WOO UNIVERSITY

Oculoplastics and TED: Advanced Care Update

Raymond Douglas, MD, PhD

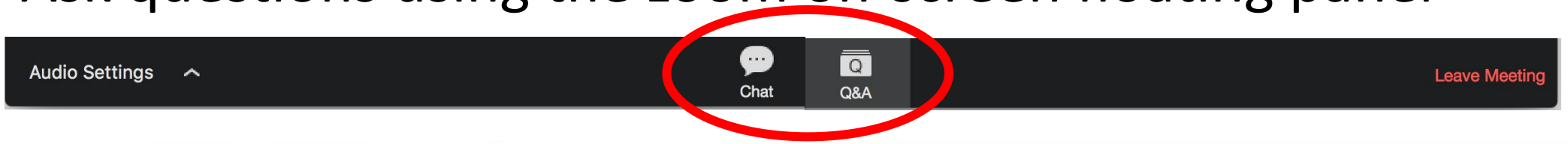
WOO UNIVERSITY

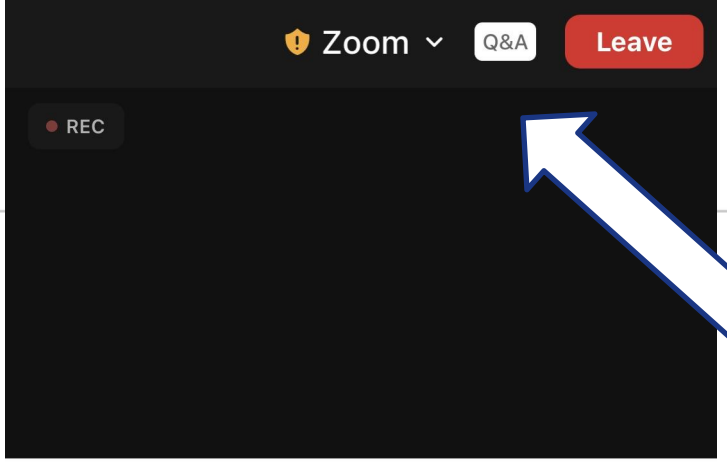
WELCOME!

Host: Dr. Elise Kramer

Thank you to Horizon Therapeutics for providing an unrestricted educational grant to support this event.

- For each hour of CE units, attendees must be online for a minimum of 50 minutes
- For a COPE certificate, please fill out the survey link in the chat. Also, the survey link will appear when the webinar ends.
- CE certificates will be delivered by email and sent to ARBO with OE tracker numbers
- We will also display a QR code at the end of the event if you have the OE tracker app on your phone.
- **CE certificates will be emailed within 4 weeks**
- Ask questions using the zoom on-screen floating panel





Opportunity to Partner

Optometrists are at the frontline to recommend treatment for cataract and glaucoma patients.

Established relationships with patients

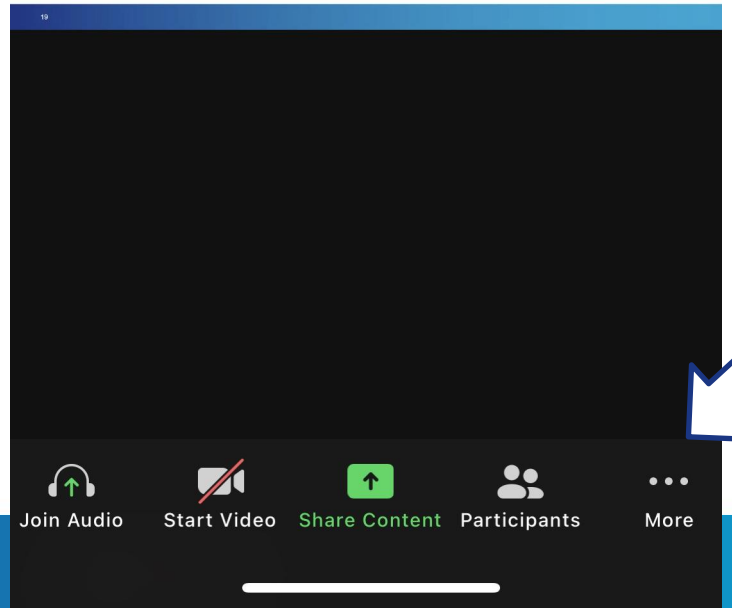
- Ability to inform patients of the best technologies available
- Needs, wants, expectations, and lifestyle

Reduce patient and physician burden

- Cost/pharmacy visits and prior authorizations
- Ocular surface disease and potential effects on visual acuity

Ability to impact patients' post-operative lifestyle

- ONE TIME opportunity during cataract surgery to address a patient's cataract, refractive needs (astigmatism and presbyopia) as well as their glaucoma



Speaker Bio –

Dr. Raymond Douglas, AKA “The Eye Guy,” is an experienced board-certified aesthetic and reconstructive oculoplastic specialist. Patients with Thyroid Eye Disease (TED), Graves’ Eye Disease, previous unsuccessful surgery, cancers of the eyelids or face and trauma-induced injuries seek Dr. Douglas’ expert, customized care at both his primary practice in Beverly Hills and international practice, LA Face, in Shanghai, China. His expertise in treating difficult cases of disfigurement due to thyroid-associated eye diseases, cosmetic and reconstruction surgeries has made him a highly respected educational and surgical authority for both reconstructive and cosmetics arts of facial plastics.

Dr. Douglas graduated with academic distinction from the University of Pennsylvania where he began his medical training and PhD in immunology and autoimmune inflammatory disorders. He went on to complete a sub-specialized fellowship in Orbital Facial Plastic and Reconstructive Surgery at the UCLA Jules Stein Eye Institute. To date, he has held several prestigious positions at the UCLA School of Medicine, Harbor-UCLA Medical Center, Greater Los Angeles Veterans Hospital, Veterans Administration Ann Arbor Healthcare System and the University of Michigan Kellogg Eye Center. He is also Chief Medical Officer for Flowmetric Inc., a medical device company developing aging and inflammation testing for the consumer market to launch in 2020.

In addition to his private practices, Dr. Douglas is a clinical research author, advocate and educator internationally recognized for his groundbreaking research on treatments and restorative surgical techniques for Thyroid Eye Disease. While traditional surgery focuses solely on the functional issues of TED, Dr. Douglas has pioneered a specific technique (Aesthetic Orbital Decompression, AKA “Eye Lipo”), which addresses both eye aesthetic and function. This precise and artistic corrective approach has enabled patients a significantly quicker recovery time with less scarring and reduced risk of complications.

Financial Disclosures

- Former Consultant/Speaker for Horizon Therapeutics
- Former Consultant for Viridian Therapeutics
- Chief Scientific Officer Sling Therapeutics

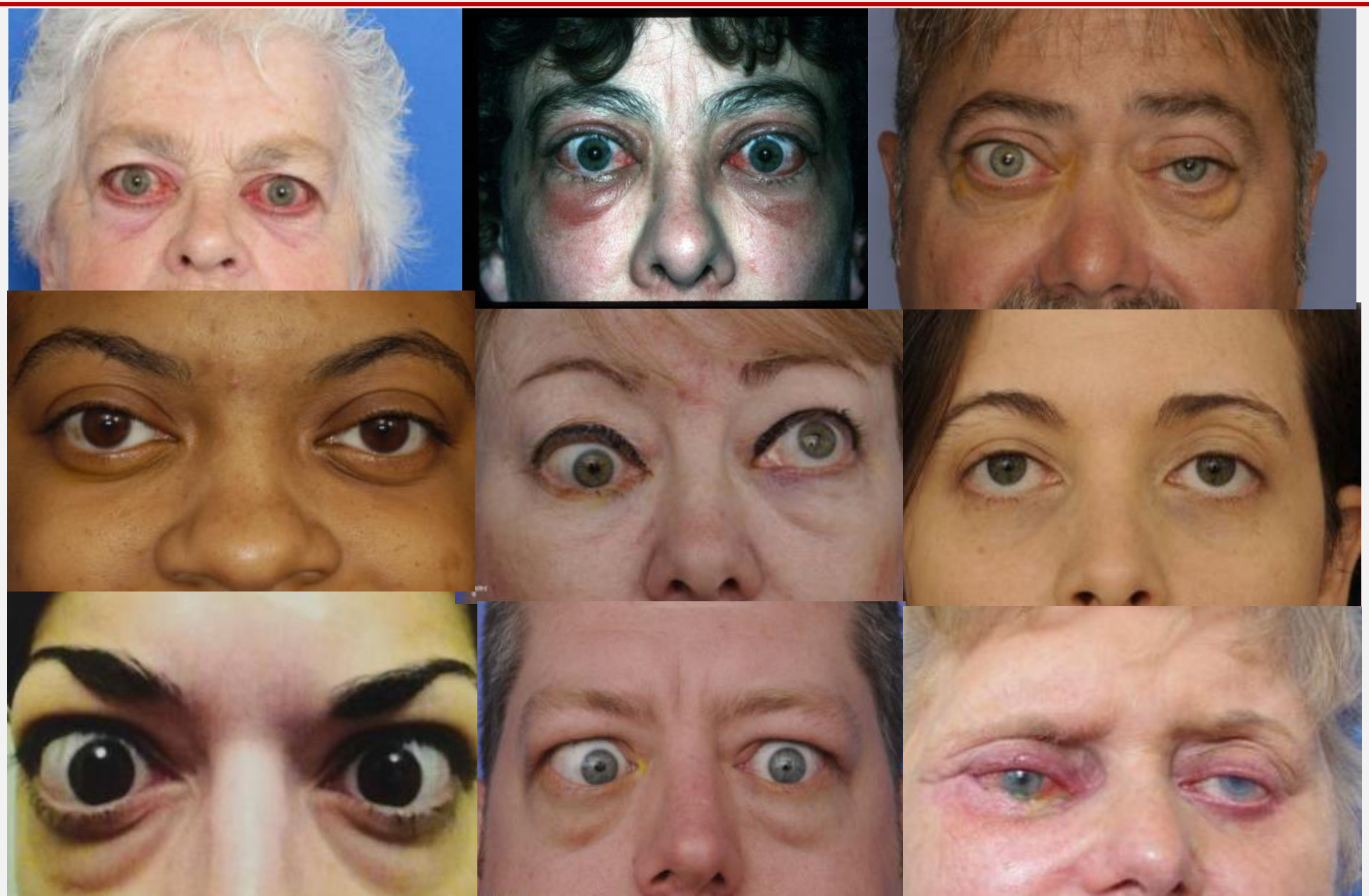
All financial relationships have been mitigated.

FINANCIAL DISCLOSURE :

CONSULTANT FOR NOVEL TED THERAPIES:

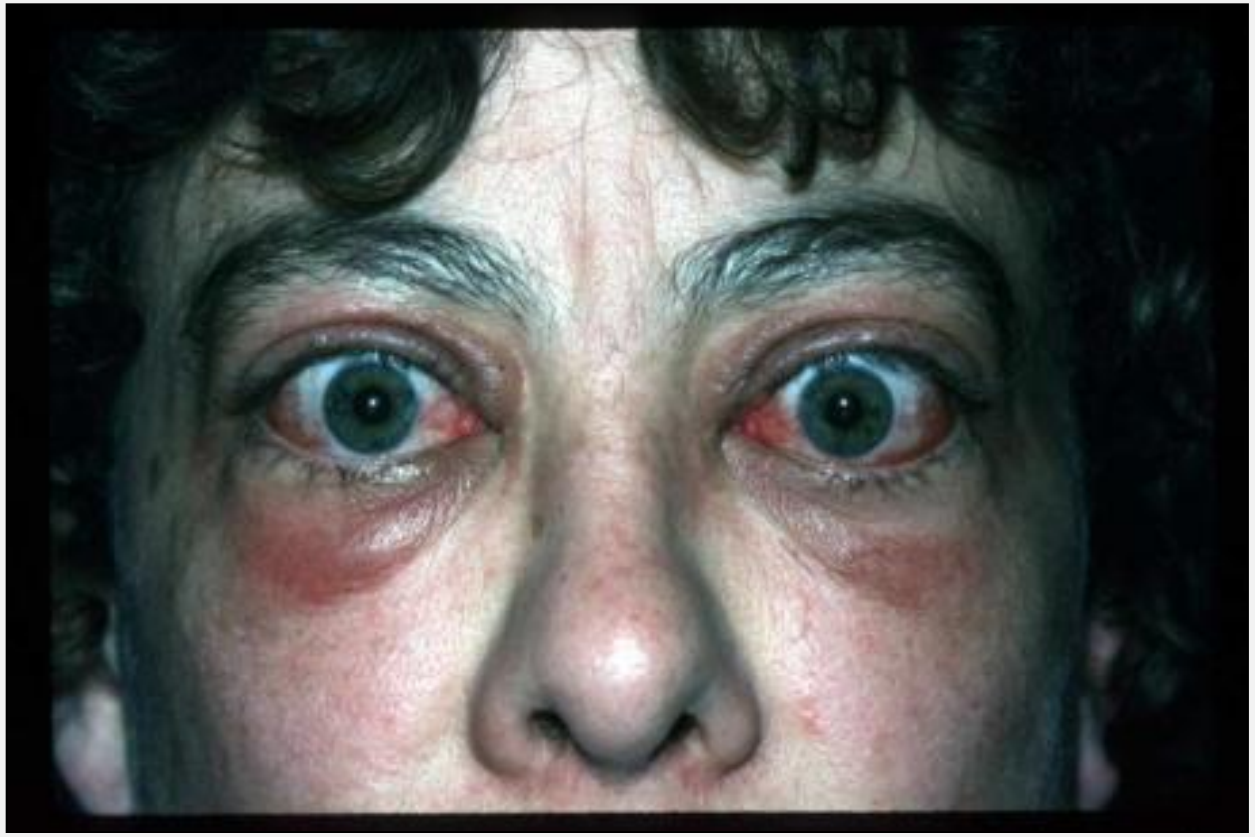
HORIZON PHARMA
IMMUNOVANT CORP
VERIDIAN CORP

The Faces of Thyroid Eye Disease



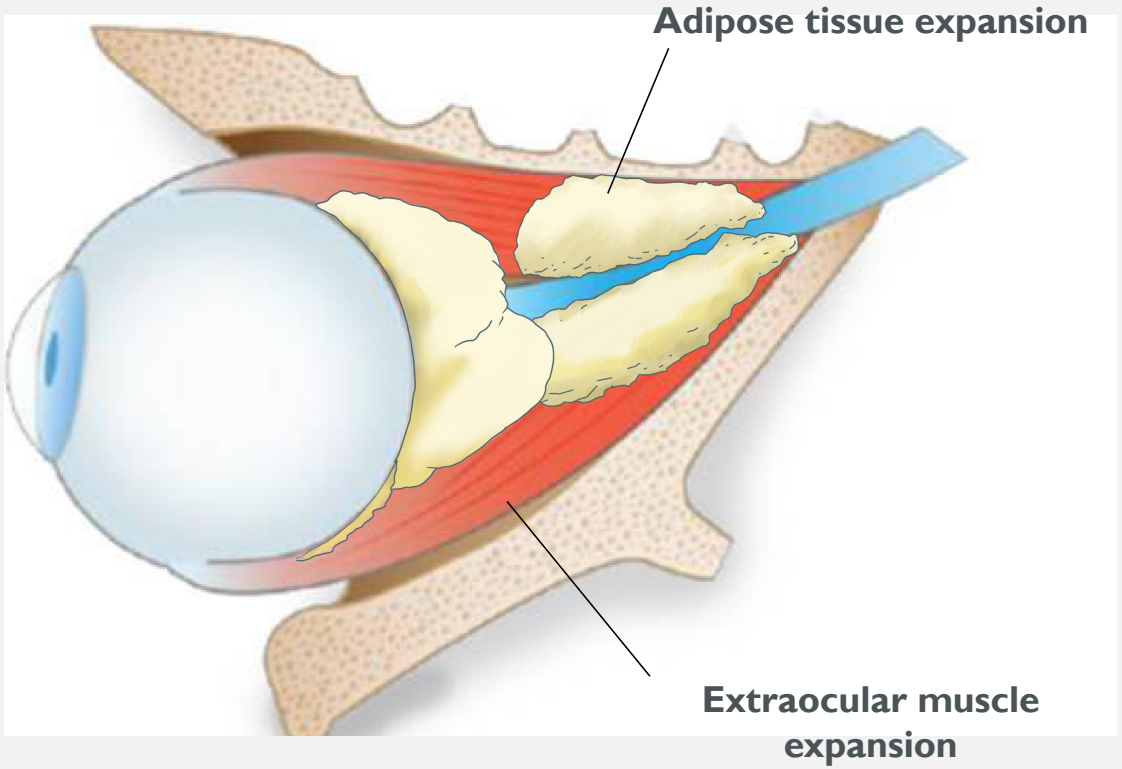
THYROID EYE DISEASE

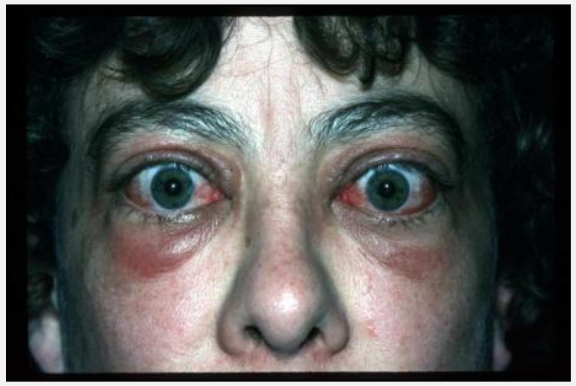
- Most commonly associated with Graves hyperthyroidism
- 80% develop TED within 18 months of GD diagnosis
- F > M
- Proptosis, eyelid retraction, strabismus, eyelid edema, chemosis, caruncular edema, compressive optic neuropathy



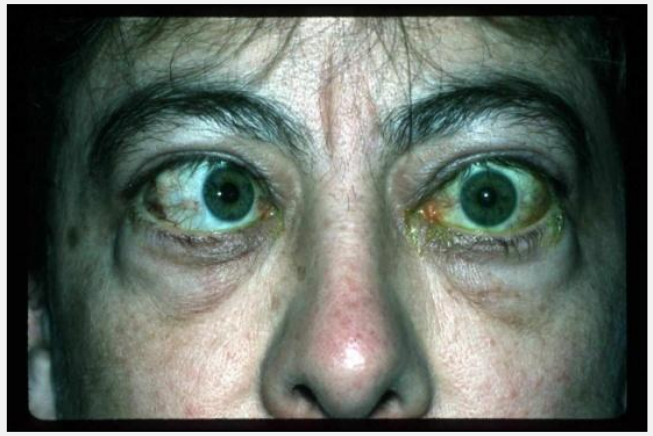
TED: INFLAMMATION, TISSUE EXPANSION, AND REMODELING IN THE ORBIT

Increased pressure in the fixed bony orbit causes short-term inflammation and long-term consequences





