HCP Community	• HCP call center for information and support • Continuing medical education • Peer-reviewed publications • Academic grand rounds • Expert speaker programs, newsletters and webinars
Educate and Support Patients	• Call center patient hotline to provide information on teprotumumab • 24/7 specialty pharmacy network • Advocacy group educational programming

Positive Benefit / Risk for Teprotumumab in Thyroid Eye Disease

- No FDA-approved treatments
- Existing treatments do not impact proptosis or diplopia

Benefits	Generally Manageable Risks

• Clinically significant reduction in proptosis
• Improvement in diplopia (double vision)
• Reduced inflammation
  • Orbital pain, eyelid and conjunctival swelling and redness
• Improved patients' quality of life
  • Functional vision
  • Appearance
	• Hyperglycemia, infection and infusion reactions
	• Hearing impairment
	• Muscle spasms
	• Potential for IBD exacerbation
	• Potential for embryo-fetal toxicity based on animal studies

IBD: inflammatory bowel disease

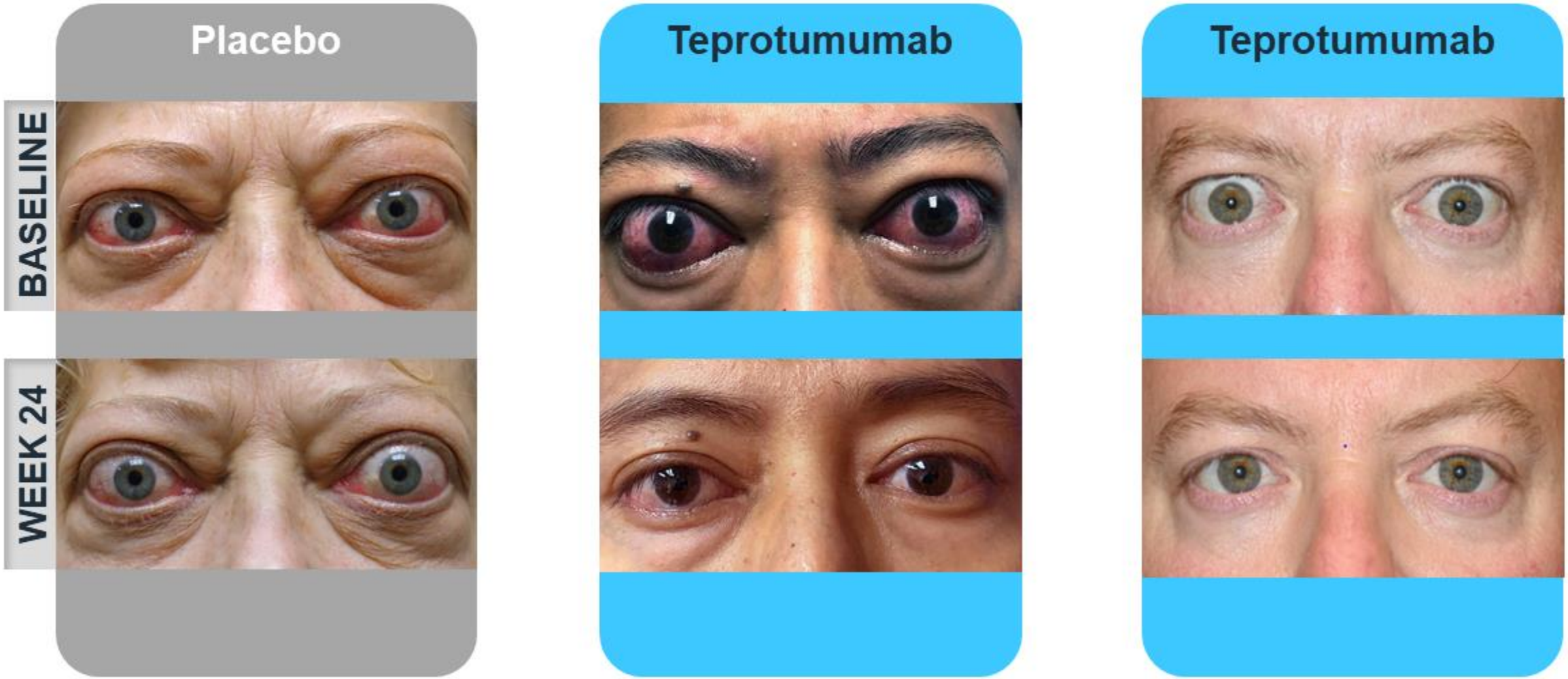
Teprotumumab for Treatment of Thyroid Eye Disease Clinical Perspective