Active



Inactive

Disease

Inflammation → Fibrosis

18-24m

5-7yrs

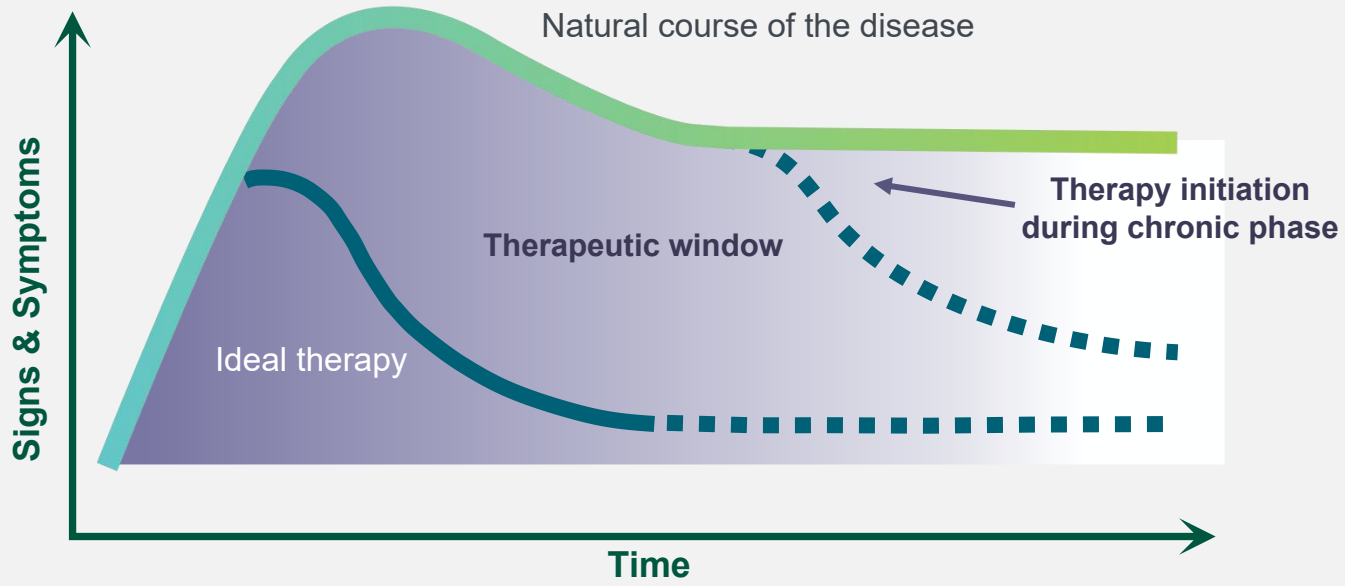
Time

ACUTE AND CHRONIC TED

Traditional Characterization of Acute and Chronic TED

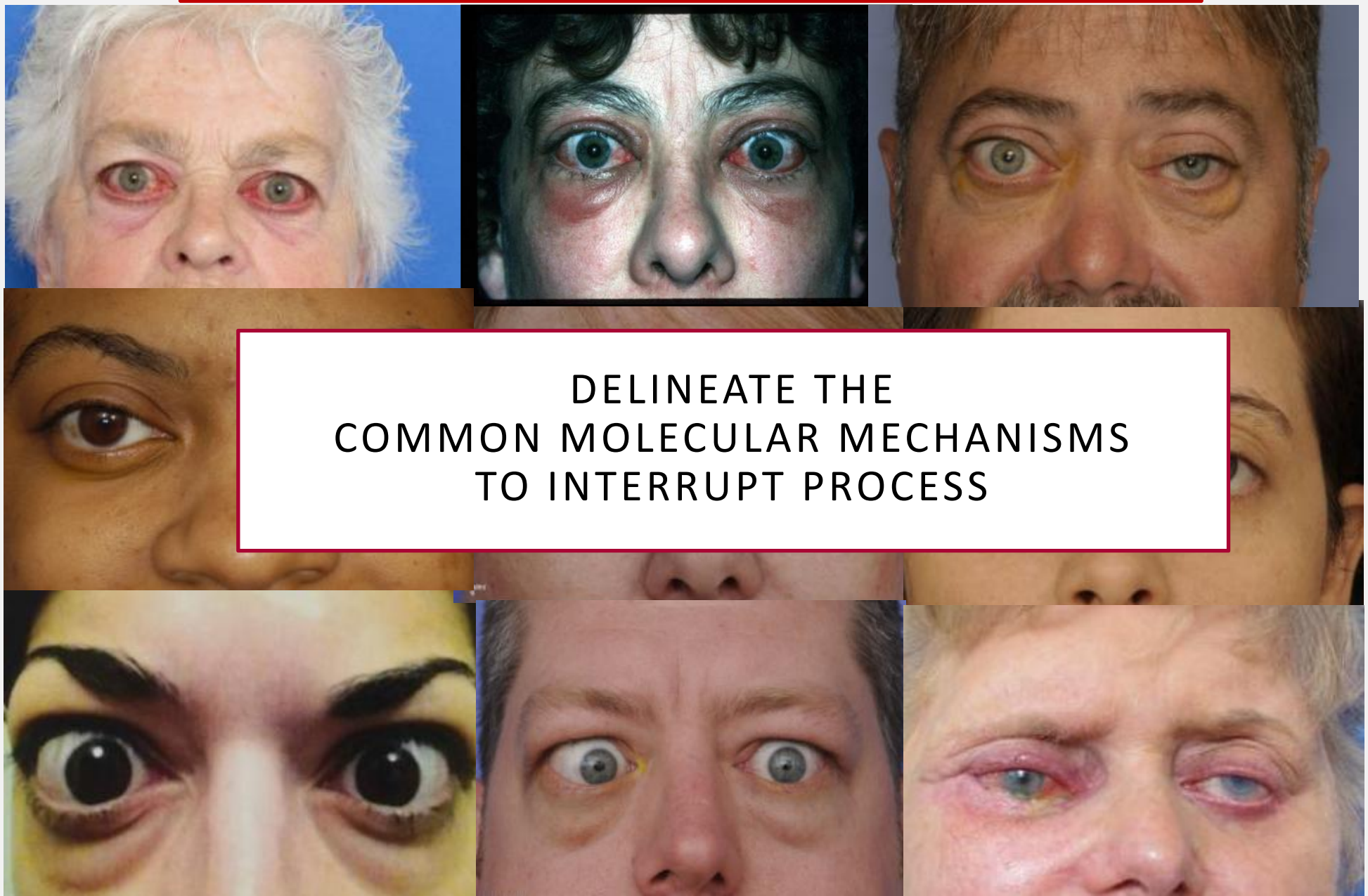
	Time Since Diagnosis	Signs and Symptoms
Acute	2 years or less	Progressive/changing symptomatology (proptosis, diplopia, inflammatory signs/symptoms)
Chronic	>2 years	Stable/nonchanging proptosis, diplopia, inflammatory signs/symptoms

Natural History of TED



PATHOGENESIS

Heterogeneous disease



DELINEATE THE
COMMON MOLECULAR MECHANISMS
TO INTERRUPT PROCESS

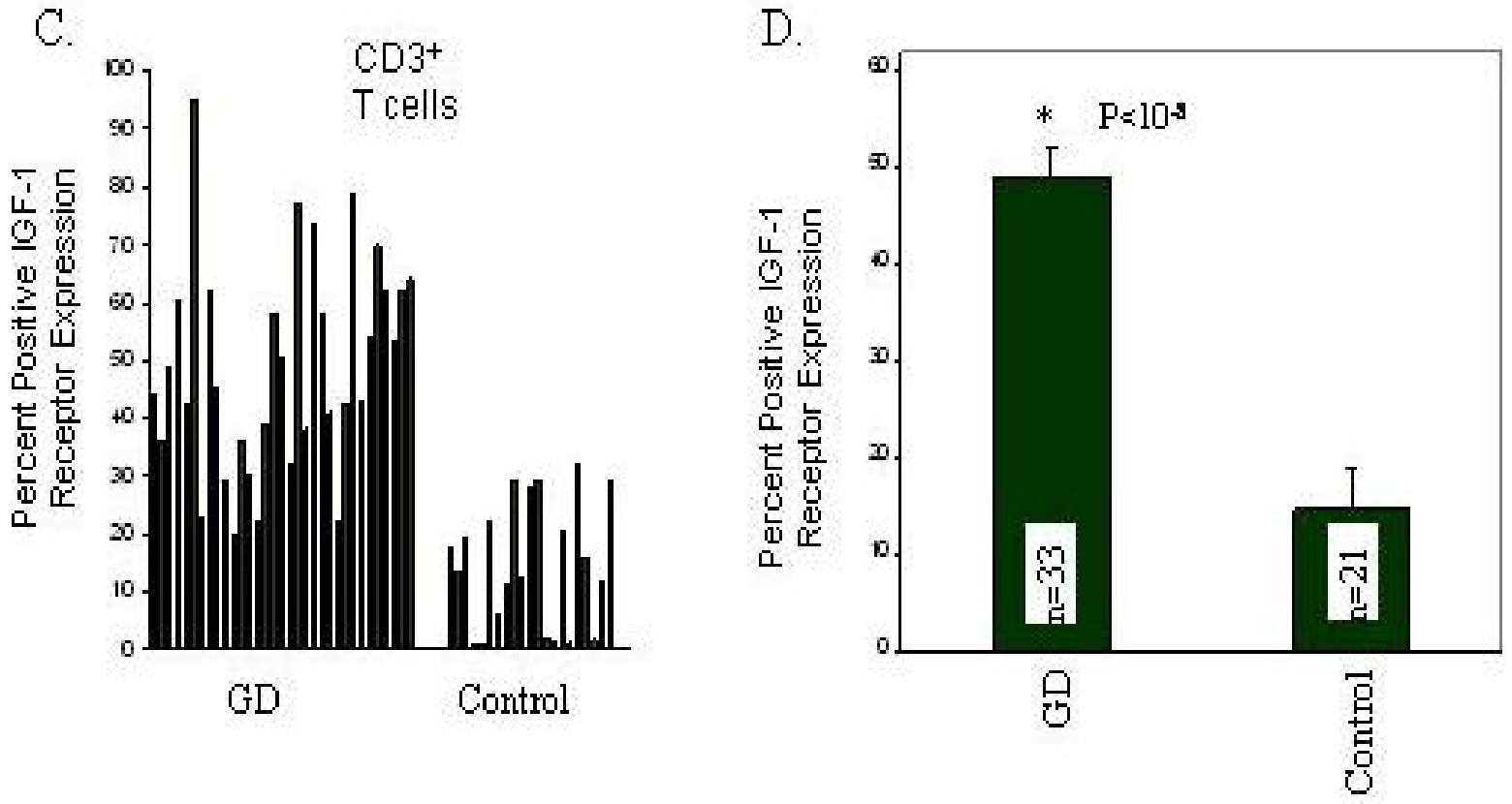
Heterogeneous disease

DELINEATE THE
COMMON MOLECULAR
MECHANISMS
TO INTERRUPT PROCESS

INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR

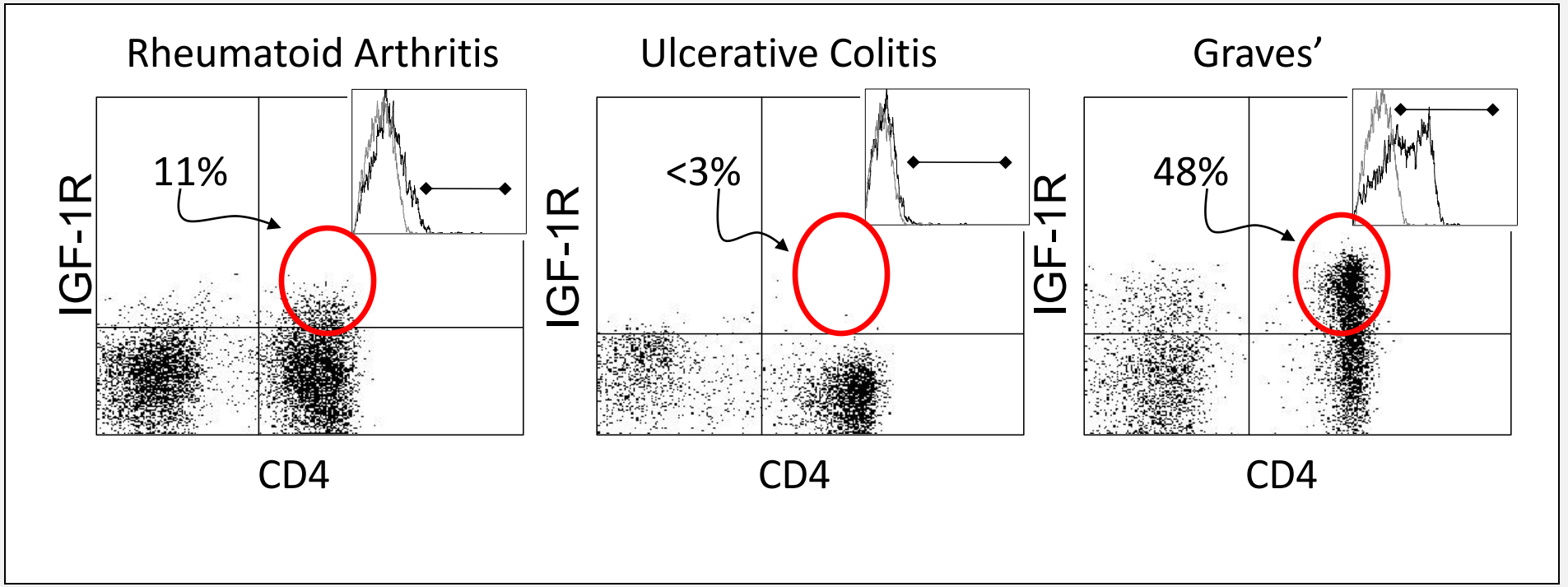
- Overexpressed on Graves' Disease (GD) fibroblasts
- Signaling of fibroblasts and immune cells mimics pathologic findings
- Antibodies to these receptors in GD patients

IGF-1R OVEREXPRESSION IS A HALLMARK OF GD

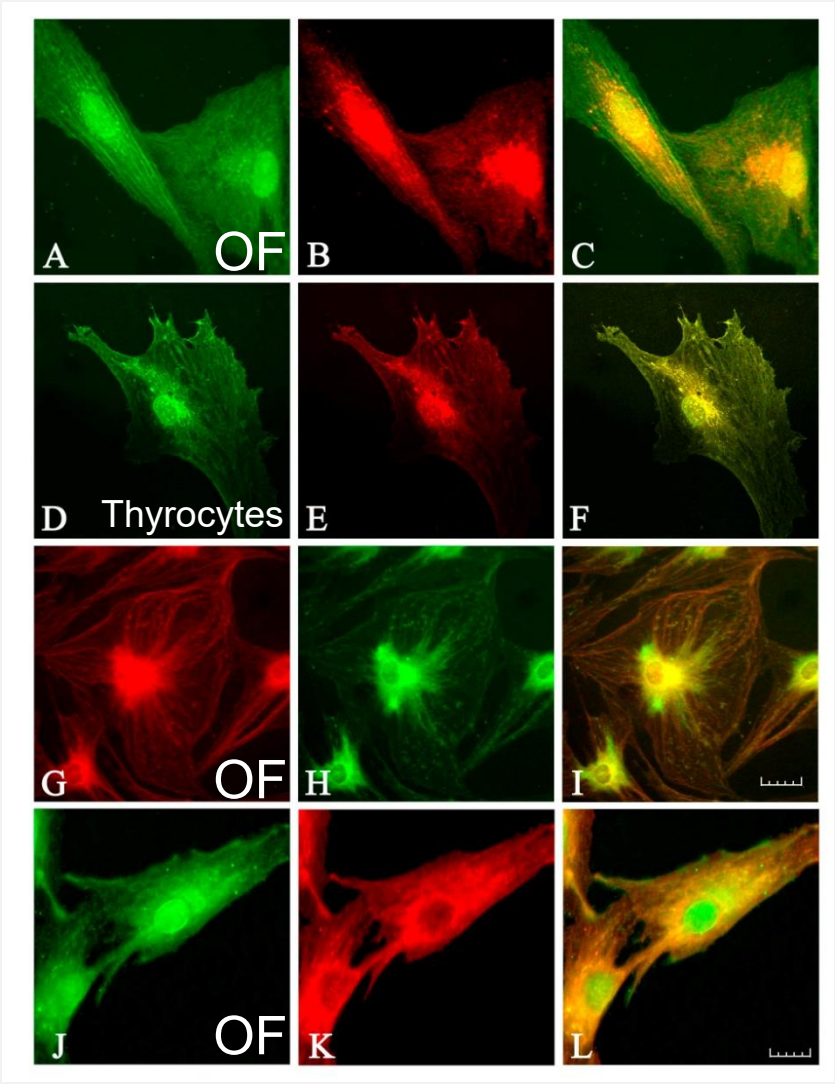


Douglas RS, et al. *J Immunology,* 2007. 178(5):3281-3287.

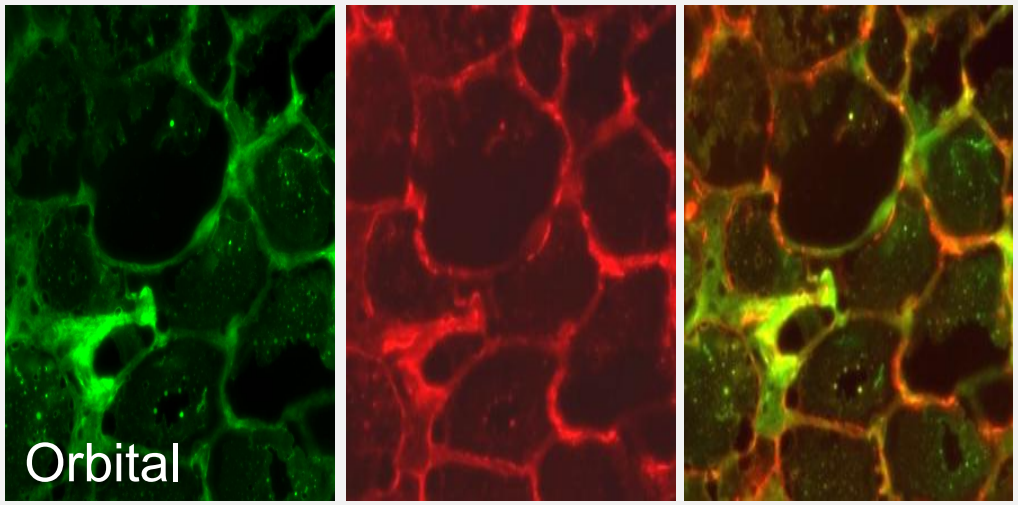
IGF-1R$^+$ T CELLS ARE MORE FREQUENT IN GRAVES DISEASE BUT NOT ALL AUTOIMMUNE DISEASES

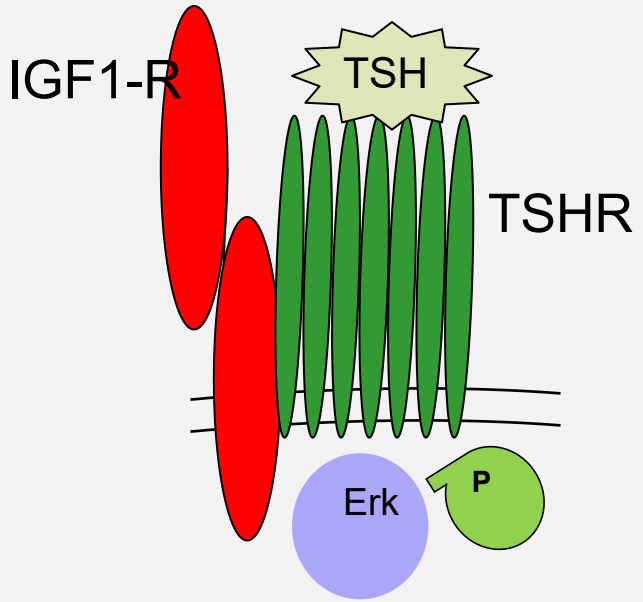


TSH-R and IGF-1R interact

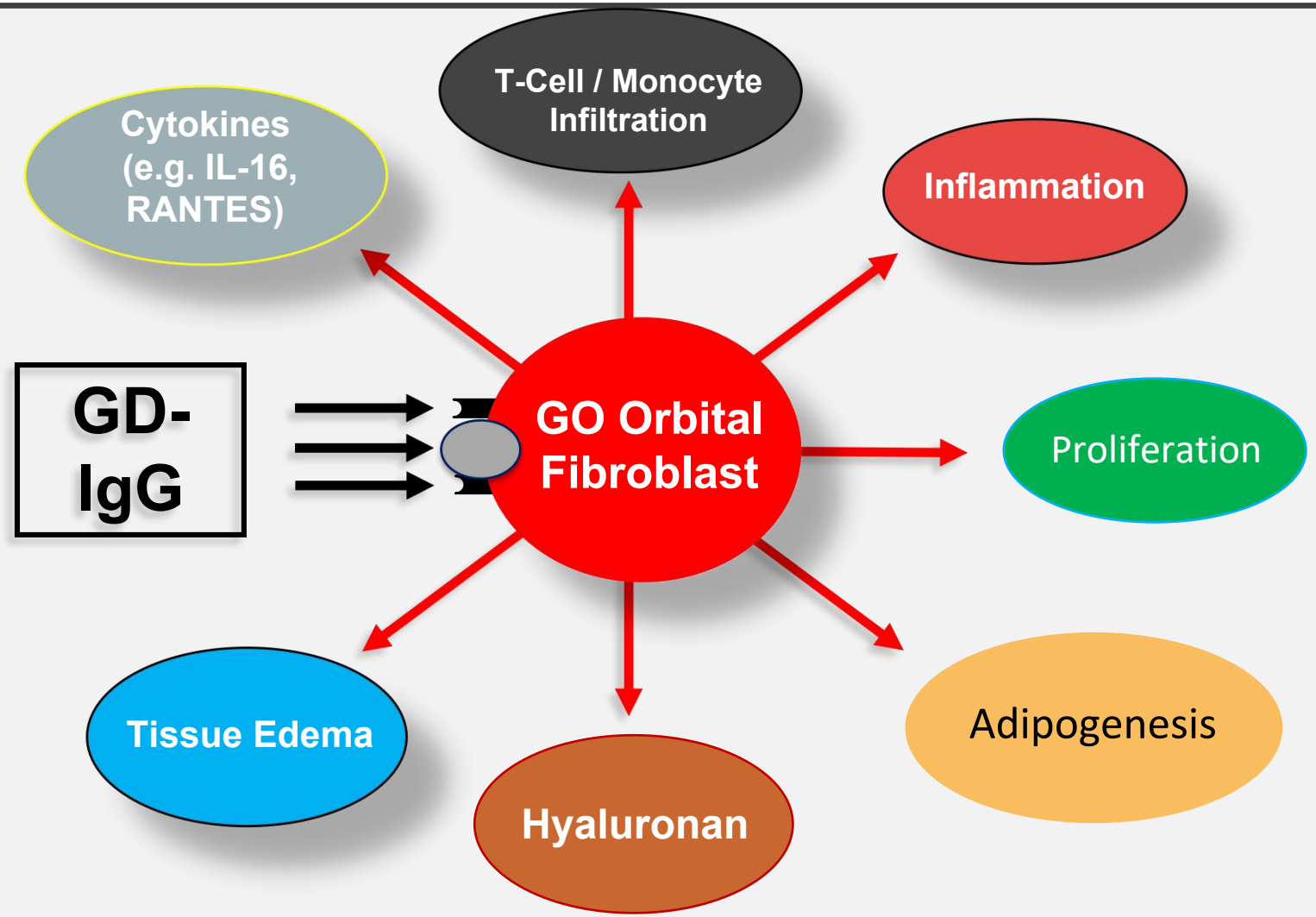


J Immunology, 2008



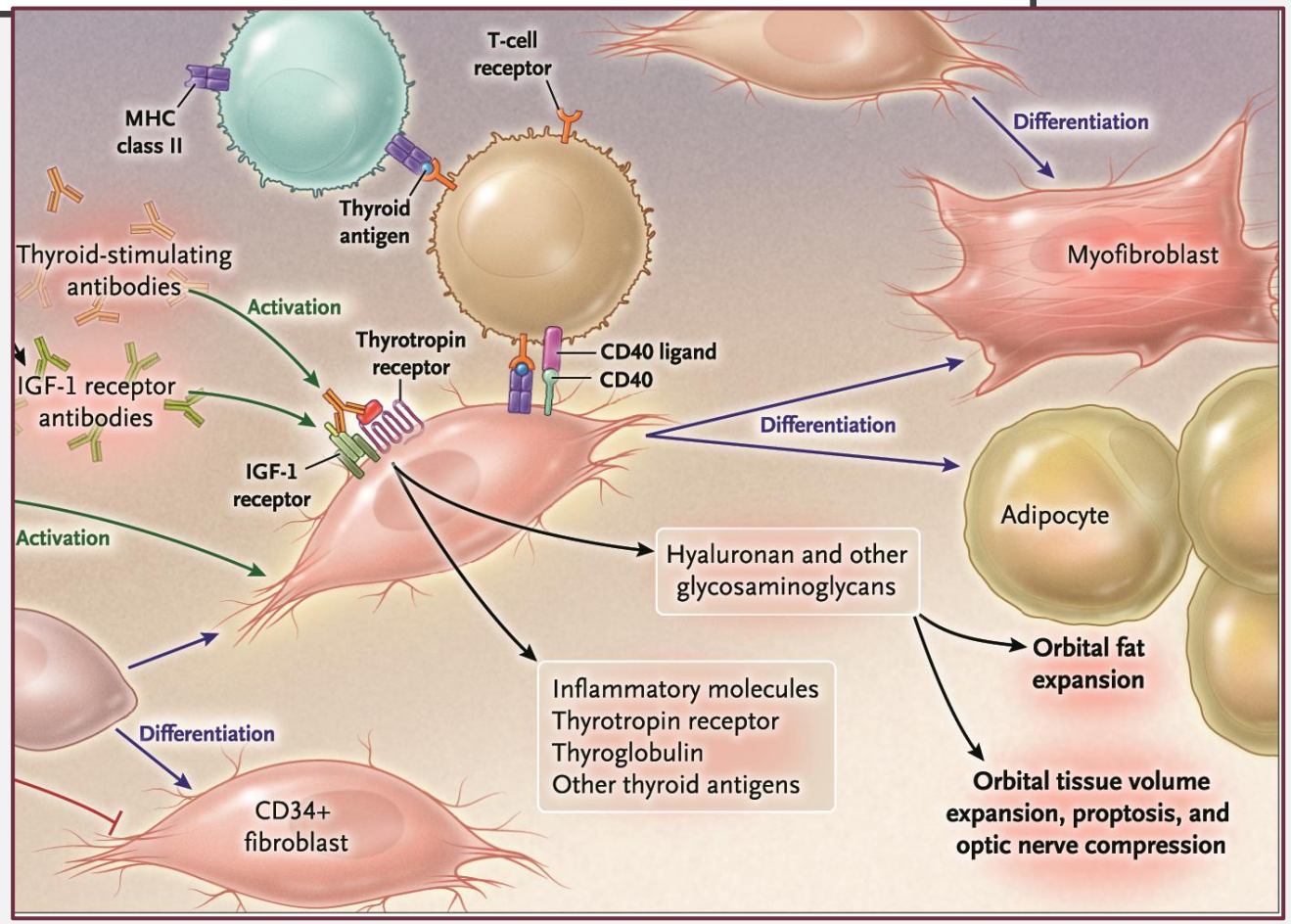


THYROID EYE DISEASE: MECHANISM



THYROID EYE DISEASE (TED) IS DRIVEN BY AUTOANTIBODY ACTIVATION OF IGF-1R

- IGF-1R is overexpressed in TED orbital fibroblasts[12]
- Activation of IGF-1R stimulates release of inflammatory cytokines and production of hyaluronan[13,14]
- IGF-1R and TSHR colocalize in orbital fibroblasts[12]



From *The New England Journal of Medicine*, Terry J. Smith, Laszlo Hegedüs, Graves' disease, 375, 1556.

CD, cluster of differentiation; IGF-1R, insulin-like growth factor-1 receptor; MHC, major histocompatibility complex; TSHR, thyroid-stimulating hormone receptor.

CONVENTIONAL VS NOVEL TREATMENT

TREATMENT FOR THYROID EYE DISEASE (TED) SHOULD FOCUS ON LONG TERM CONSEQUENCES

Short-term Inflammation	
• Conjunctival chemosis	• Periorbital and lid erythema and edema
• Conjunctival redness	• Lid retraction (upper and lower)
• Keratoconjunctivitis sicca	• Exposure keratopathy
• Photophobia	• Lagophthalmos
• Foreign body sensation	• Lid lag
• Pain	• Orbital ache

Long-term Consequences	
• Lid retraction	• Strabismus
• Exposure keratopathy	• Diplopia
• Corneal ulceration	• Dysthyroid optic neuropathy
• Severe dry eye	• Decrease in visual acuity
• Proptosis	• Color vision deficiency
• Retro-orbital ache	• Visual field defect

What Conventional Treatments Exist?

EUGOGO RECOMMENDED STEROID REGIMEN

- The currently recommended regimen for IV glucocorticoid therapy is a cumulative dose of 4.5 g of methylprednisolone, divided into 12 weekly infusions (6 weekly infusions of 0.5 g, followed by 6 weekly infusions of 0.25g)

Bartalena L et al. *Eur Thyroid J*. 2016;5:9-26

Research

JAMA Ophthalmology | Original Investigation

Proptosis and Diplopia Response With Teprotumumab and Placebo vs the Recommended Treatment Regimen With Intravenous Methylprednisolone in Moderate to Severe Thyroid Eye Disease

A Meta-analysis and Matching-Adjusted Indirect Comparison

Raymond S. Douglas, MD, PhD; Roger Dailey, MD; Prem S. Subramanian, MD, PhD; Giuseppe Barbesino, MD; Shoaib Ugradar, MD; Ryan Batten, MSc; Rana A. Qadeer, MSc; Chris Cameron, MSc, PhD

IMPORTANCE Thyroid eye disease can be a debilitating autoimmune disorder characterized by progressive proptosis or diplopia. Teprotumumab has been compared with placebo in randomized clinical trials, but not with intravenous methylprednisolone (IVMP), which sometimes is used in clinical practice for this condition.

Invited Commentary

Supplemental content

Douglas RS et al, JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2021.6284
Published online February 17, 2022.

STUDIES USING THE RECOMMENDED EUGOGO IV STEROID REGIMEN

Author, year	N (week 12)	Study design and patient population	Baseline proptosis	Adverse events (AEs)
Kahaly 2005	35	Randomized, single-blind; euthyroid; TED duration <6mths	23.75 ± 2.14	8 AEs were reported in 6 patients, of which palpitations were the most common.
Aktaran 2007	25	Prospective randomized, single-blind; euthyroid; TED duration <6mths	22.2 ± 2	Weight gain was the most commonly reported AE. 12% of patients had palpitations and hot flashes on the day of treatment.
Bartalena 2012	54	Randomized, double-blind; euthyroid; mean TED duration 12.4mths	22.2 ± 3	Mild AEs were reported in 18 patients. Major AEs were reported in 3 patients: major depression, occurrence of diabetes mellitus requiring therapy and profound muscle weakness
Xing 2014	54	No immunosuppressives or radiotherapy in the previous 3mths; median TED duration 7mths	22.10 ± 2.76	Not reported
Yang 2015	31	Retrospective; euthyroid; no previous treatment for TED except local measures; median TED duration 7mths	23.04 ± 3.8	Mild AEs were observed in 14 patients. A major AE occurred in 1 patient who developed diabetes mellitus, requiring use of hyperglycemic medication.
Zhu 2014	38	Prospective randomized; no immunosuppressives or radiotherapy in the previous 3mth; mean TED duration 13.6mths	22.06 ± 3.17	Weight gain and hypokalemia were the most common AEs.
He 2017	15	Prospective randomized controlled; euthyroid; no previous IV methylprednisolone; median TED duration 7mths	17.2 ± 2.1	17 patients experienced AEs, of which weight gain and hidrosis were most common. No severe AEs occurred.
Kahaly 2018	73	Randomized, open-label; euthyroid; No immunosuppressives or corticosteroids in the previous 3mths; mean TED duration 15mths	21.27 ± 3.68	29 (19 grade 1 and 10 grade 2) treatment related AEs were reported in 20% of patients.
Li 2020	20	Prospective; euthyroid; No immunosuppressives, orbital radiotherapy or surgery; mean TED duration 8mths	18.9 ± 2.42	Weight gain was most common AE. Mild increase in BP and blood glucose was observed in a low proportion during therapy. No other severe AEs were recorded.

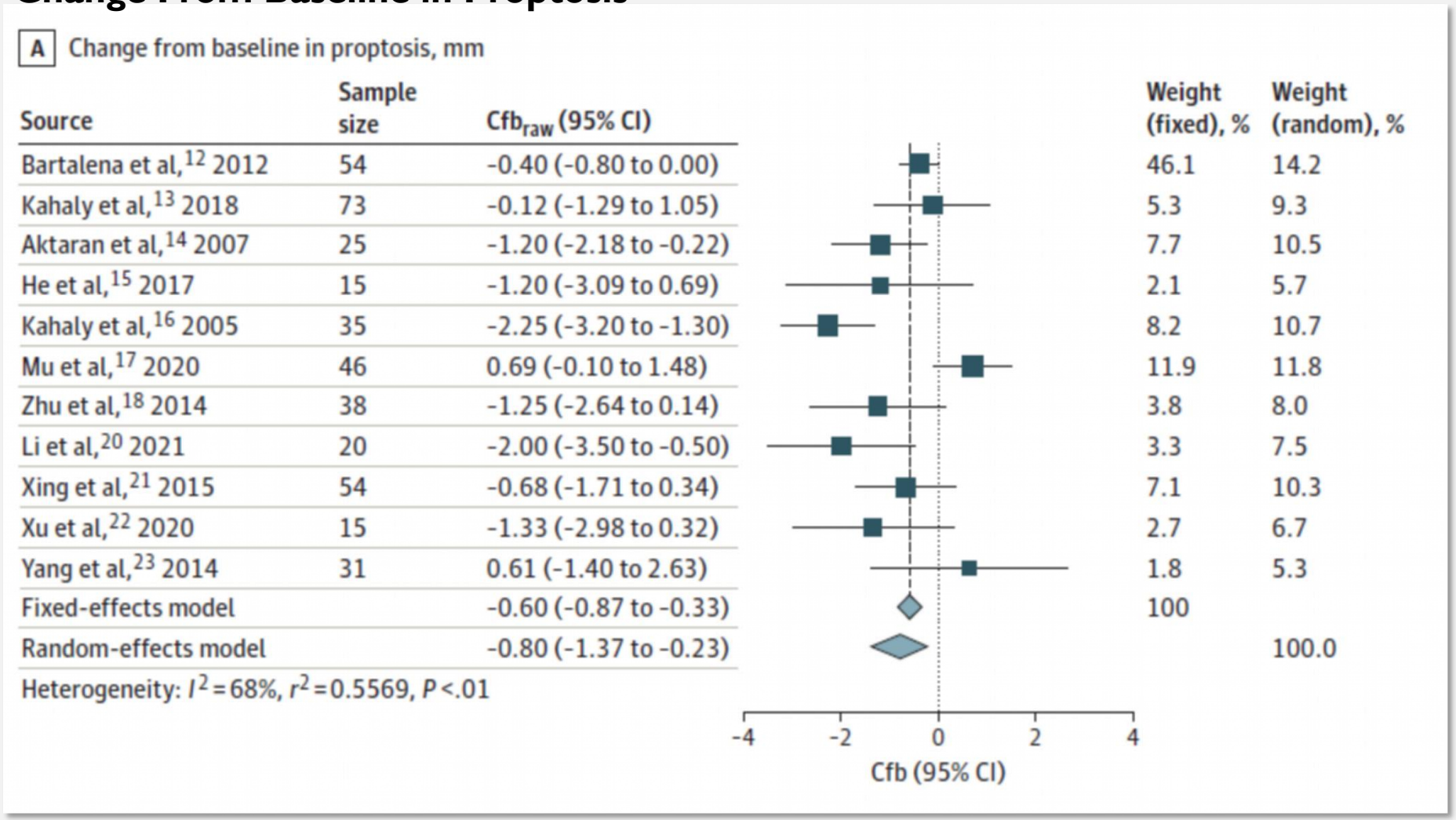
Zhu et al. *JCEM*. 2014;99(6):1999-2007; Kahaly et al. *Lancet Diabetes Endocrinol*. 2018;6(4):287-298; Kahaly et al. JCEM. 2005;90(9):5234-5240; Bartalena et al. *JCEM*. 2012;97(12):4454-63; He et al. *Endocrine J*. 2017;64(2):141 – 149; Yang et al. *Ophthal Plast Reconstr Surg*. 2014;30:157-161; Aktaran et al. *Int J Clin Pract*. 2007;61(1):45-51; Xing et al. *Br J Ophthalmol*. 2015;99:1686 – 1691; Li et al. *J Endocrinol Invest*. 2020:doi 10.1007/s40618-020-01322-5.

OBSERVED PROPTOSIS CHANGES

Author, year	N at BL	N at week 12	Mean proptosis at BL (mm)	Mean proptosis at week 12 (mm)	Mean change in proptosis at week 12 (mm)
Kahaly 2005	35	35	23.75	21.5	-2.25
Aktaran 2007	25	25	22.2	21	-1.2
Bartalena 2012	54	54	22.2	21.8	-0.4
Xing 2014	54	54	22.10	21.42	-0.68
Yang 2014	32	31	23.04	23.66	0.62
Zhu 2014_12 week	39	38	22.06	20.81	-1.25
He 2017	18	15	17.2	16	-1.2
Kahaly 2018	81	73	21.27	21.15	-0.12
Li 2020	20	20	18.9	16.9	-2
Weighted mean change from baseline					**-0.76**

Zhu et al. JCEM. 2014;99(6):1999-2007; Kahaly et al. Lancet Diabetes Endocrinol. 2018;6(4):287-298; Kahaly et al. JCEM. 2005;90(9):5234-5240; Bartalena et al. JCEM. 2012;97(12):4454-63; He et al. Endocrine J. 2017;64(2):141 – 149; Yang et al. Ophthal Plast Reconstr Surg. 2014;30:157-161; Aktaran et al. Int J Clin Pract. 2007;61(1):45-51; Xing et al. Br J Ophthalmol. 2015;99:1686 – 1691; Li et al. J Endocrinol Invest. 2020:doi 10.1007/s40618-020-01322-5.

Figure 1A. Meta-analyses to Obtain Pooled Estimates for Intravenous Methylprednisolone (IVMP) for Change From Baseline in Proptosis



Cfb indicates change from baseline; Cfb$_{raw}$, raw change from baseline.