Raymond S. Douglas, M.D., Ph.D.
Director of Orbital and Thyroid Eye Disease Program
Cedars-Sinai Medical Center

Thyroid Eye Disease – Severe and Debilitating Disease

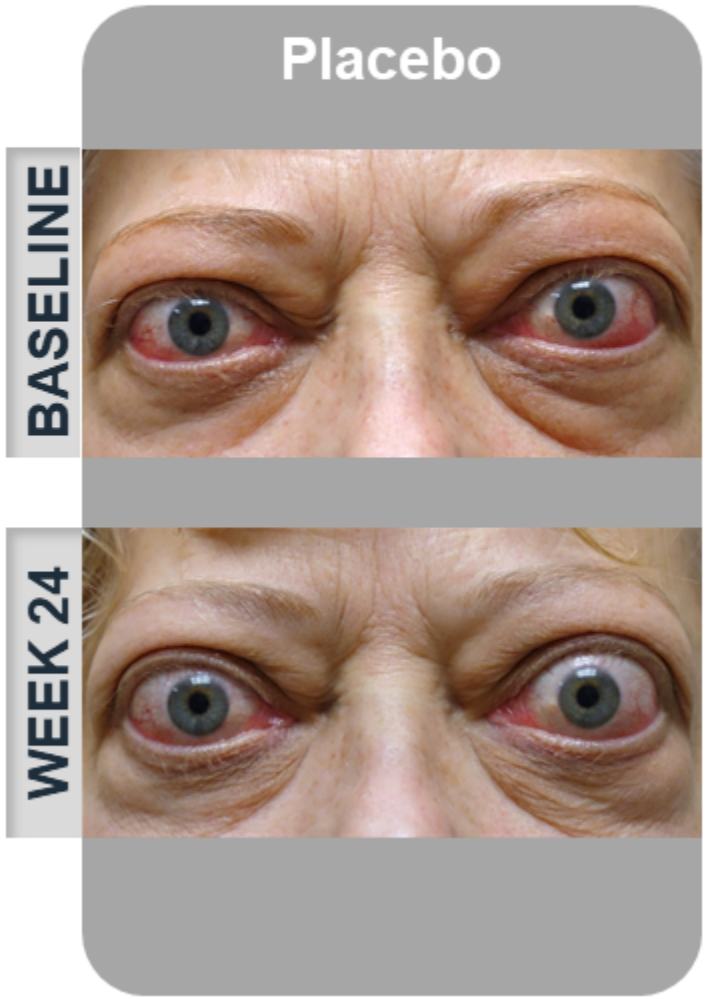
- Clinical, physical and psychological manifestations
  - Proptosis, strabismus, double and blurry vision, intense pain, distorted vision and activities of daily living
  - Permanent facial disfigurement and social isolation
- No approved treatments
  - Current options inadequate and do not address proptosis or diplopia
- Teprotumumab has potential to reverse disease and improve patients' lives

Examples of Patients in Clinical Program



Photos provided with permission from patients of Dr. Douglas

Example of Patient in Clinical Program – Placebo



	Study Eye (LEFT)			Fellow Eye (RIGHT)		
	Baseline	Week 24	CFB	Baseline	Week 24	CFB
Proptosis (mm)	29	28	-1	27	26	-1
Diplopia	1	2	1	1	2	1
CAS	7	5	-2	5	5	0

CFB: change from baseline; CAS: Clinical Activity Score
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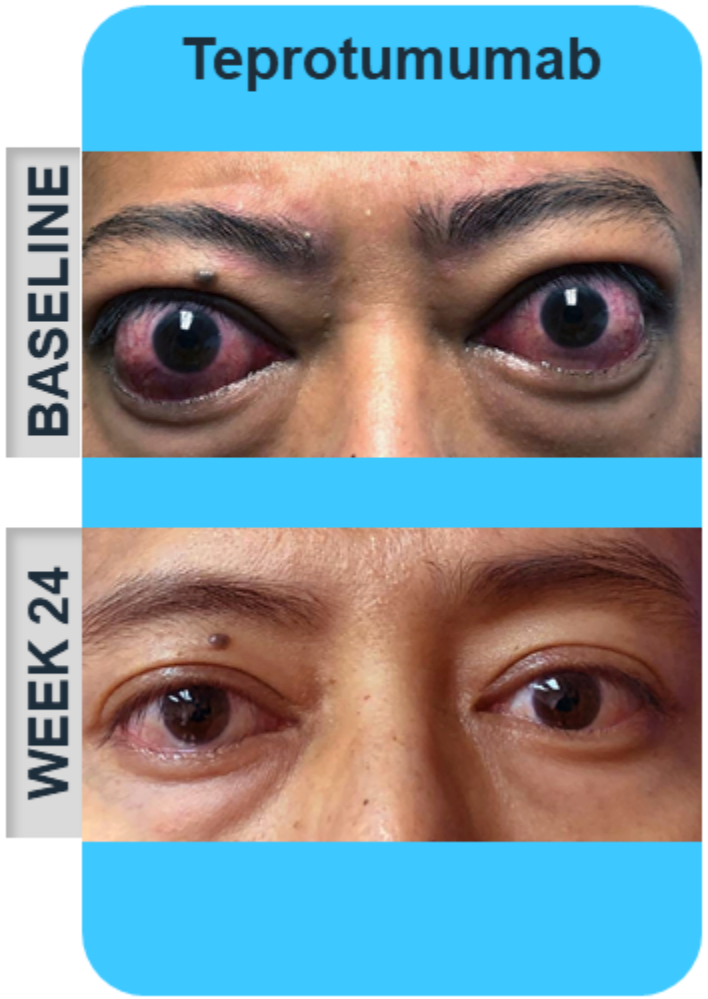
Example of Patient in Clinical Program – Teprotumumab