Douglas RS et al, JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2021.6284
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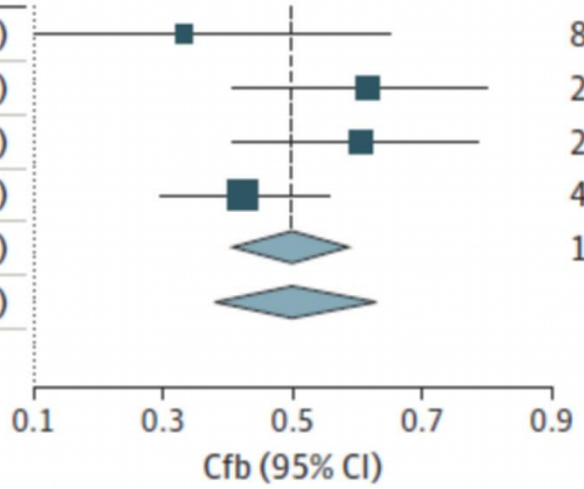
Figure 1B. Meta-analyses to Obtain Pooled Estimates for Intravenous Methylprednisolone (IVMP) for Change From Baseline in Diplopia Response

B Diplopia response

Source	No. with diplopia response	Sample size	Cfb_{raw} (95% CI)	Weight (fixed), %	Weight (random), %
He et al,[15] 2017	4	12	0.33 (0.10 to 0.65)	8.9	13.7
Kahaly et al,[16] 2005	16	26	0.62 (0.41 to 0.80)	20.6	24.3
Zhu et al,[18] 2014	17	28	0.61 (0.41 to 0.78)	22.3	25.4
Beleslin et al,[19] 2020	25	59	0.42 (0.30 to 0.56)	48.2	36.6
Fixed-effects model		125	0.50 (0.41 to 0.58)	100	
Random-effects model			0.50 (0.38 to 0.63)		100.0
Heterogeneity: $I^2 = 43\%$, $r^2 = 0.1132$, $P = .15$					



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SIDE EFFECT PROFILE OF GLUCOCORTICOIDS

System affected	Side effects
Musculoskeletal	Osteoporosis, Avascular necrosis of bone, Myopathy
Endocrine and metabolic	Hyperglycemia, Diabetes mellitus, dyslipidemia, weight gain, cushingoid features, growth suppression, adrenal suppression
Gastrointestinal	Gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis
Cardiovascular	Hypertension, coronary heart disease, ischemic heart disease, heart failure
Dermatologic	Dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss
Neuropsychiatric	Mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium
Ophthalmologic	Cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy
Immunologic	Suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections

Oray et al. *Expert Opin on drug Safety*. 2016;15(4):457-65.

STEROIDS – BOTTOM LINE

- Steroids do NOT reverse the underlying alterations of orbital tissue
- They do NOT reverse proptosis or strabismus
- Substantial side effects, but only masks symptoms?

Bartalena L, et al. *J Clin Endocrinol Metab*. 2012;97(12):4454-63.

LONG-TERM EFFICACY COMPARISONS – STEROIDS AND RITUXIMAB

Drug Treatment	Response		*P*
Methylprednisolone IV	Low Dose (n = 53)	High Dose (n = 52)	
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	.01
Rituximab	PBO (n = 12)	Rituximab (n = 13)	
Proptosis mean baseline (mm)*	23.2	24.4	
Proptosis Δ 24 weeks (mm)*	−0.4	+0.3	NS
CAS mean baseline	5.3	4.9	
CAS Δ 24 weeks	−1.5	−1.3	NS
*, averaged values from both eyes; NS, not significant			

CAS = clinical activity score; EUGOGO = European Group on Graves' Orbitopathy; RA = rheumatoid arthritis.

Bartalena L, et al. *J Clin Endocrinol Metab*. 2012;97(12):4454-63.
Stan MN, et al. *J Clin Endocrinol Metab*. 2015;100(2):432-441.

TOCILIZUMAB

- Humanized monoclonal antibody against IL-6 receptor
- **2014:** prospective nonrandomized study showed efficacy in TED refractory to IV steroids[1]
- **2018:** Multicenter, RCT showed efficacy in glucocorticoid-resistant TED; however, small study (n=32) and composed with heterogenous group of patients who had pretreatment with other immunosuppressive agents[2]
- Subcutaneous tocilizumab demonstrated efficacy in 2 patients[3]

IL = interleukin; IV = intravenous.

1. Perez-Moreiras JV, et al. *Ophthalmic Plast Reconstr Surg*. 2014;30(2):162-7.
2. Perez-Moreiras JV, et al. *Am J Ophthalmol*. 2018;195:181-90.
3. Cooperman T, et al. *Ophthalmic Plast Reconstr Surg*. 2019;35(3):e64-e66.

INNOVATION: TED-SPECIFIC TREATMENT

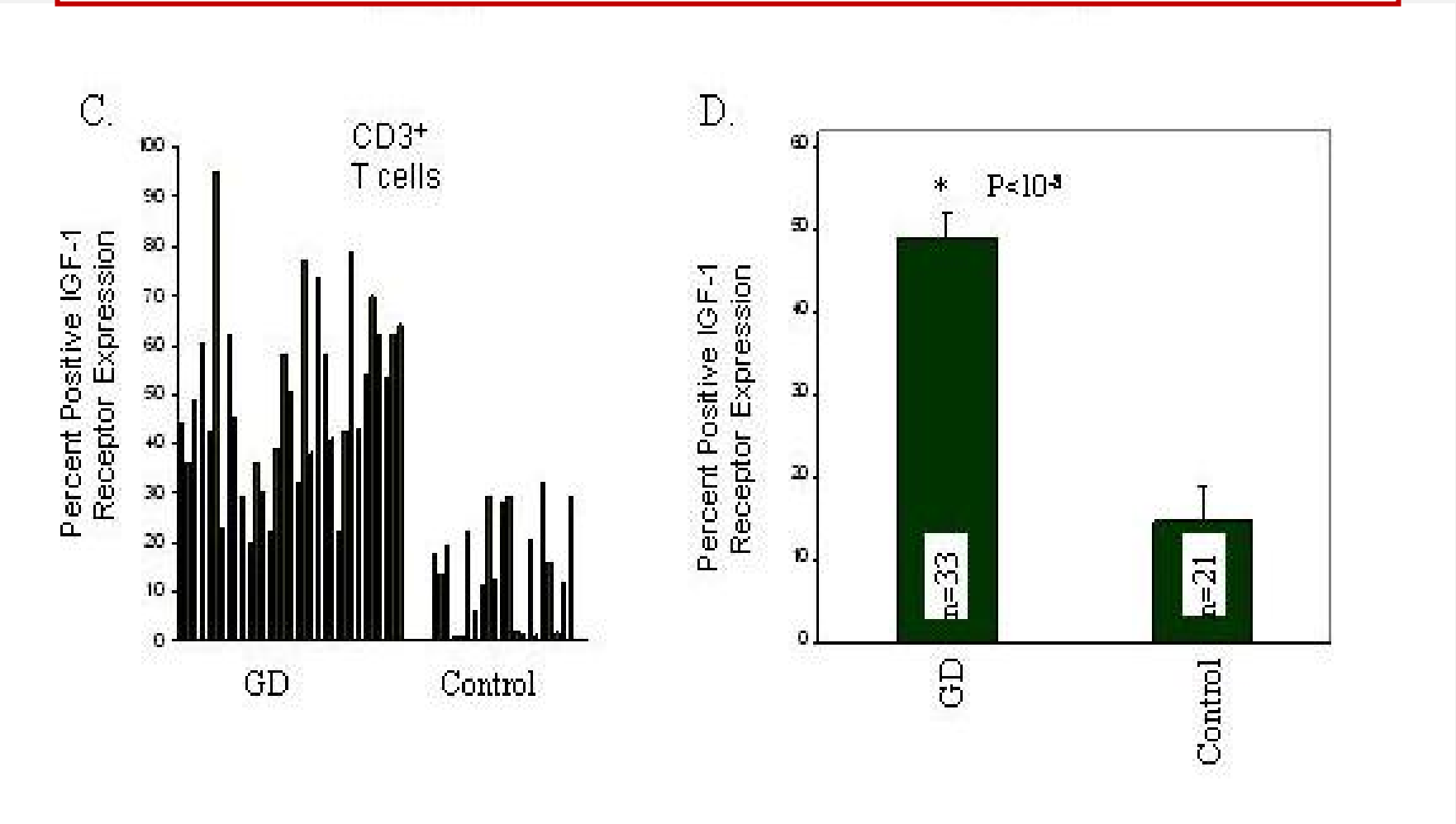
- Molecular targeting of antigen

INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR

- Overexpressed on Graves' disease (GD) fibroblasts and immune cells
- Signaling of fibroblasts and immune cells mimics pathologic findings
- Antibodies to these receptors in GD patients

Smith TJ, et al. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):291-302.

IGF-1R OVEREXPRESSION IS A HALLMARK OF GD

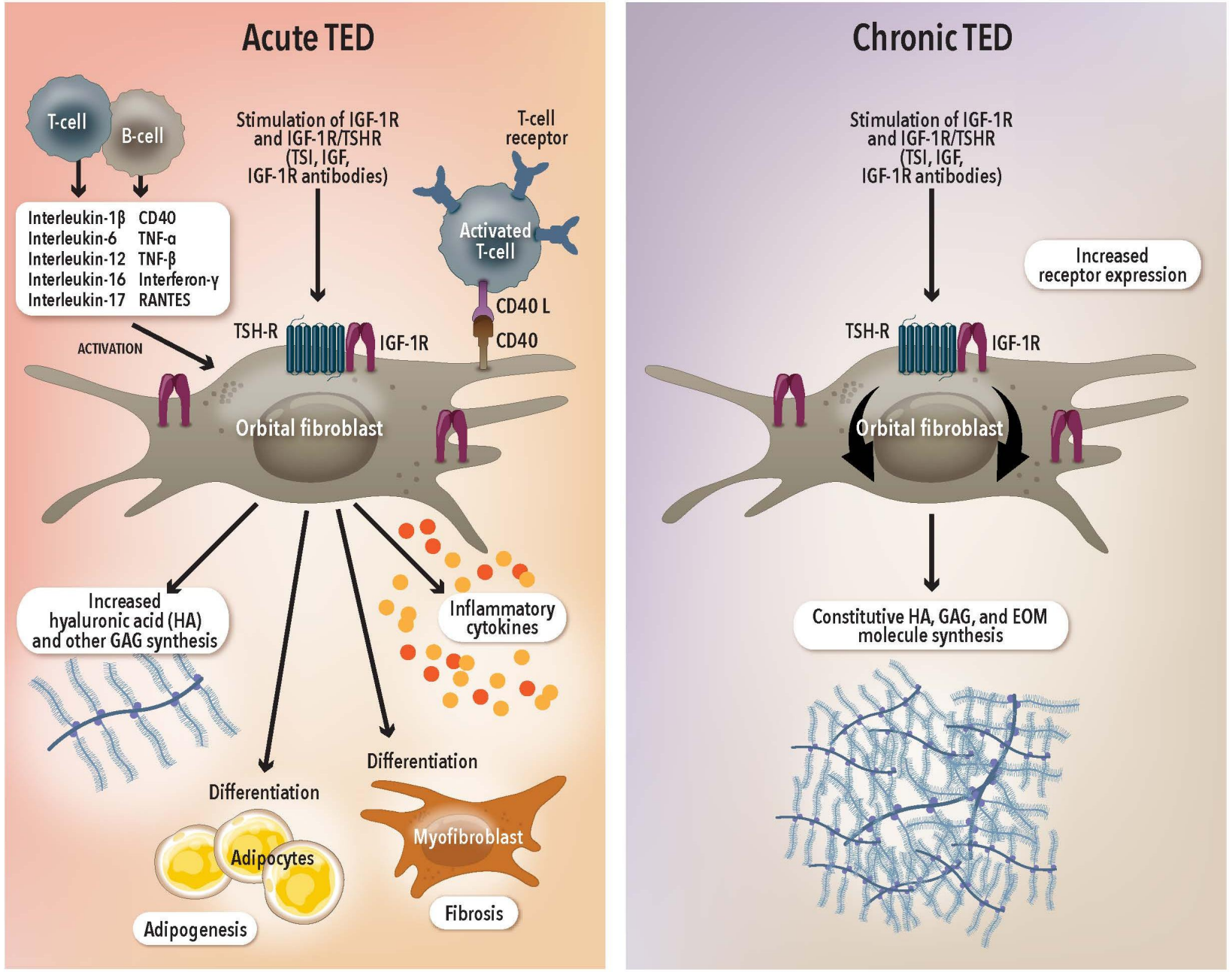


Douglas RS, et al. *J Immunology,* 2007. 178(5):3281-3287.

TEPROTUMUMAB: MECHANISM OF ACTION

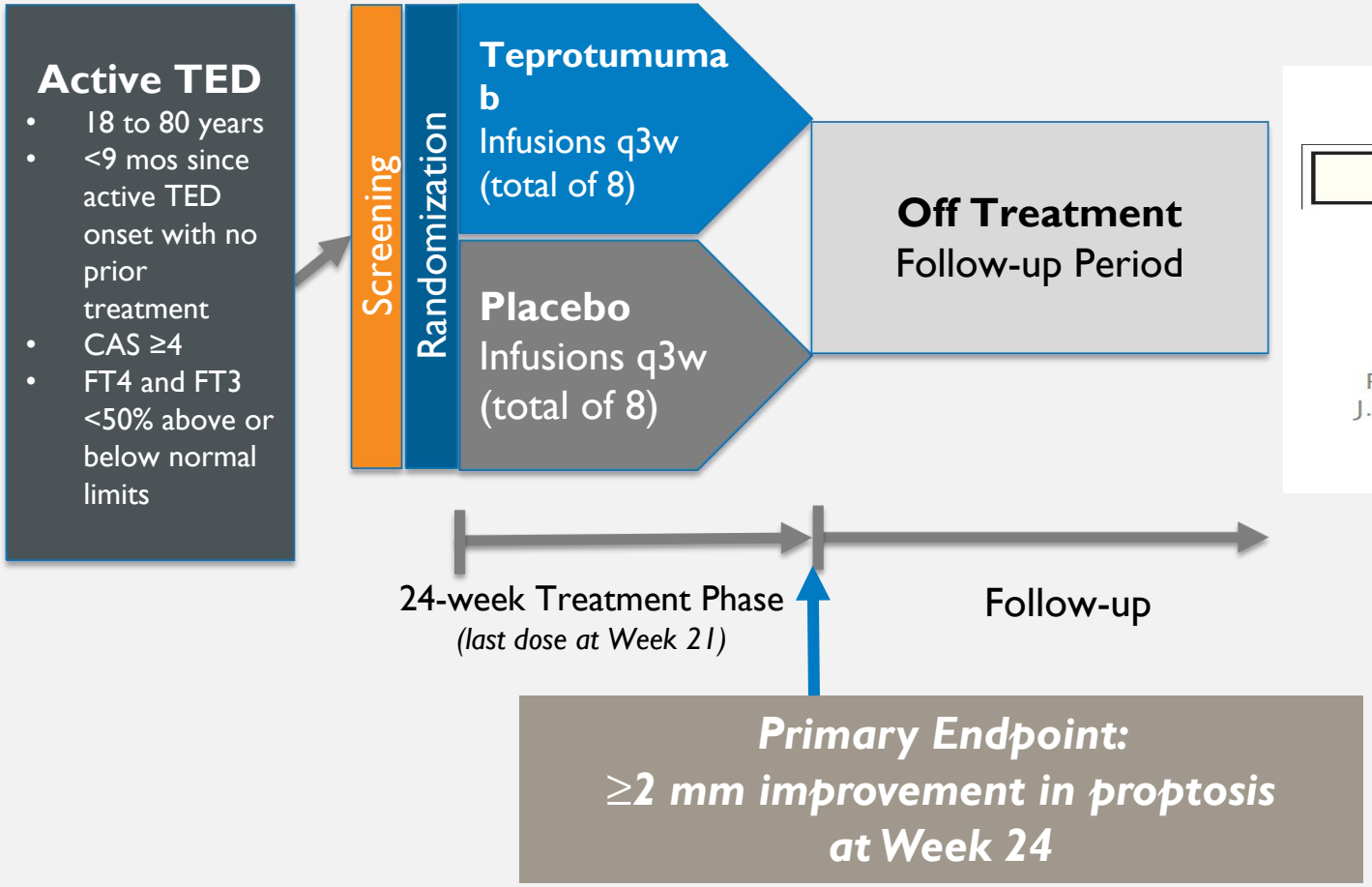
- Fully human monoclonal antibody inhibitor of IGF-1R
- Targeted binding to IGF-1R of the IGF-1R/TSHR signaling complex
- Blocks autoantibodies from attacking orbital cells
- Turns off IGF-1R/TSHR signaling at disease source
- Reduces inflammation + prevents excessive cell growth and hyaluronan build up behind eye

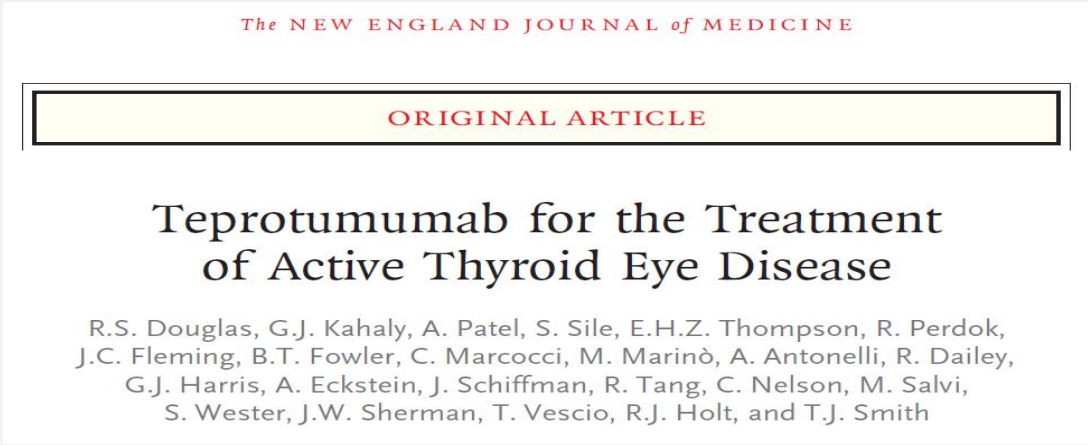
Douglas RS. *Eye (Lond)*. 2019;33(2):183-90; Smith TJ, Hegedüs L. *N Engl J Med*. 2016;375(16):1552–1565.


Acute TED
T-cell
B-cell
Interleukin-1β
Interleukin-6
Interleukin-12
Interleukin-16
Interleukin-17
CD40
TNF-α
TNF-β
Interferon-γ
RANTES
Stimulation of IGF-1R and IGF-1R/TSHR (TSI, IGF, IGF-1R antibodies)
T-cell receptor
Activated T-cell
CD40 L
CD40
ACTIVATION
TSH-R
IGF-1R
Orbital fibroblast
Increased hyaluronic acid (HA) and other GAG synthesis
Inflammatory cytokines
Differentiation
Differentiation
Adipocytes
Adipogenesis
Myofibroblast
Fibrosis
Chronic TED
Stimulation of IGF-1R and IGF-1R/TSHR (TSI, IGF, IGF-1R antibodies)
Increased receptor expression
TSH-R
IGF-1R
Orbital fibroblast
Constitutive HA, GAG, and EOM molecule synthesis

Teprotumumab for the Treatment of Active Thyroid Eye Disease

Phase 3, 24-Week Randomized, Double-masked, Placebo-controlled Trial





FT3 = free triiodothyronine; FT4 = free thyroxine.

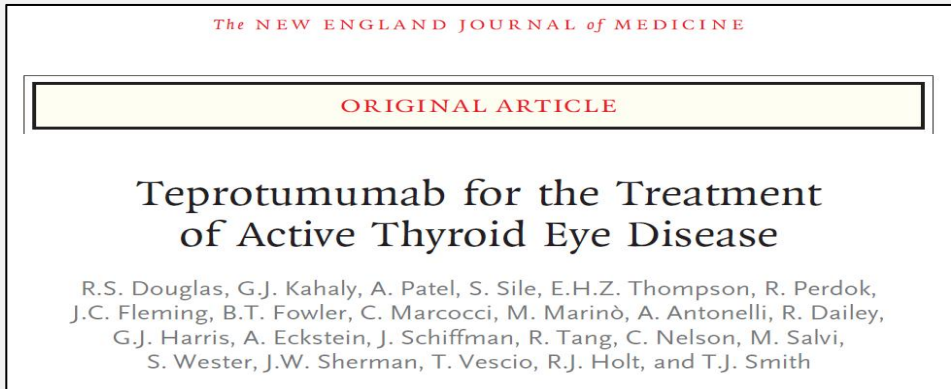
NCT03298867: Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (**OPTIC**). Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

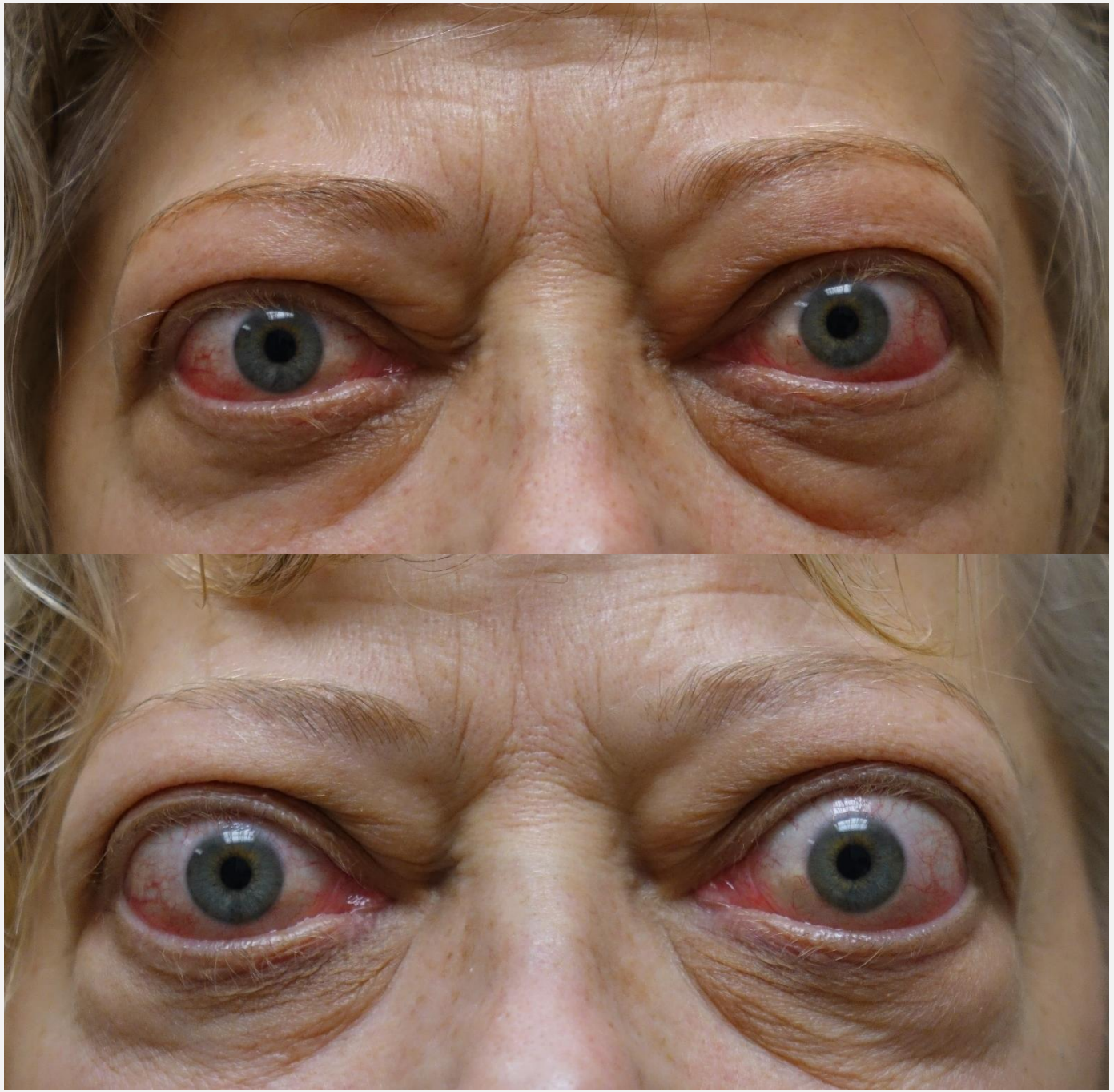
SUMMARY OF RESULTS

The primary outcome of proptosis responders (% of patients with ≥2-mm reduction in proptosis from baseline) was *significantly greater* with teprotumumab than placebo

- All secondary endpoints were also met (*P*≤.001)
  - Overall responder rate at Week 24 (primary endpoint in the phase 2 study)
  - Percent of participants with a CAS value of 0 or 1 at Week 24
  - Percent of patients with a change from baseline of at least 1 grade in diplopia (double vision)
  - Mean change in proptosis from baseline through week 24
  - Mean change in Graves' ophthalmopathy quality of life score from
  - baseline through week 24

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.





Placebo Patient

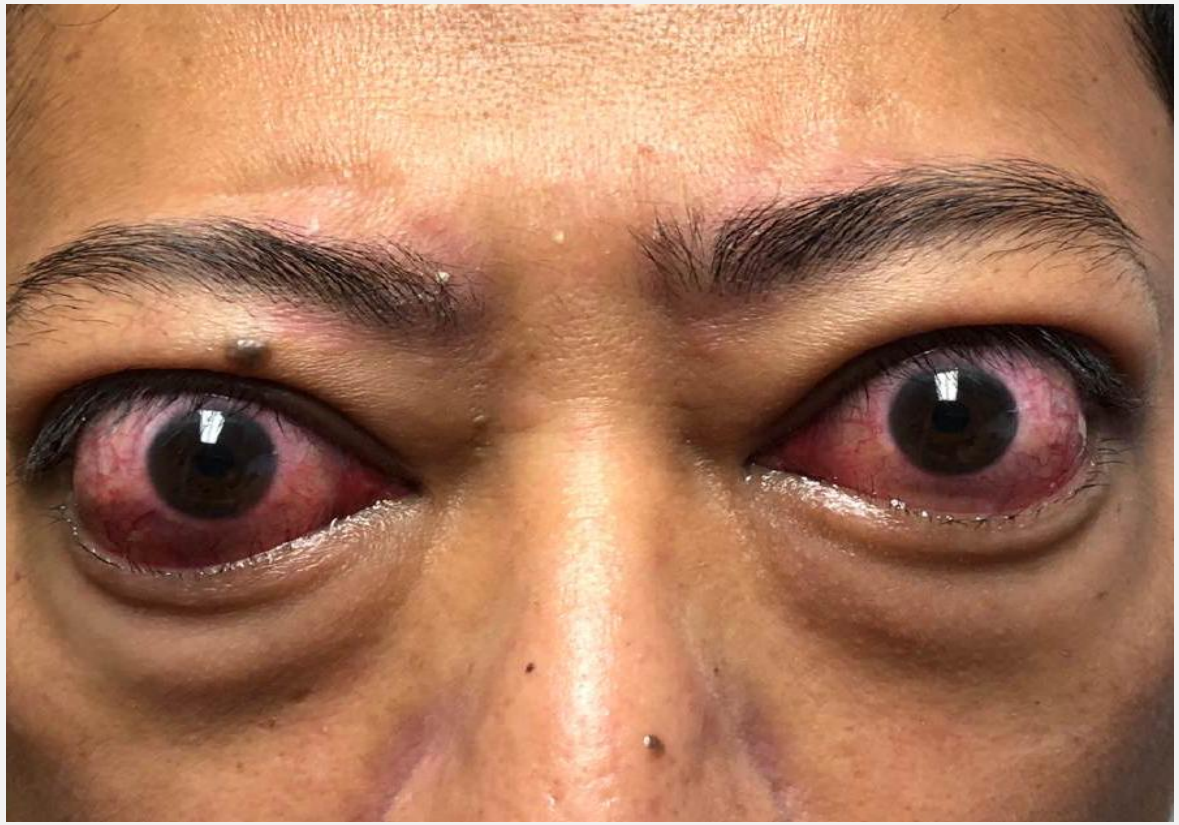
Pretreatment

Week 24

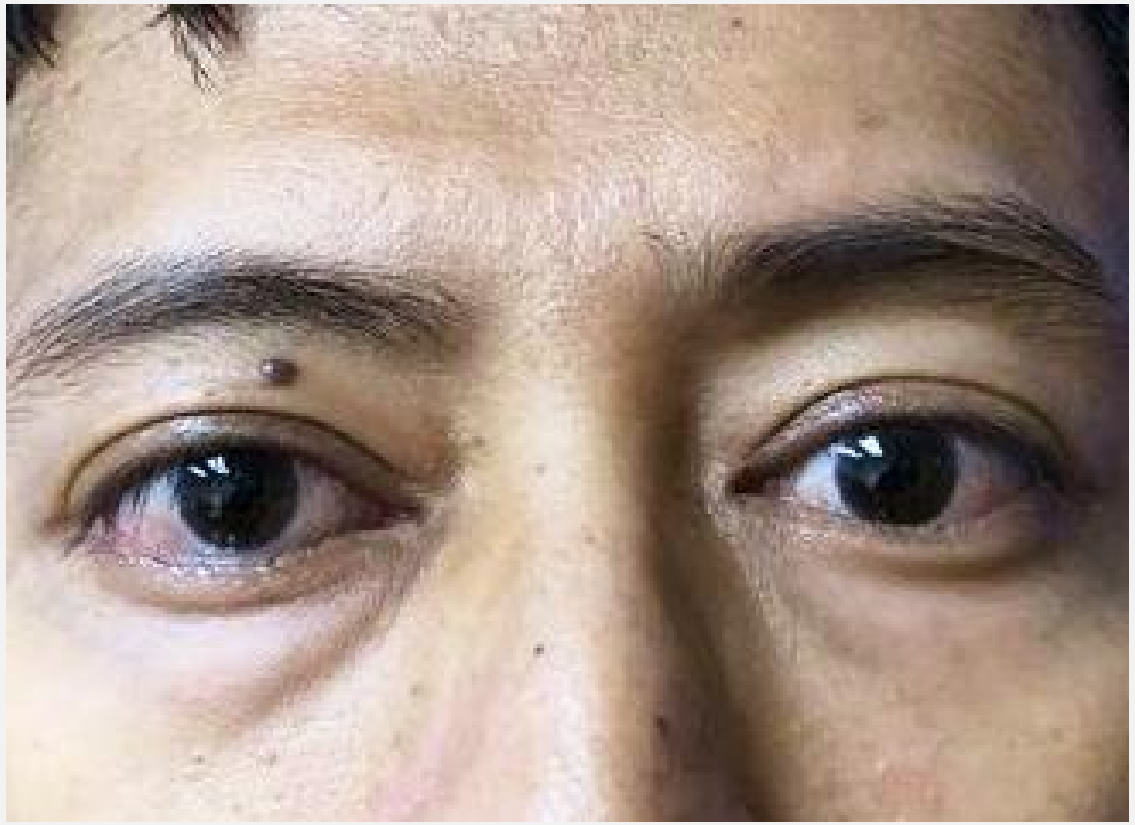
Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

TEPROTUMUMAB

OPTIC Trial



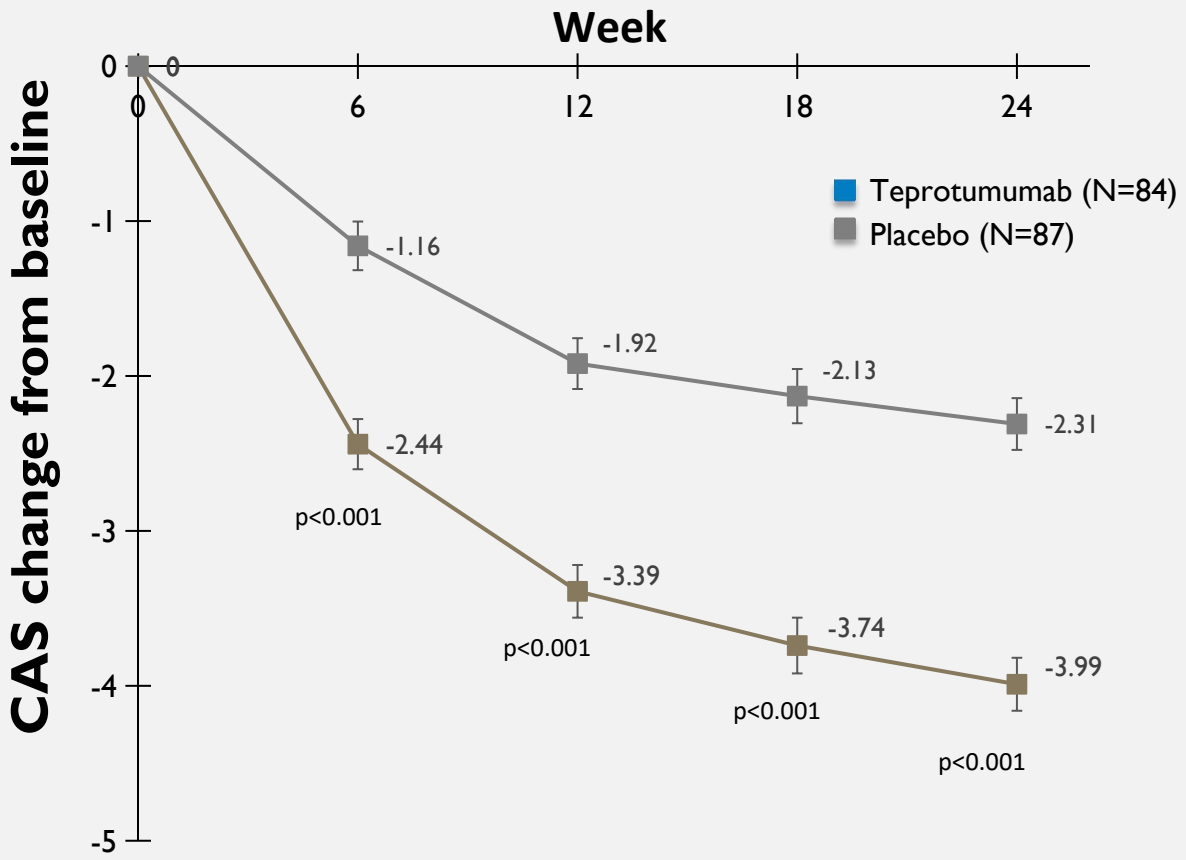
Pretreatment



Week 24

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

CLINICAL ACTIVITY SCORE REDUCTIONS



Disease Inactivation: 61.9% of teprotumumab-treated patients had absent TED activity (CAS of 0 or 1) vs 21.8% of placebo-treated patients at week 24 (*P*<.001)

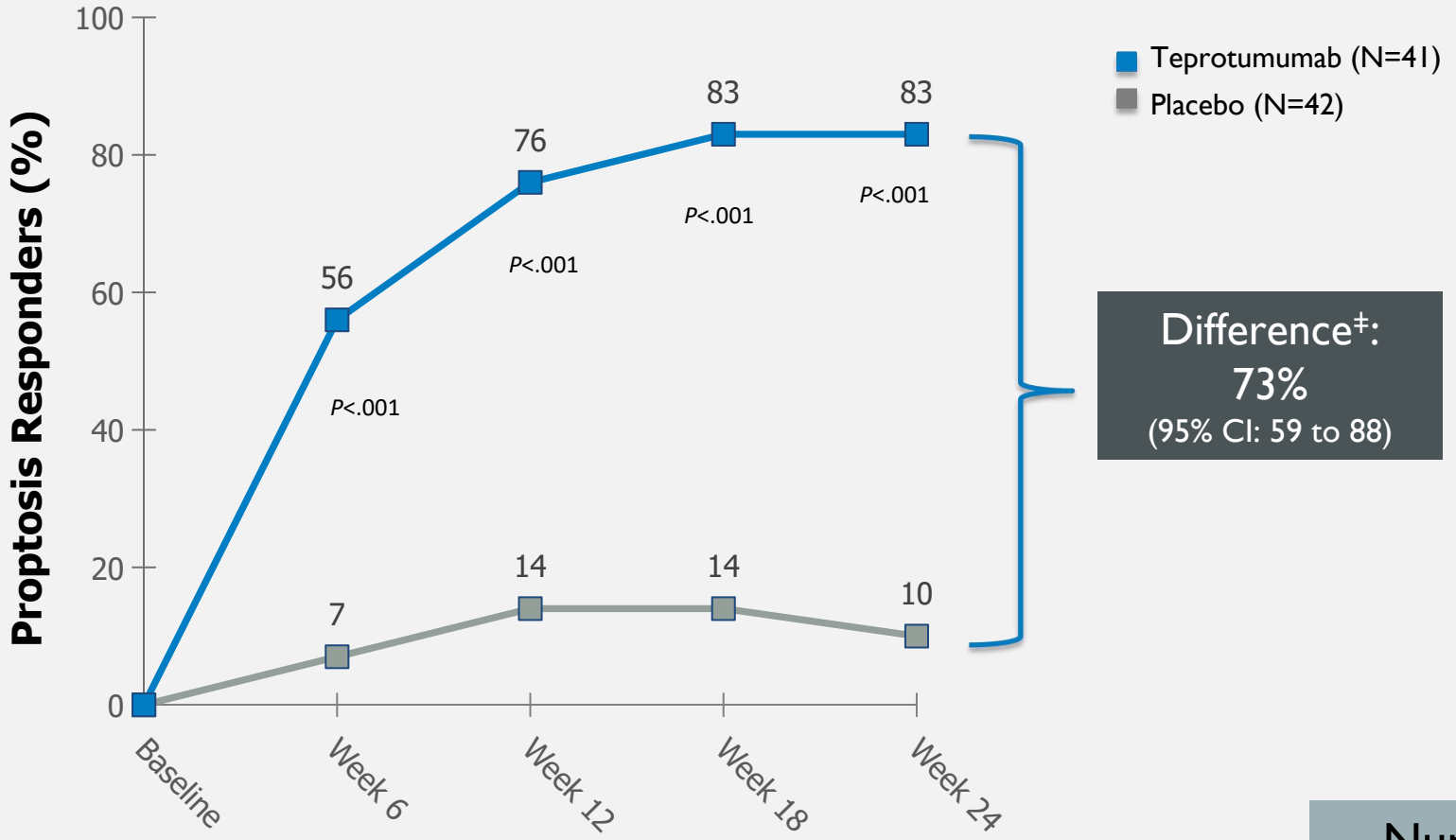
GO = Graves' ophthalmopathy

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352;
Image from Kahaly GJ, et al. *Thyroid.* 2019;29(Suppl 1).
https://www.liebertpub.com/doi/pdf/10.1089/thy.2019.29085.abstracts.

OPTIC Trial

PROPTOSIS RESPONSE (REDUCTION OF ≥2 MM)

Primary Outcome



‡Stratified Difference in Response Rates. Estimates from the 2 strata (tobacco user, tobacco nonuser) are combined with Cochran-Mantel-Haenszel weights.