	Study Eye (RIGHT)			Fellow Eye (LEFT)		
	Baseline	Week 24	CFB	Baseline	Week 24	CFB
Proptosis (mm)	24	19	-5	24	19	-5
Diplopia	0	0	0	0	0	0
CAS	5	1	-4	5	1	-4

CFB: change from baseline; CAS: Clinical Activity Score
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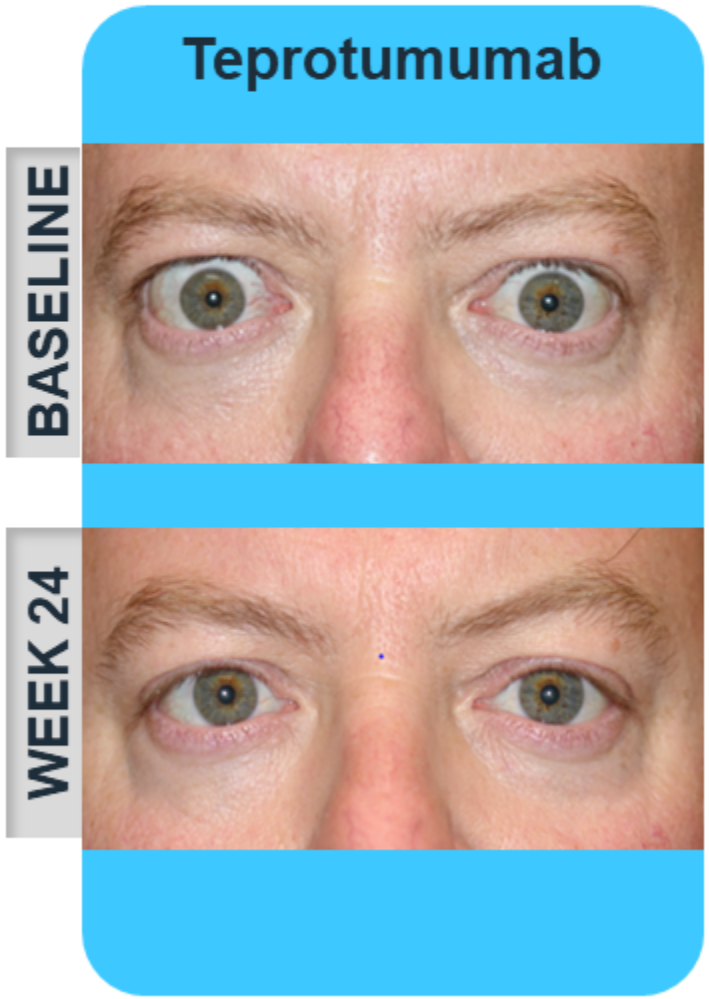
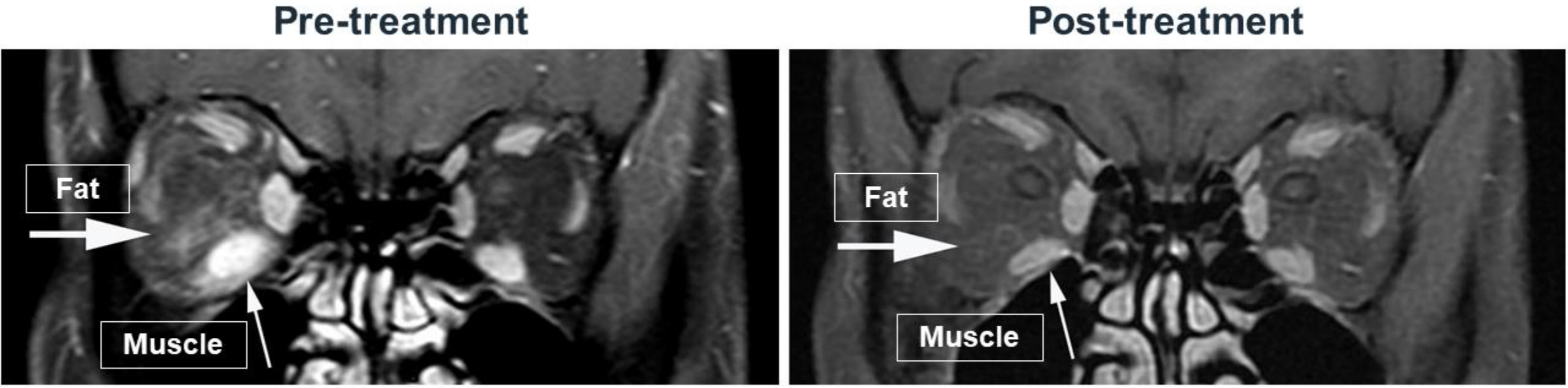
Example of Patient in Clinical Program – Teprotumumab