Number needed to treat (NNT) of 1.36

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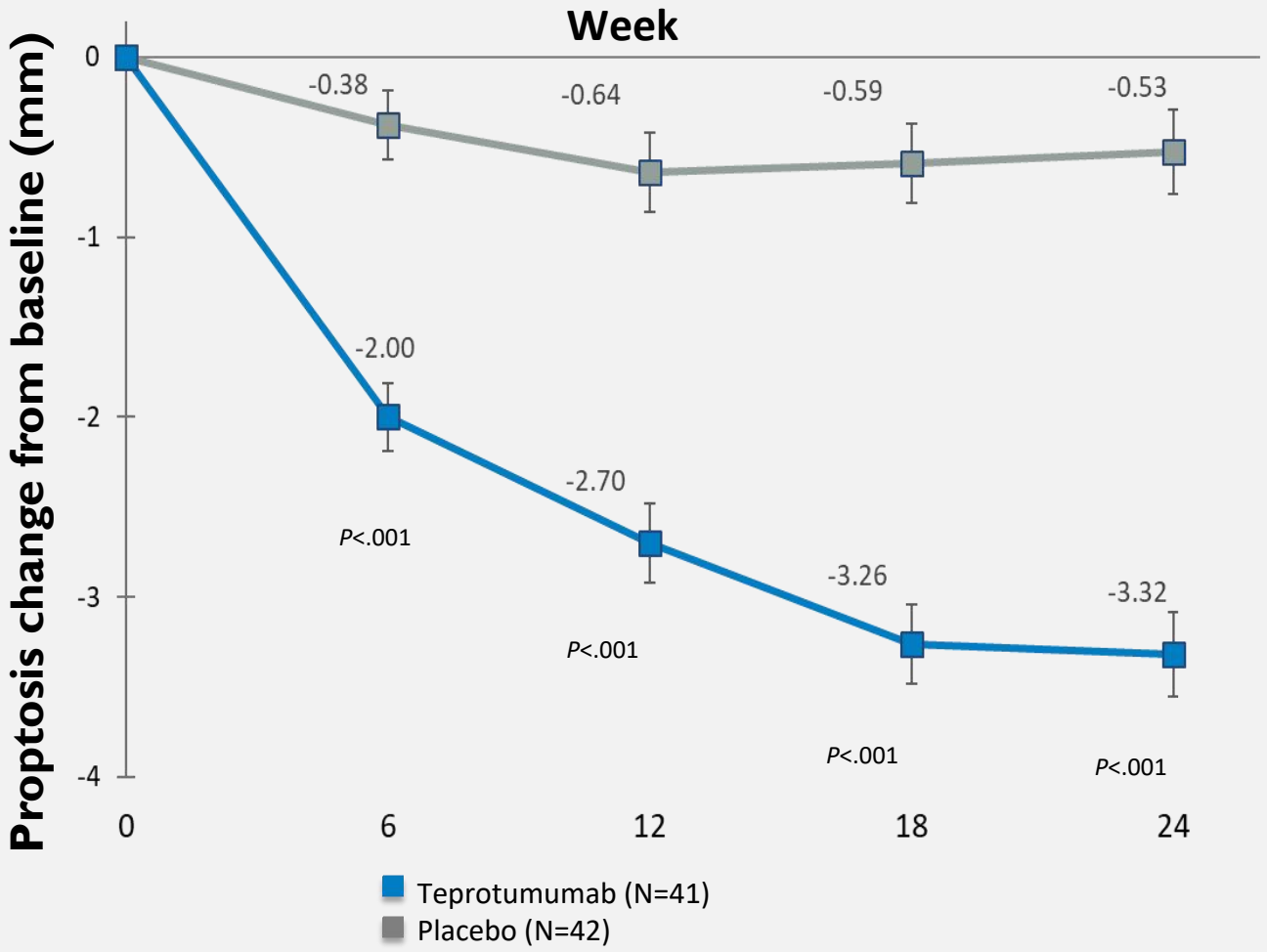
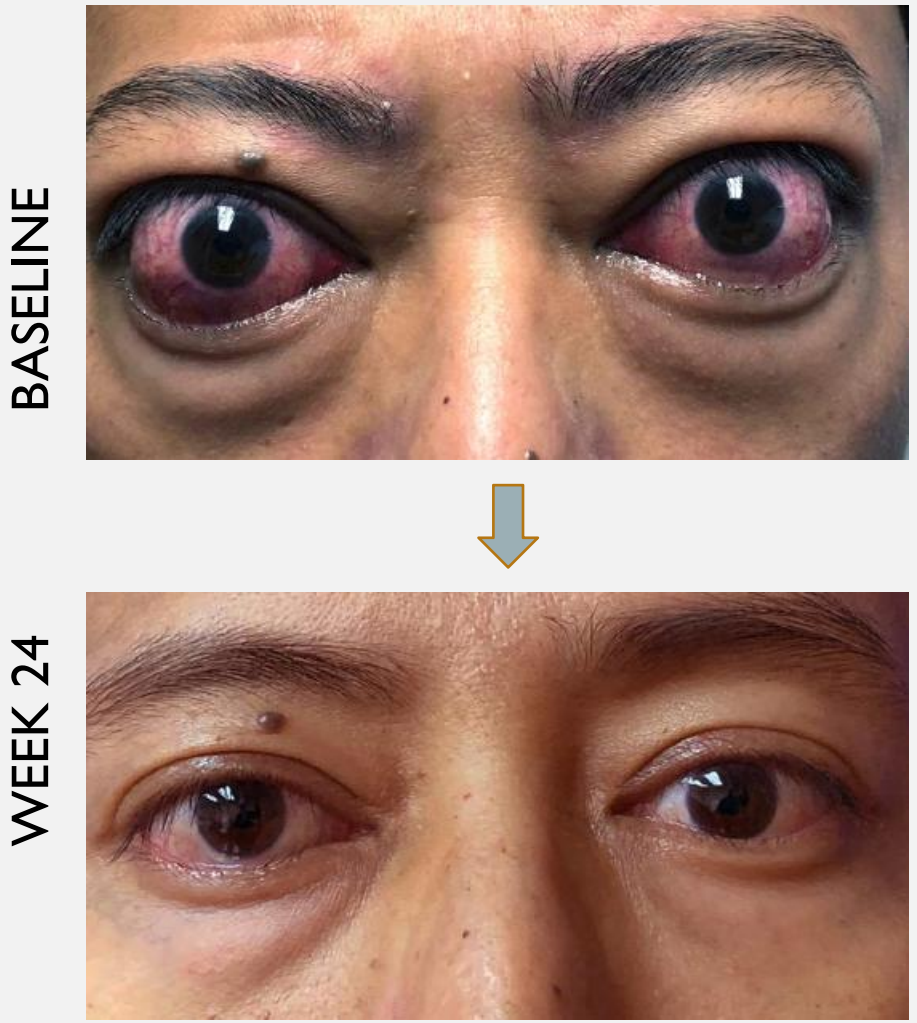
PROPTOSIS REDUCTIONS

OPTIC Trial



Teprotumumab

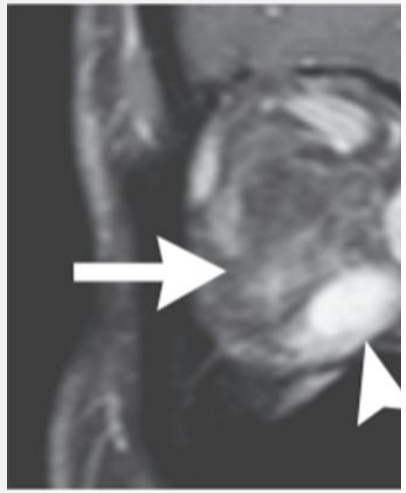


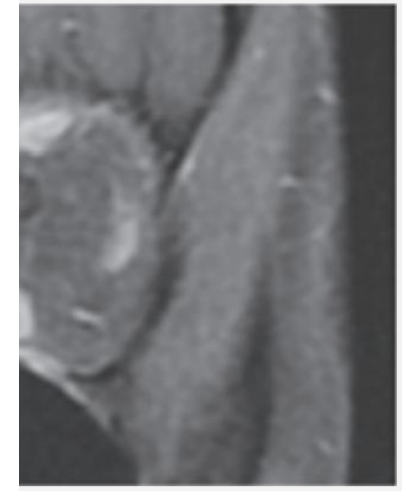
Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix, including the following terms: baseline score, tobacco use status (nonuser, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean ± standard error.

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

- 10 patients receiving Teprotu
- Mean age 43 years (range 31
- Pre and Post treatment scan
- 3D volumetric analysis of or

P … al Dose





TEPROTUMUMAB REDUCES EXTRAOCULAR MUSCLE AND ORBITAL FAT VOLUME IN THYROID EYE DISEASE

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*Author for Correspondence

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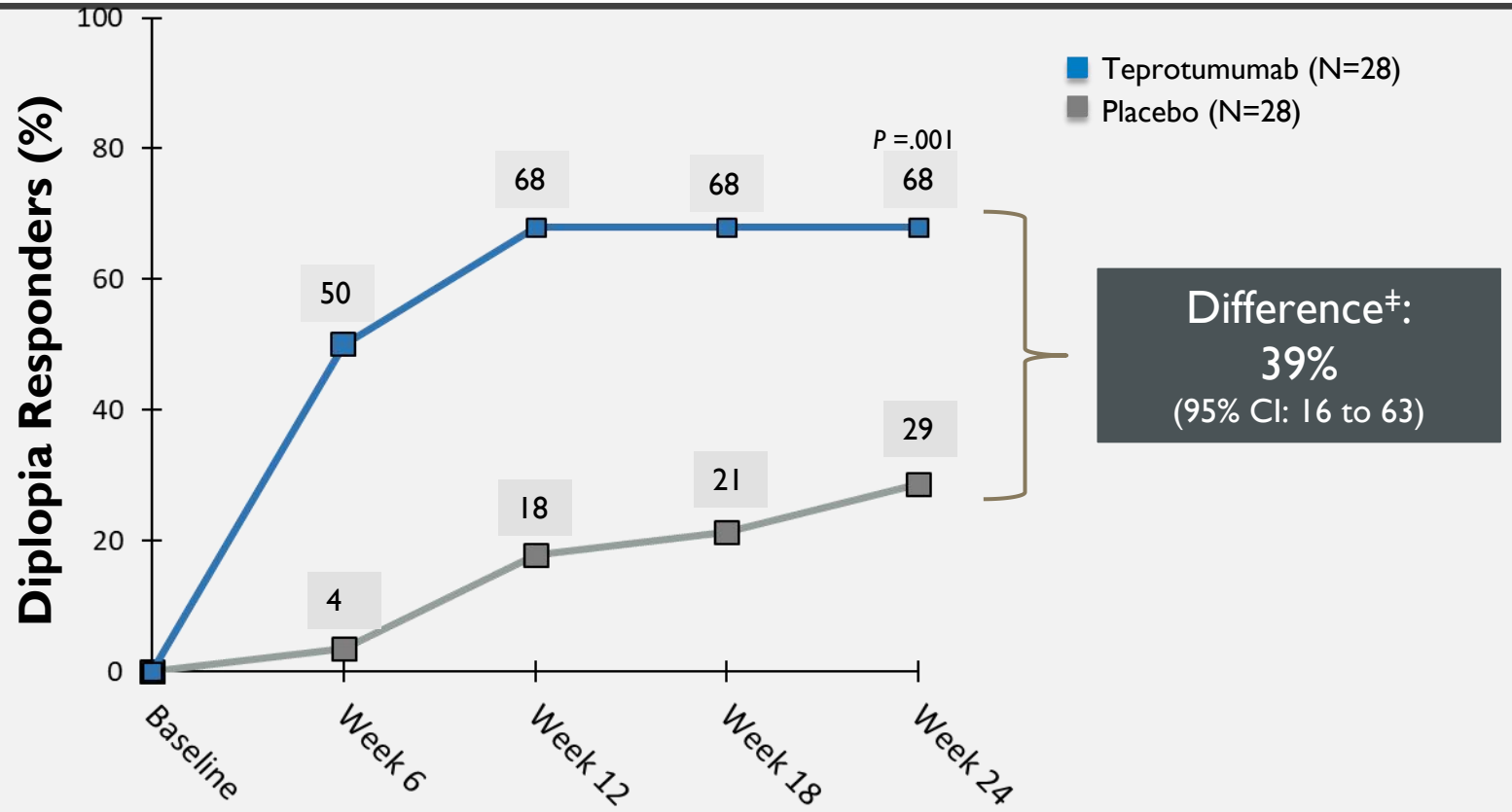
Acknowledgements and Conflict of Interest:
RD - Consultant Horizon Therapeutics, Consultant Immunovant
AK –Employer, Horizon Therapeutics

Running head: Teprotumumab decreases orbital tissue volume

Key words: Thyroid eye disease, teprotumumab

Hertel	<0.01	-3.8 mm

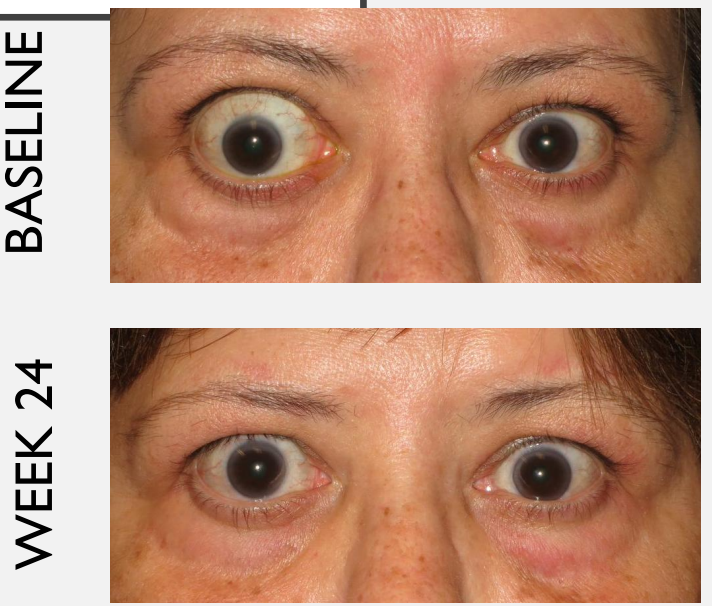
DIPLOPIA RESPONDERS: ≥1 GRADE IMPROVEMENT IN THOSE WITH BASELINE DIPLOPIA



Note: 28 patients in each group had diplopia at baseline.
‡Stratified difference in response rates. Estimates from the 2 strata (tobacco user, tobacco nonuser) are combined with Cochran-Mantel-Haenszel weights.

Image and permission courtesy of Raymond Douglas, MD, PhD.
Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

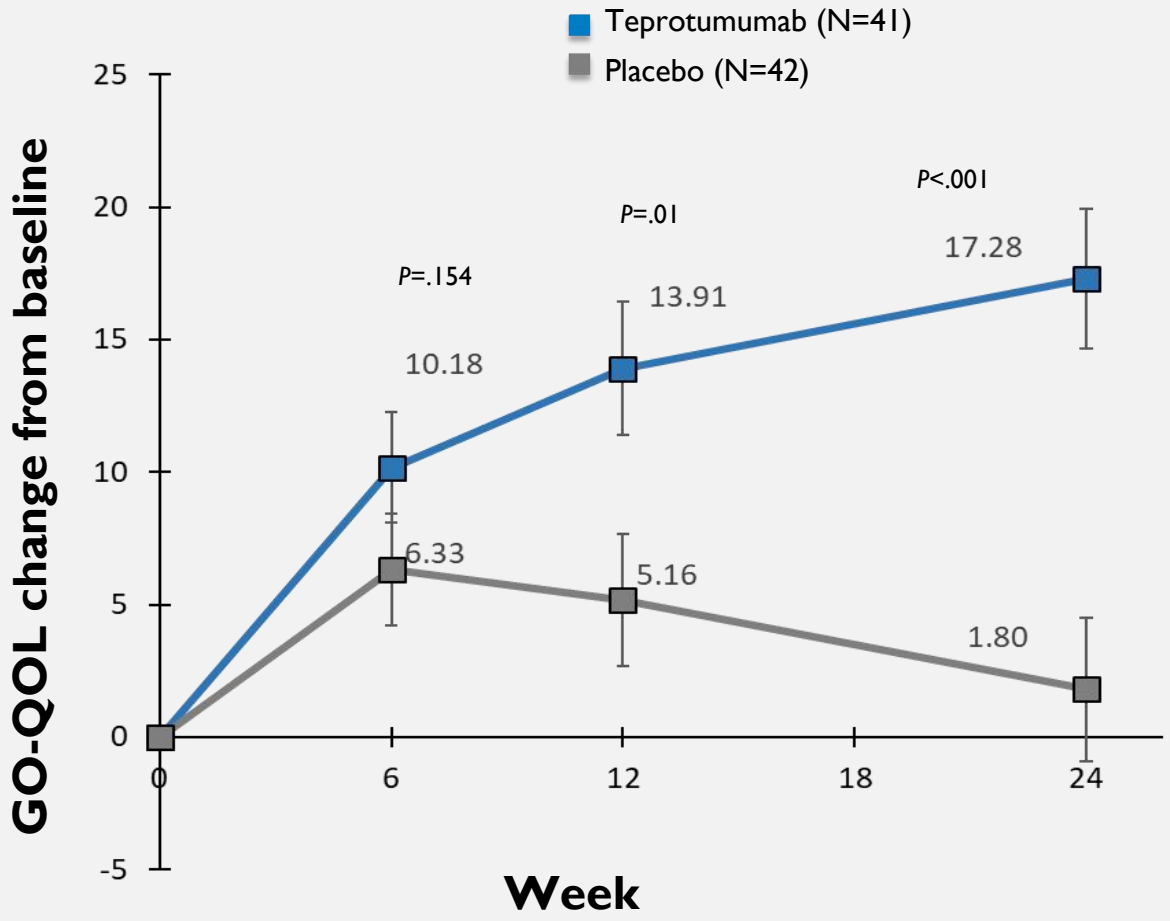
Teprotumumab



Diplopia Score

0	No diplopia
1	Intermittent, ie, diplopia in primary position of gaze, when tired or when first awakening
2	Inconstant, ie, diplopia at extremes of gaze
3	Constant, ie, continuous diplopia in primary or reading position

GO-QOL IMPROVEMENTS – OVERALL



Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline score, tobacco use status (nonuser, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean ± standard error.

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

Drivers of decreased QOL:

- TED activity[1-4] and ocular pain[1,5]
- Disease severity[2-4,6,7]:
  - Proptosis[4,8-10] and asymmetric proptosis (≥3 mm difference between eyes)[4]
  - Diplopia[1,3-5,11]
  - Blurred vision[1]

1. Kahaly GJ, et al. *Clin Endocrinol (Oxf).* 2005;63(4):395-402. 2. Choi YJ, et al. *Eye (Lond).* 2012;26(4):544-51. 3. Lin IC, et al. *J Formos Med Assoc.* 2015;114(11):1047-54. 4. Villagelin D, et al. *Front Endocrinol (Lausanne).* 2019;10:192. 5. Kahaly GJ, et al. *Thyroid.* 2002;12(3):237-9. 6. Park JJ, et al. *Br J Ophthalmol.* 2004;88(1):75-8. 7. Delfino LC, et al. *Arch Endocrinol Metab.* 2017;61(4):374-81. 8. Bartalena L, et al. *Endocr Rev.* 2000;21(2):168-99. 9. Gerding MN, et al. *Thyroid* .1997;7(6):885-9. 10. Tehrani M, et al. *Eur J Ophthalmol.* 2004;14(3):193-9. 11. Bradley EA, et al. *Ophthalmology.* 2006;113(8):1450-4.