	Study Eye (RIGHT)			Fellow Eye (LEFT)		
	Baseline	Week 24	CFB	Baseline	Week 24	CFB
Proptosis (mm)	25	22	-3	24	21	-3
Diplopia	1	0	-1	1	0	-1
CAS	6	0	-6	6	0	-6

CFB: change from baseline; CAS: Clinical Activity Score
Photos provided with permission from patients of Dr. Douglas

MRI Demonstrates Improved Orbital Muscle and Fat Effects After Teprotumumab Treatment



Teprotumumab Provides Substantial Benefits for Patients with Thyroid Eye Disease

- Rapid onset with continued improvement through 24-week treatment period
  - Visible and patient perceived improvement at first assessment at 6 weeks
- Depth of effect
  - Average results similar to surgery, reversing natural history of Thyroid Eye Disease
- Favorable safety profile
  - Few discontinuations

Conclusions

- First effective treatment for Thyroid Eye Disease
- Single 6-month course led to prolonged response in patients who responded
- Appropriate first-line therapy

Teprotumumab for Treatment of Thyroid Eye Disease

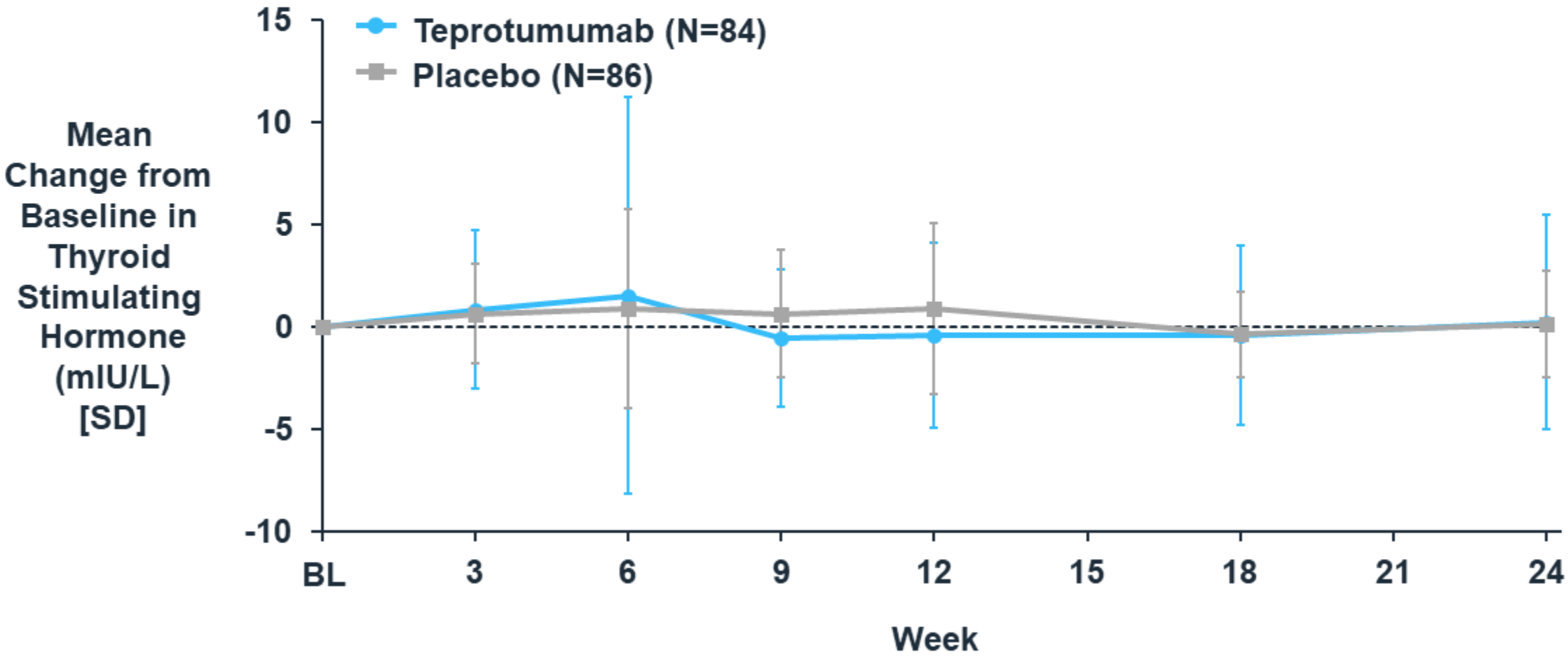
December 13, 2019

Horizon Therapeutics

Dermatologic and Ophthalmic Drugs Advisory Committee

BACK-UP SLIDES

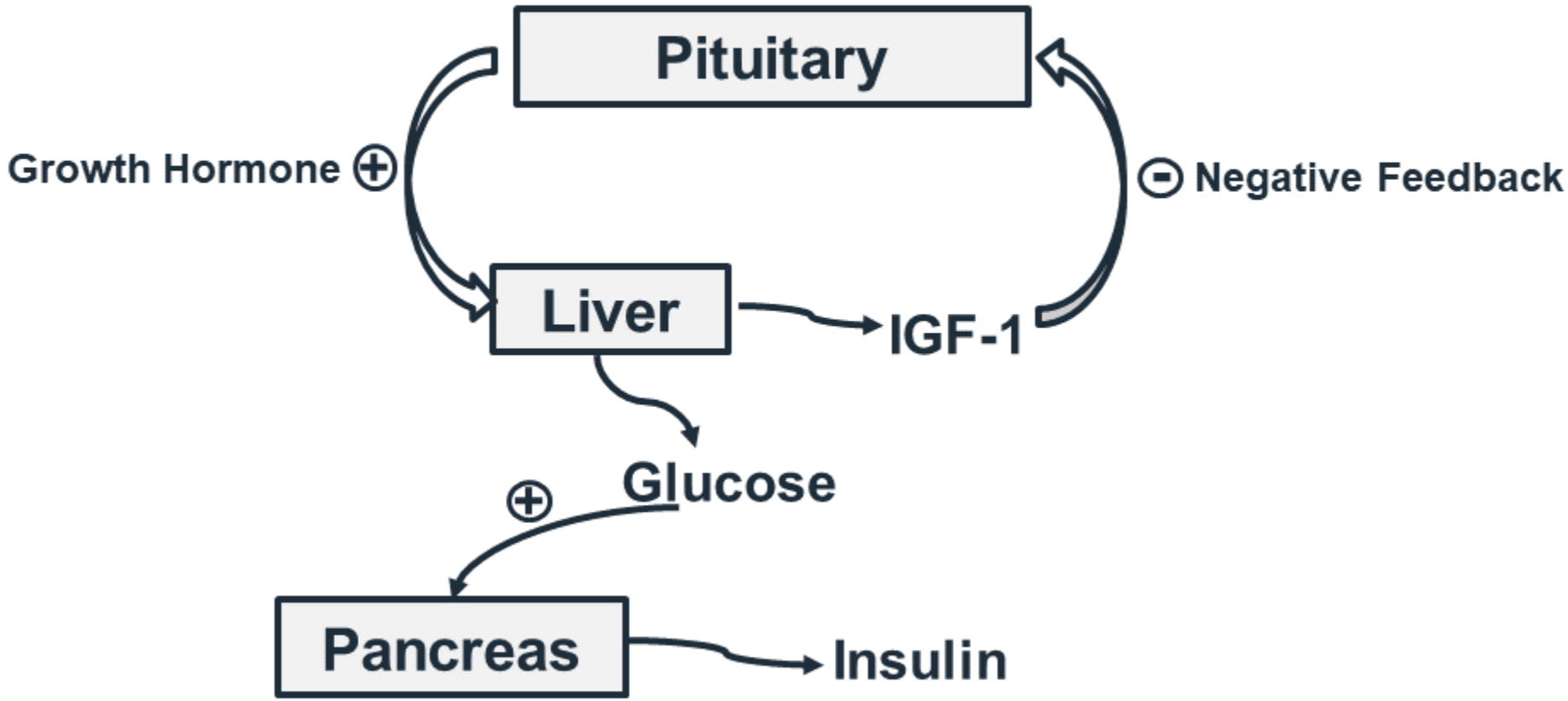
Pooled Studies: Change from Baseline in Thyroid Stimulating Hormone



Commonly Used Concomitant Medications were for Thyroid Disease

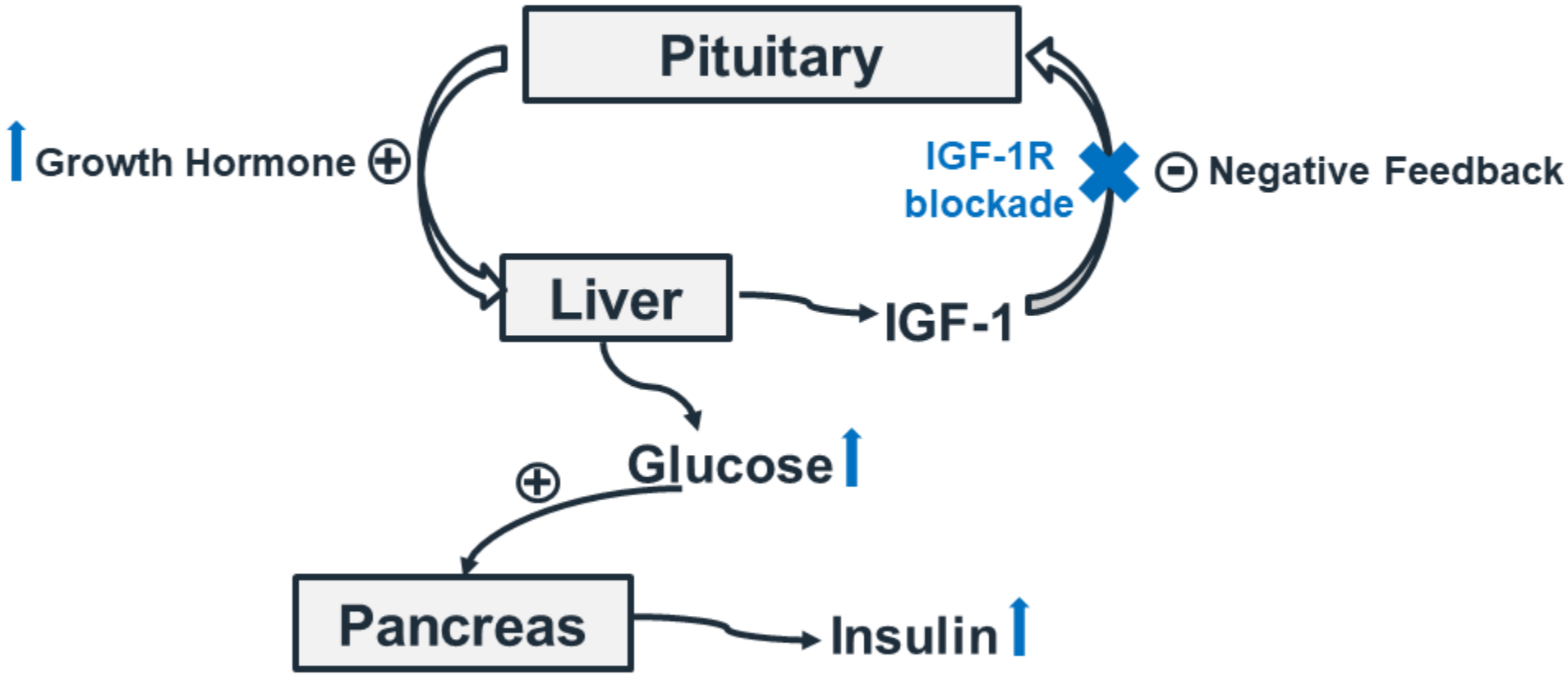
	Double-Masked Population	
	Teprotumumab N=84 (%)	Placebo N=86 (%)
Sulfur-containing Imidazole for Graves' Disease	44.0%	53.5%
Thyroid Hormones for Hypothyroidism	54.8%	43.0%