SAFETY PROFILE

Treatment-emergent Adverse Events Occurring in >5% of Patients:

Number of patients (%)	Placebo (n=42)	Teprotumumab (n=41)
Muscle Spasm	4 (10)	13 (32)
Alopecia	5 (12)	8 (20)
Nausea	4 (10)	6 (15)
Fatigue	1 (2)	5 (12)
Diarrhea	5 (12)	4 (10)
Headache	4 (10)	4 (10)
Dry skin	0 (0)	4 (10)
Dysgeusia	0 (0)	4 (10)
Stomatitis	1 (2)	3 (7)
Amenorrhoea	0 (0)	3 (7)
Dizziness	0 (0)	3 (7)
Cough	3 (7)	2 (5)
Abdominal pain upper	3 (7)	2 (5)
Influenza	3 (7)	1 (2)

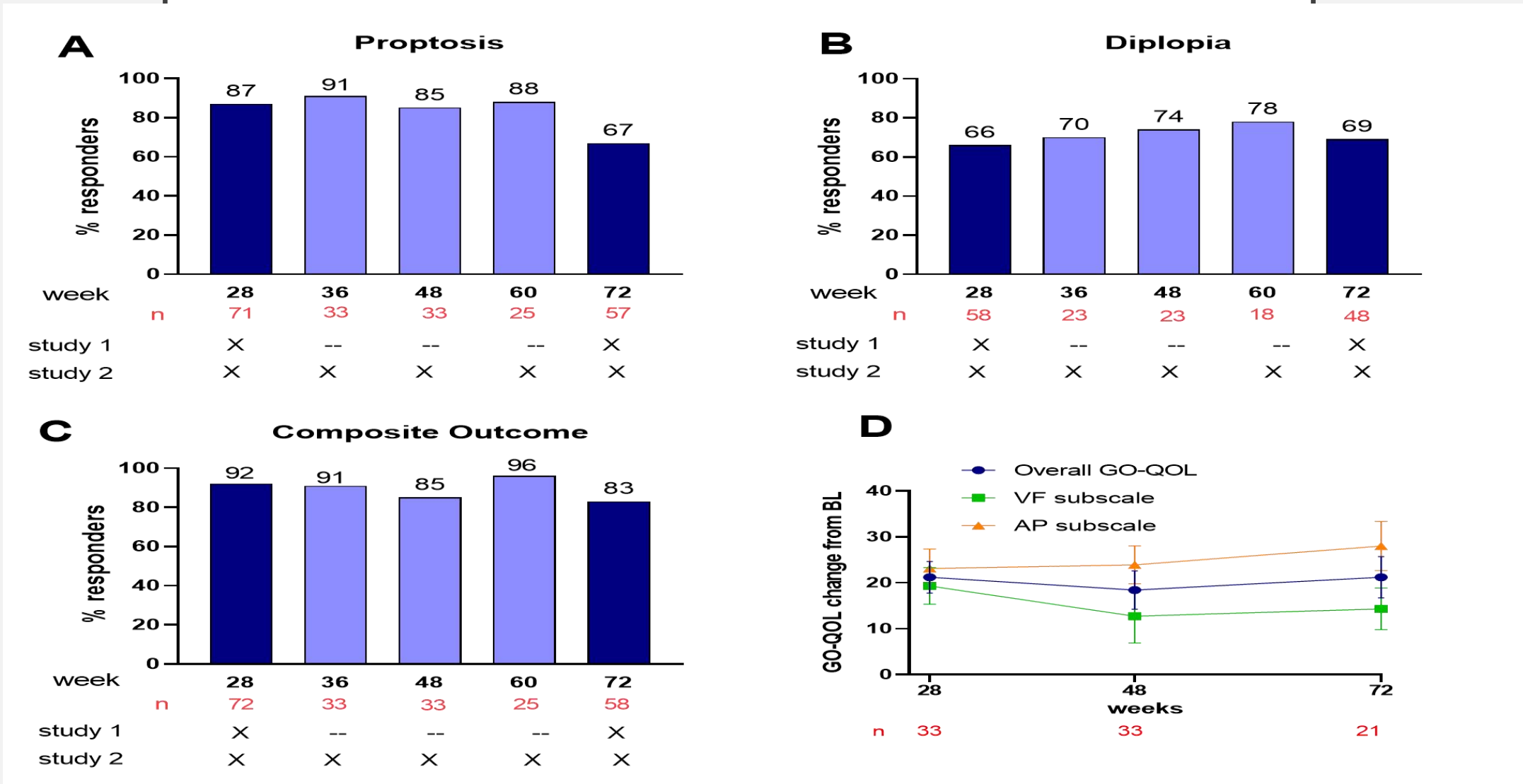
Majority of treatment-emergent adverse events were mild to moderate in intensity and no nonserious events led to discontinuation

Adapted from Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

RESPONSE TO TEPROTUMUMAB IS DURABLE

- 28 weeks and 60 weeks after initiation of Teprotumumab treatment (off treatment for 7 and 39 weeks)

- Proptosis responders: 87% and 88%.
- Diplopia Responders: 66% and 78%
- 95% with inactive disease



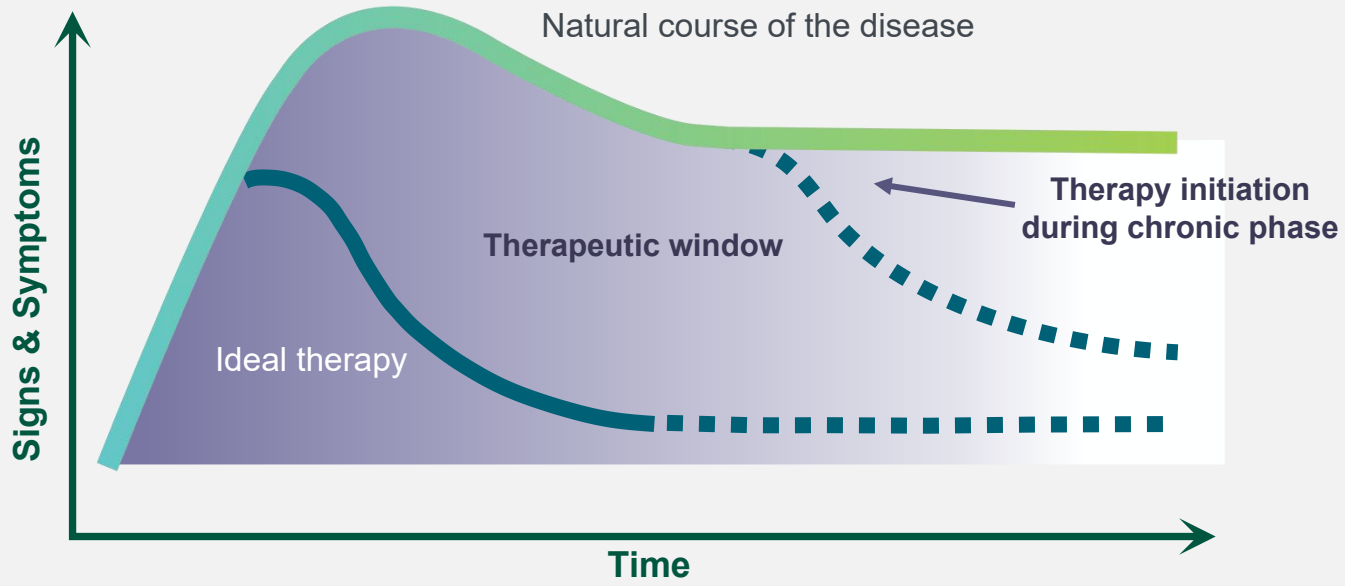
Kahaly GJ, Douglas RS et al, Lancet Diabetes Endocrinol 2021

ACUTE AND CHRONIC TED

Traditional Characterization of Acute and Chronic TED

	Time Since Diagnosis	Signs and Symptoms
Acute	2 years or less	Progressive/changing symptomatology (proptosis, diplopia, inflammatory signs/symptoms)
Chronic	>2 years	Stable/nonchanging proptosis, diplopia, inflammatory signs/symptoms

Natural History of TED

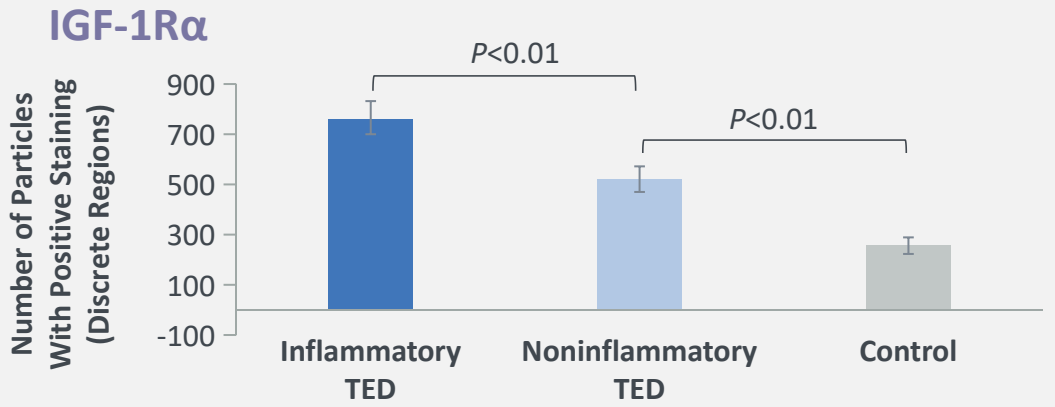


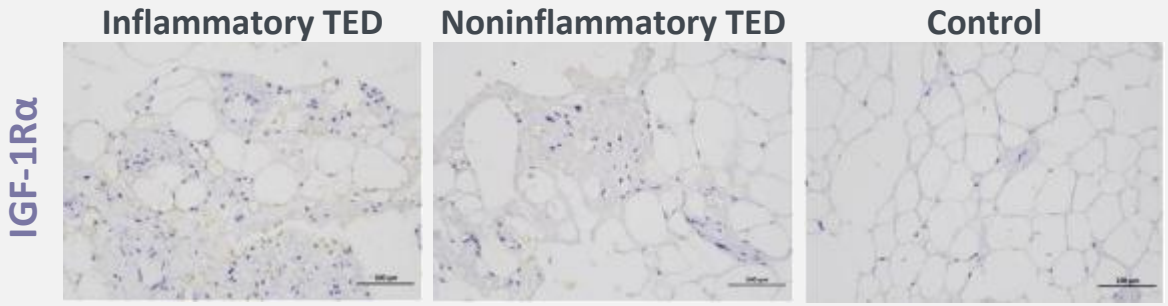
TEPROTUMUMAB ALSO REVERSES CHRONIC TED

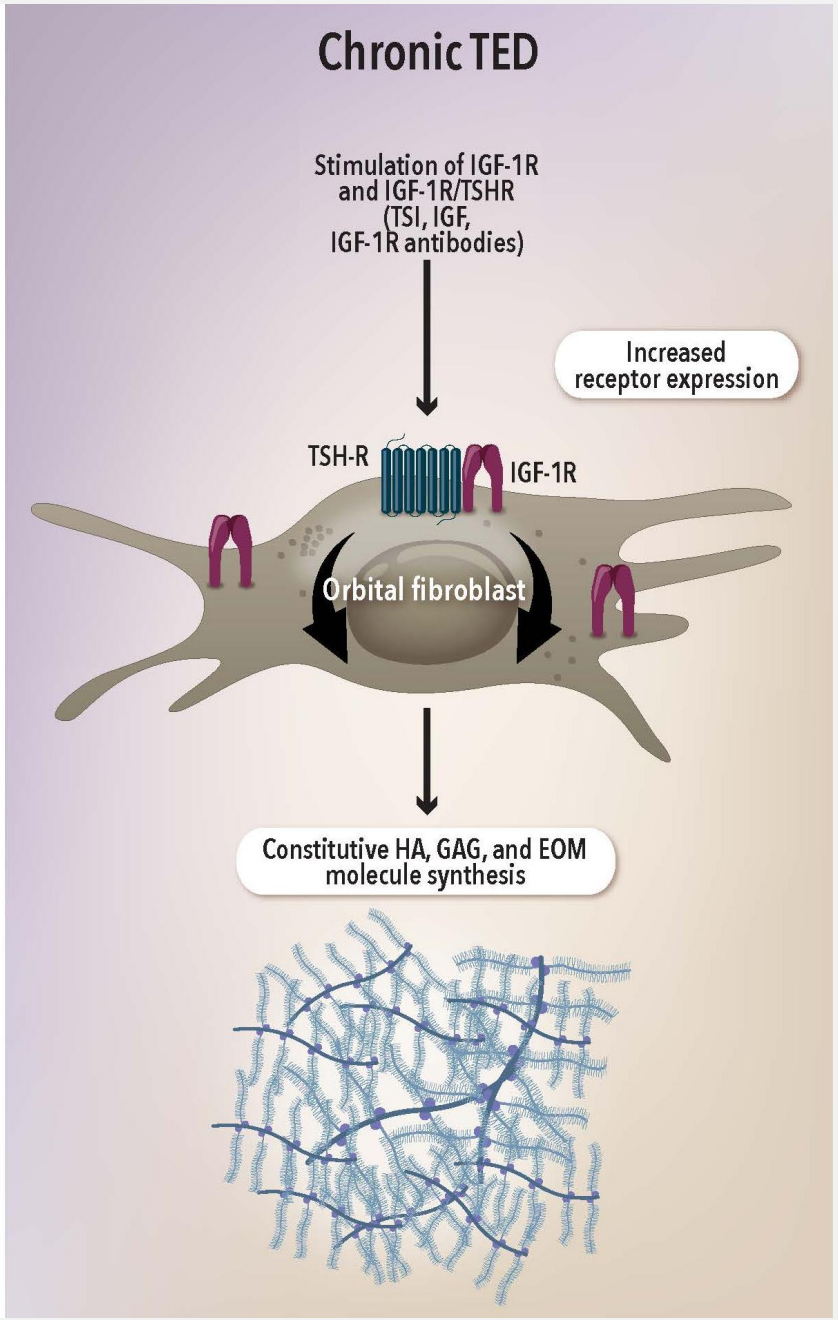
- How can this be possible !
- Overexpression of IGF-1R on fibroblasts from Active and Chronic patients
- Inhibits the metabolic turnover of extracellular molecules.

Noninflammatory TED Study*

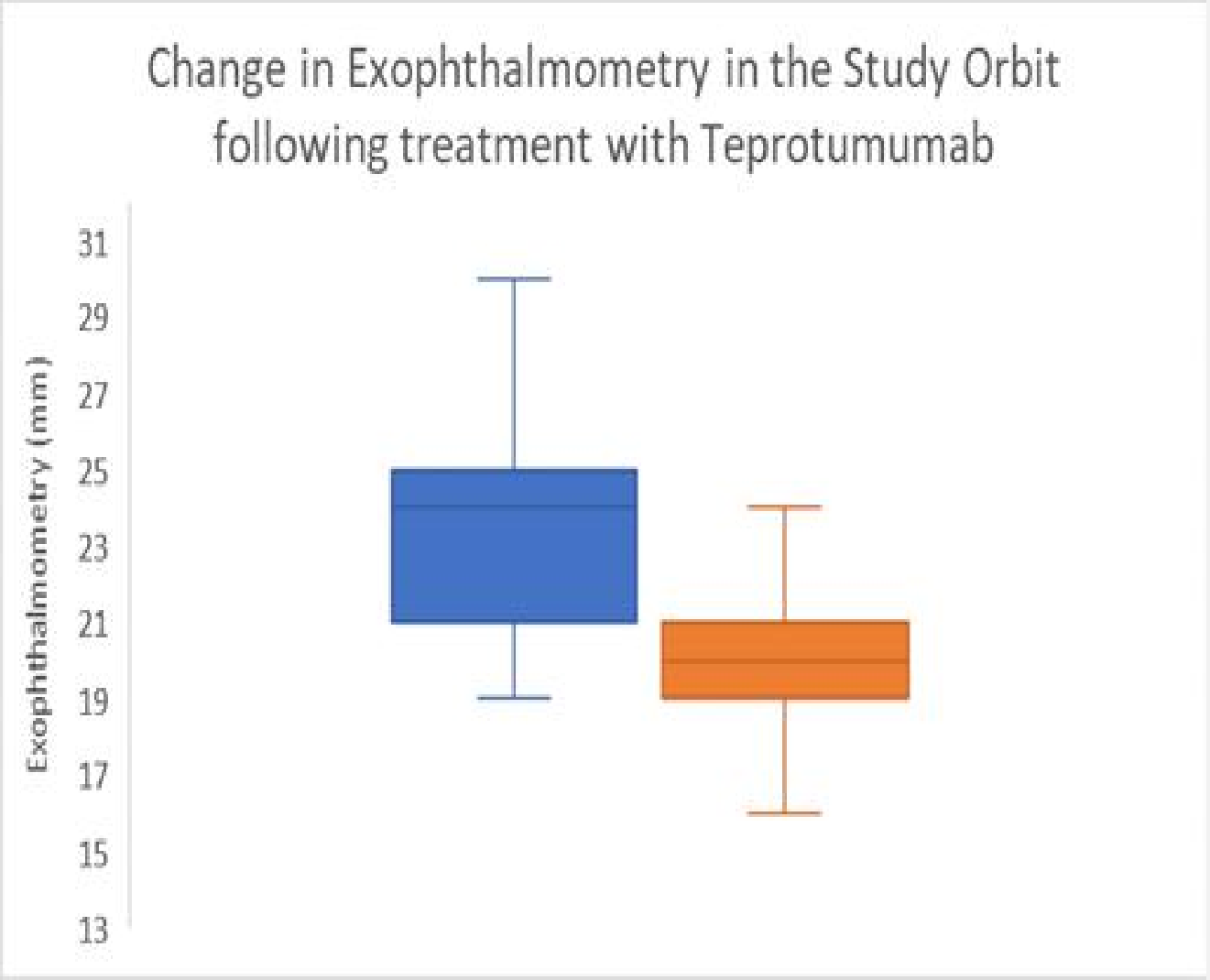
Significantly increased expression of insulin-like growth factor-1 receptor (IGF-1R) was seen in the orbital tissue of patients with inflammatory and noninflammatory TED compared with controls






Chronic TED
Stimulation of IGF-1R and IGF-1R/TSHR (TSI, IGF, IGF-1R antibodies)
Increased receptor expression
TSH-R
IGF-1R
Orbital fibroblast
Constitutive HA, GAG, and EOM molecule synthesis

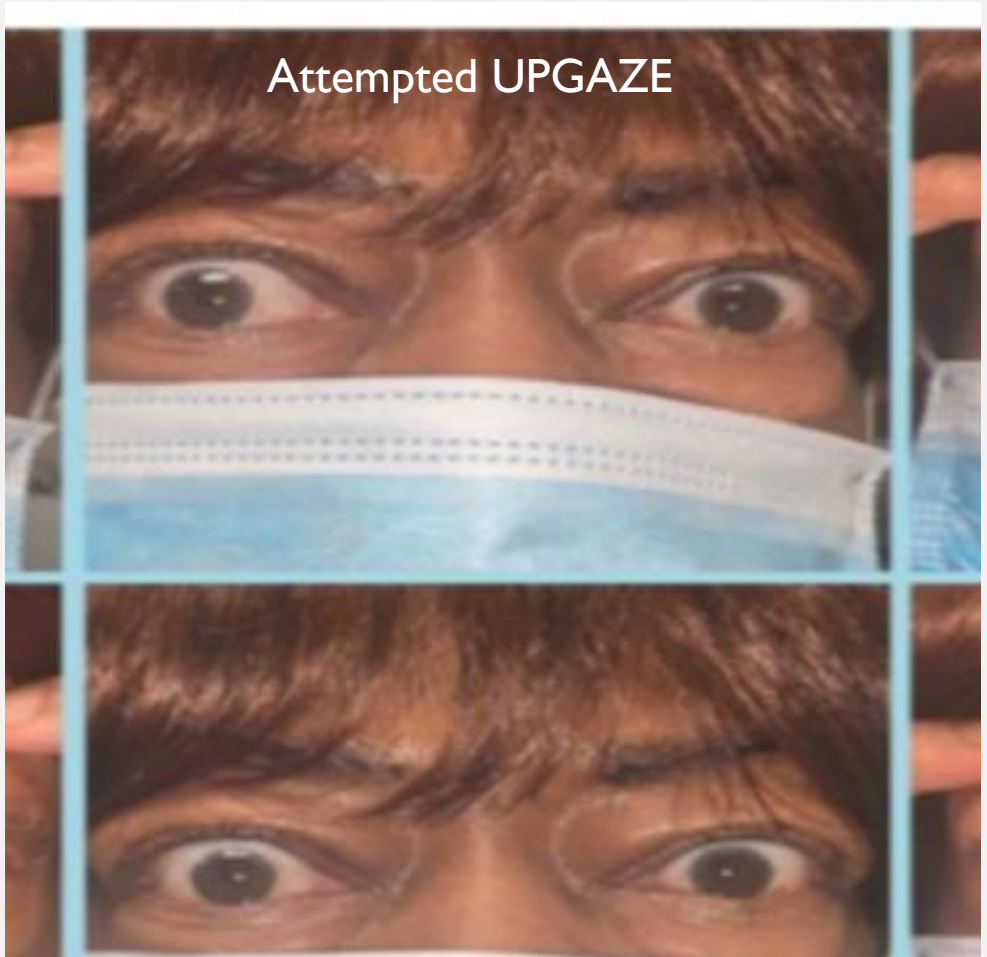
TEPROTUMUMAB REDUCES PROPTOSIS IN PATIENTS WITH CHRONIC TED



- Greater than 3 mm reduction in proptosis over the course of treatment.