Hyperglycemia: Mechanistic Plausibility Due to IGF-1R Inhibition



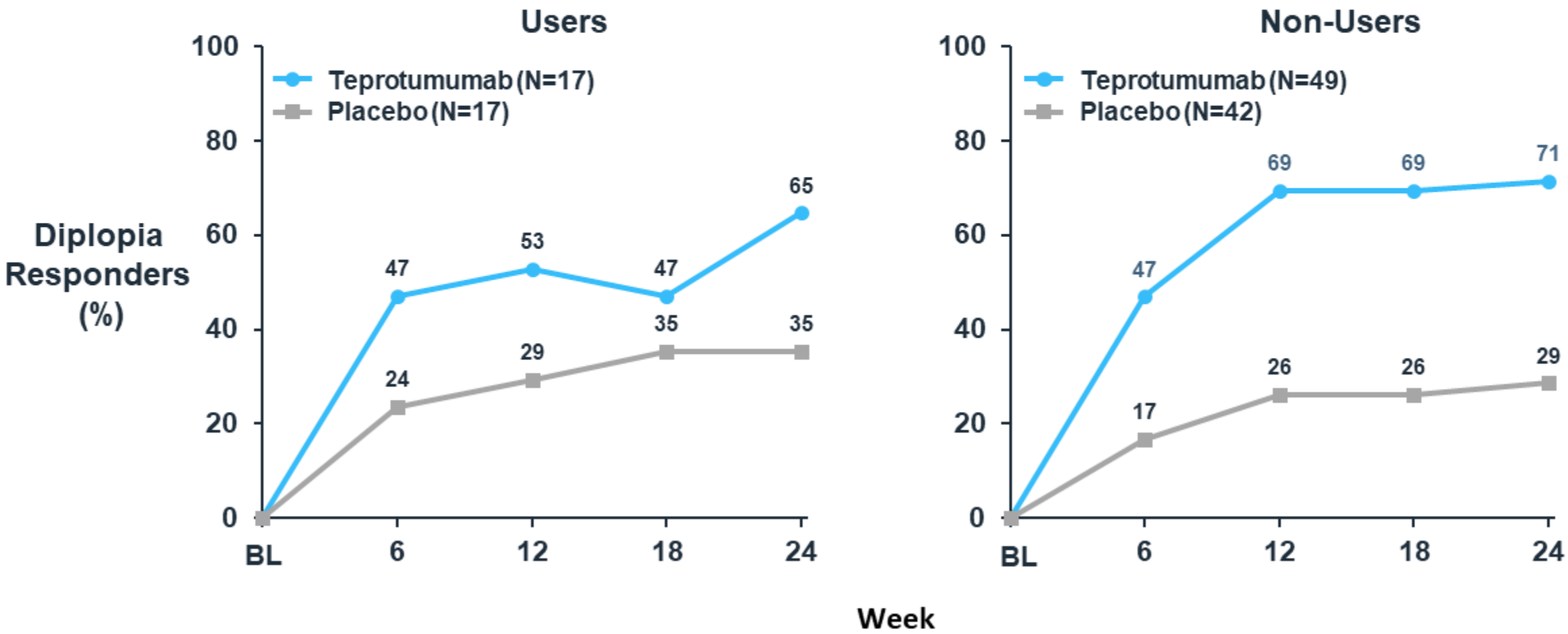
- IGF-I production by the liver entails stimulation by growth hormone
- IGF-I negatively regulates growth hormone secretion by the pituitary

Hyperglycemia: Mechanistic Plausibility Due to IGF-1R Inhibition

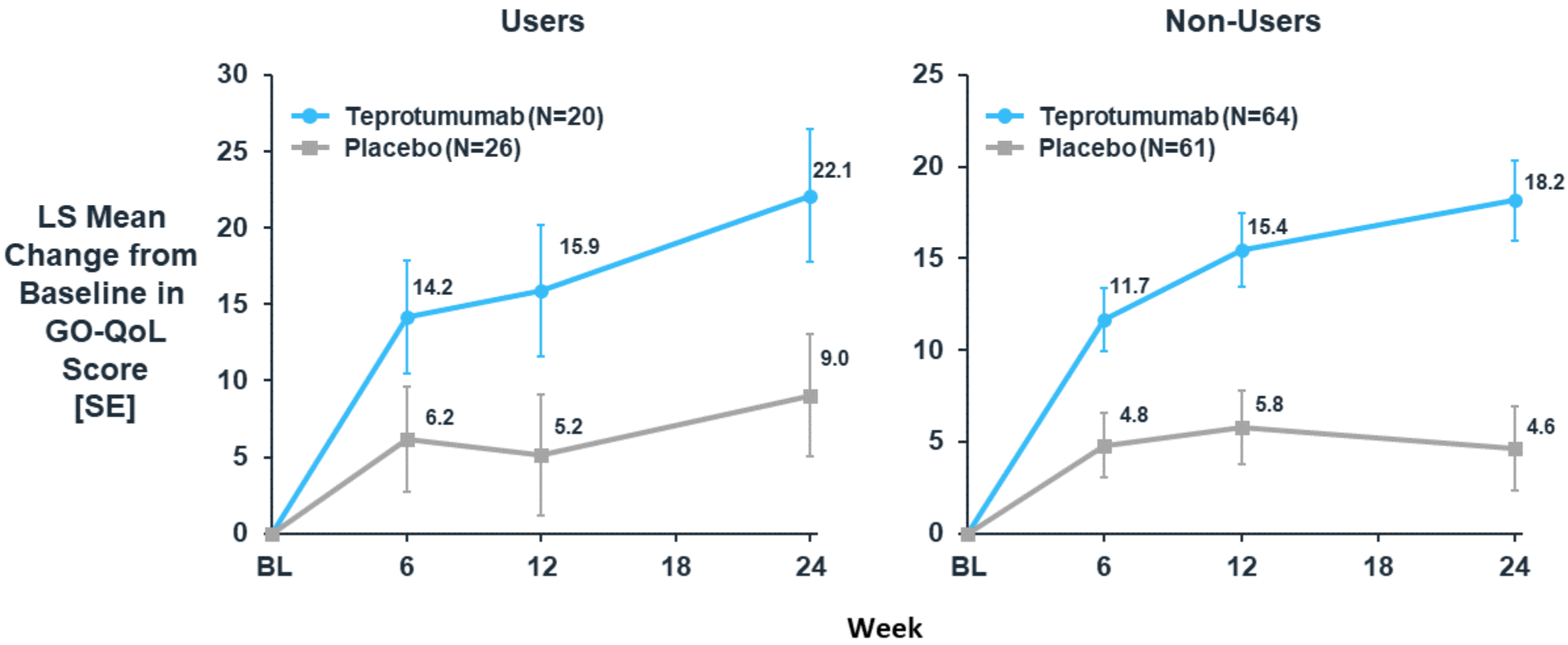


- IGF-1R blockade could cause loss of feedback inhibition, leading to greater glucose and insulin levels

Diplopia Response by Tobacco Use Status (Pooled Analysis)



Improvement in GO-QOL by Tobacco Use (Pooled Analysis)



Hearing Impairment in Oncology Studies

Oncology Study No.	Study Population	Study Design	SMQ Hearing impairment n/N (%)
BO19373	Advanced solid tumors	Open-label MAD	3/97 (3%)
NO21157	Age ≥ 2 years; recurrent or refractory sarcomas	Open-label	9/317 (3%)
NO21160	Stage 3b/4 NSCLC	RCT in combo with erlotinib	5/116 (4%)
NO21746	Stage 3b/4 NSCLC	Open-label in combo with erlotinib	1/34 (3%)
NO22068	Advanced malignancies	Open-label in combo with different standard chemo	6/104 (6%)
NP22002	Early breast CA prior to surgery	Open-label, single dose	1/8 (13%)

No hearing impairment in NO21200 (N=34), NO21161 (N=6), NO21884 (N=11)

Pooled Studies: Patients Who Received Radioactive Iodine Therapy at Baseline and Proptosis Responders

Patients Who Received Radioactive Iodine	Double-Masked Population	
	Teprotumumab N=9	Placebo N=9
Responders	9 (100%)	0
Non-responders	0	9 (100%)

Patients in OPTIC-X Who also had Muscle Spasm in Study 2

- 2 patients in OPTIC-X who previously received Teprotumumab in Study 2 experienced mild muscle spams in Study 2
- Upon re-treatment they also reported an event of muscle spams with no change in severity

Exclusion of Bleeding Diathesis in the Thyroid Eye Disease Program

- Patients with bleeding diathesis were excluded in the Thyroid Eye Disease program based on the adverse events of anemia and thrombocytopenia seen in the Oncology Program
- There were no clinically meaningful thrombocytopenia or anemia seen in the Thyroid Eye Disease program
- This exclusion criteria was removed for OPTIC-X

Overall Risk Difference by AESIs

	Teprotumumab N=84	Placebo N=86	Risk Difference (95% CI)
Any hyperglycemia	9.5%	1.2%	8.4% (1.7, 15.0)
Infusion-related reaction	7.1%	4.7%	2.5% (-4.6, 9.6)
Muscle spasm	25%	7%	18.0% (7.3, 28.7)
Diarrhea	14.3%	8.1%	6.2% (-3.3, 15.6)
IBD	1.2%	0	1.2%
Hearing loss	9.5%	0	9.5%