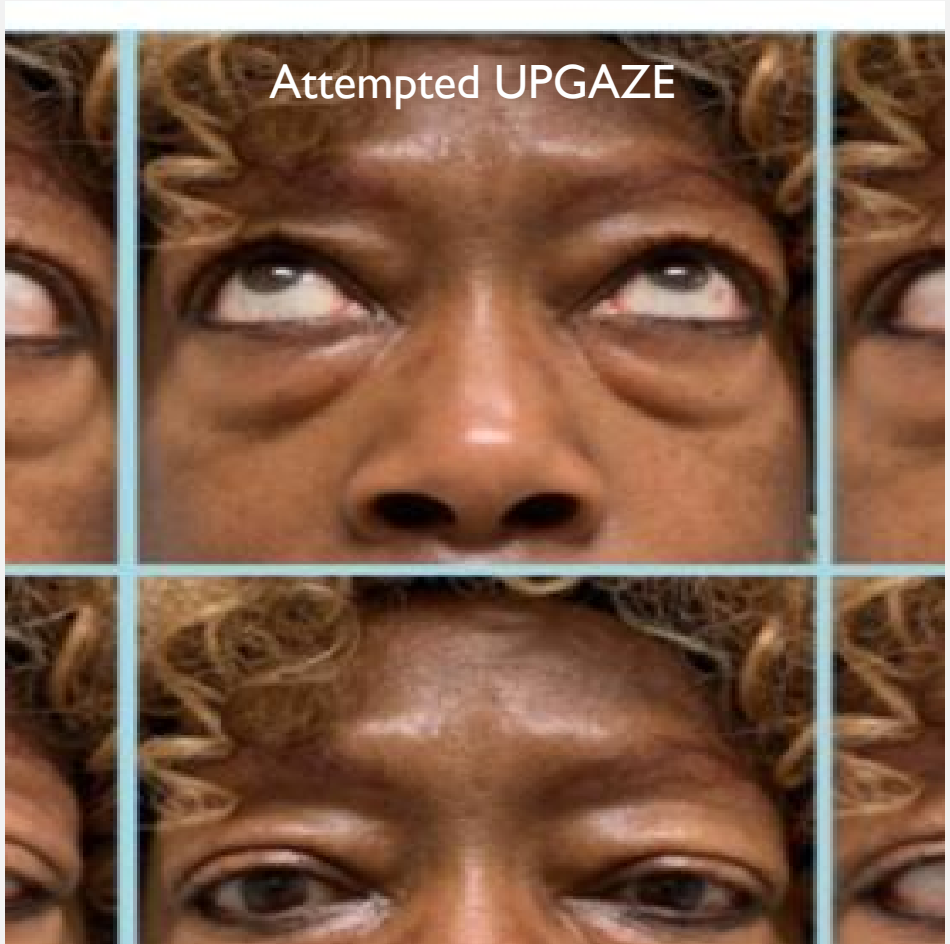
IMPROVED DOUBLE VISION

Before Teprotumumab



8 Infusions of Teprotumumab

After Teprotumumab



EFFICACY COMPARISON – DECOMPRESSION SURGERY

Study	n (Pts.)	n (Eyes)	Change in Proptosis (mm)	Comment
Rootman et al. 2016 (UCLA) Retrospective	169	319	–3.8	33% Patients postoperatively developed strabismus requiring further surgery
Wu et al. 2016 (U Michigan) Retrospective	356	420	–3.8	Strabismus leading to binocular diplopia the most common complication
OPTIC Study Week 24*			–3.3	No evidence of strabismus complication – in contrast, marked improvement in subjective diplopia

*Data are mean reductions from baseline for patients with values at Week 24

Note: decompression surgery is performed on inactive TED – does not constitute a direct comparison for active disease

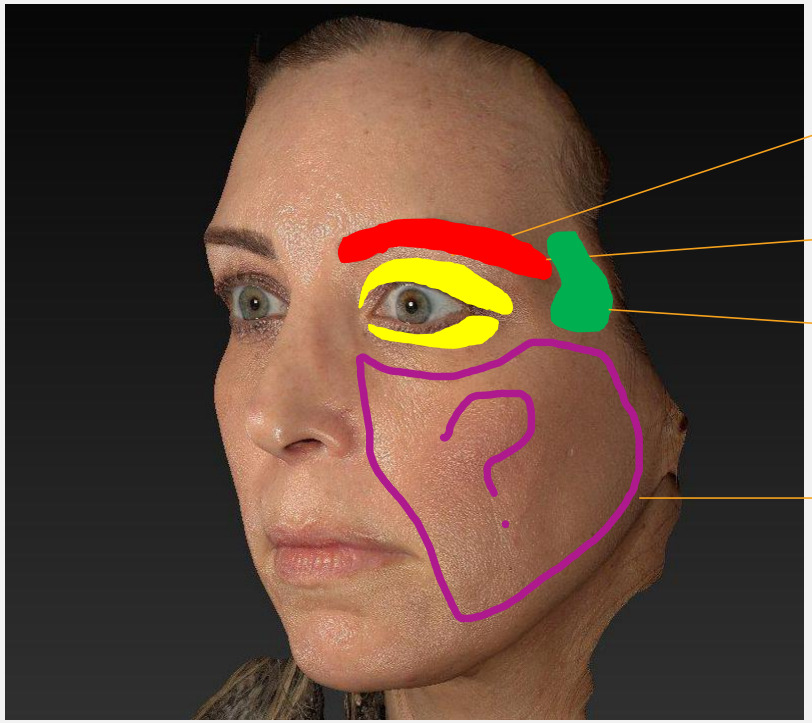
Recent reports suggest comparable reductions in proptosis

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

TISSUE SPECIFIC EFFECTS?

THYROID ASSOCIATED ORBITOPATHY

- Soft-tissue changes are not restricted to the orbit



Orbital soft tissue expansion

Brow fat expansion[1,2,3]

Temporal fat expansion[4]

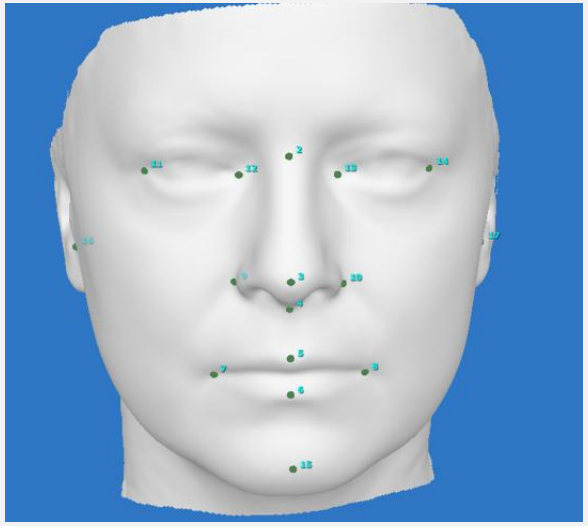
? Facial – Superficial and deep fat compartments

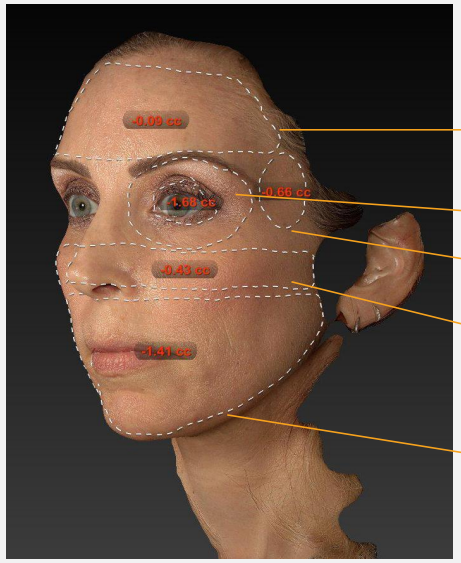
Retroperitoneal fat expansion in GD[5]

1. Hwang CJ, Khadavi NM, Papageorgiou K, et al. . Histopathology of brow fat in thyroid-associated orbitopathy. *Ophthalmic Plast Reconstr Surg*. 2012;28:27–29.
2. Savar LM, Menghani RM, Chong KK, et al. . Eyebrow tissue expansion: an underappreciated entity in thyroid-associated orbitopathy. *Arch Ophthalmol*. 2012;130:1566–1569.
3. Papageorgiou KI, Hwang CJ, Chang SH, et al. . Thyroid-associated periorbitopathy: eyebrow fat and soft tissue expansion in patients with thyroid-associated orbitopathy. *Arch Ophthalmol*. 2012;130:319–328
4. Choudhary MM, Zhang KR, Johnson S, et al. . Temporal fat pad volume in patients with thyroid eye disease. *Ophthalmic Plast Reconstr Surg*. 2020;36:194–197
5. Yoshida H, Nakajima K, Hayashi H, Kimura S, Irie Y. An unusual finding of giant fat-rich retroperitoneal masses in a patient with Graves' disease. Oxford Med. Case Reports. 2020; 2020(7): 203–206

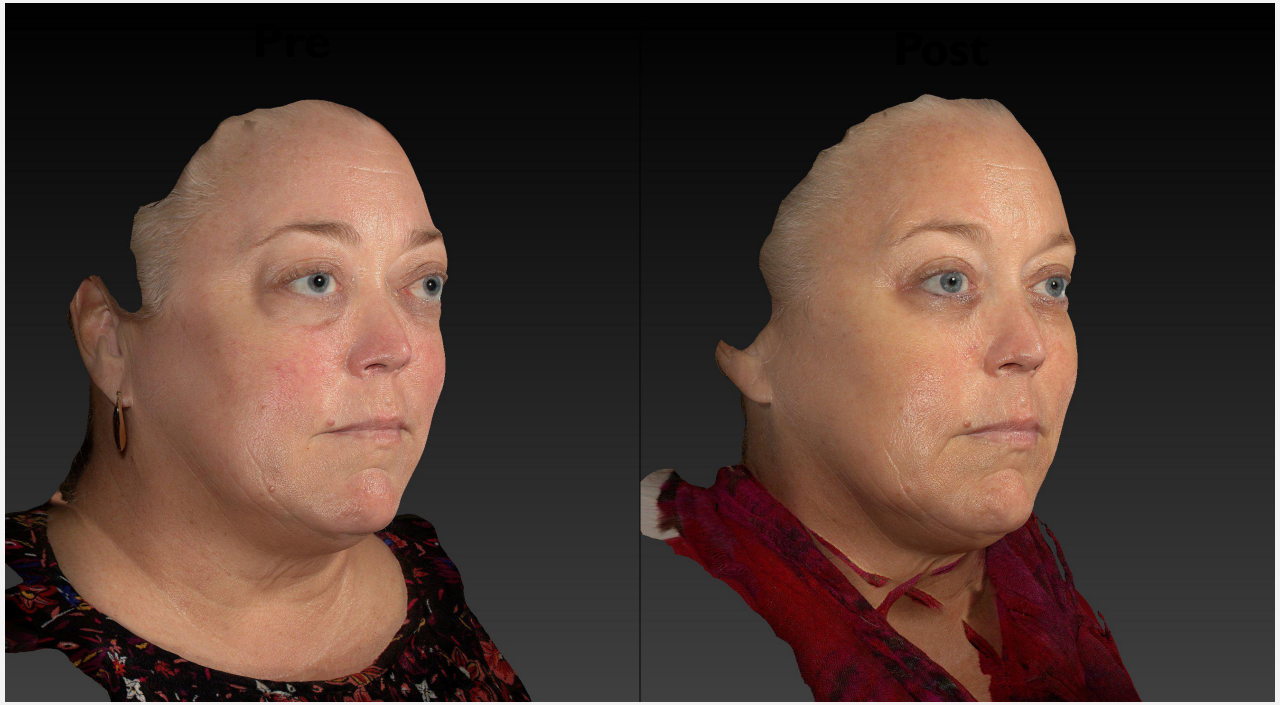
3D STEREOPHOTOGRAMMETRIC IMAGING

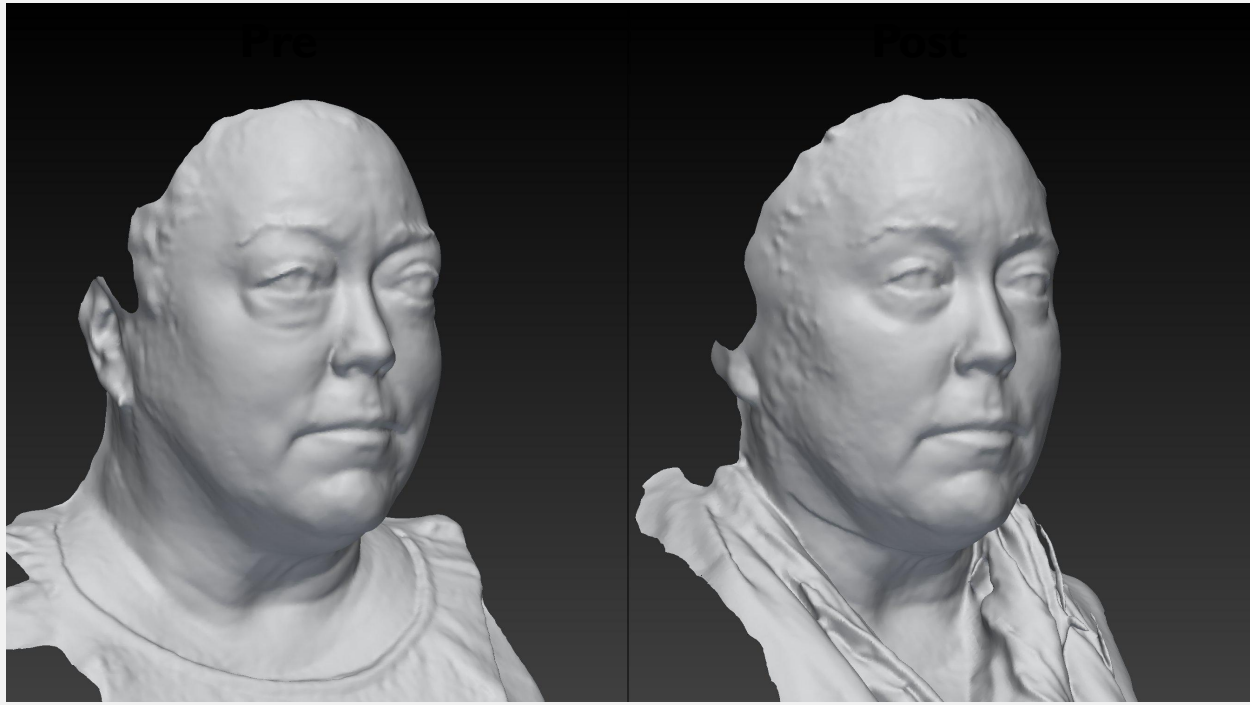
- H2 Vectra 3D imaging system (Canfield Scientific, Fairfield, N.J.) used to capture 3d facial imaging at each visit
- Standard landmarks used to register images to compare pre and post conditions





FACIAL VOLUME REDUCTION AFTER TEPROTUMUMAB





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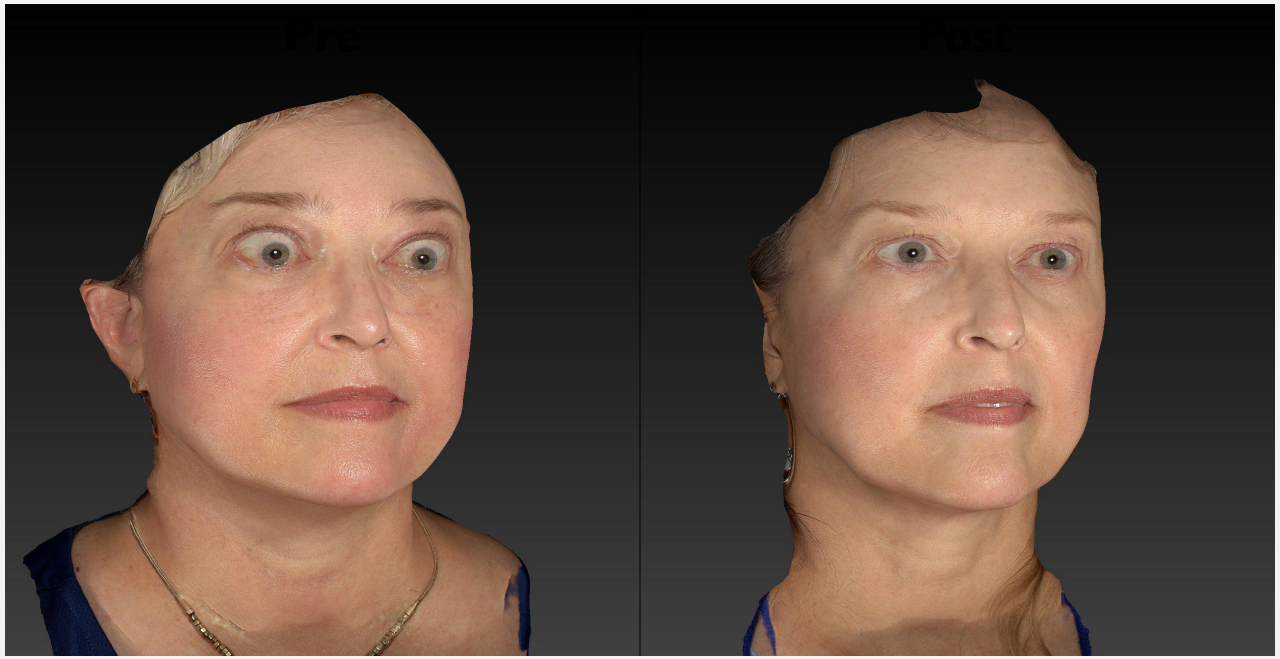
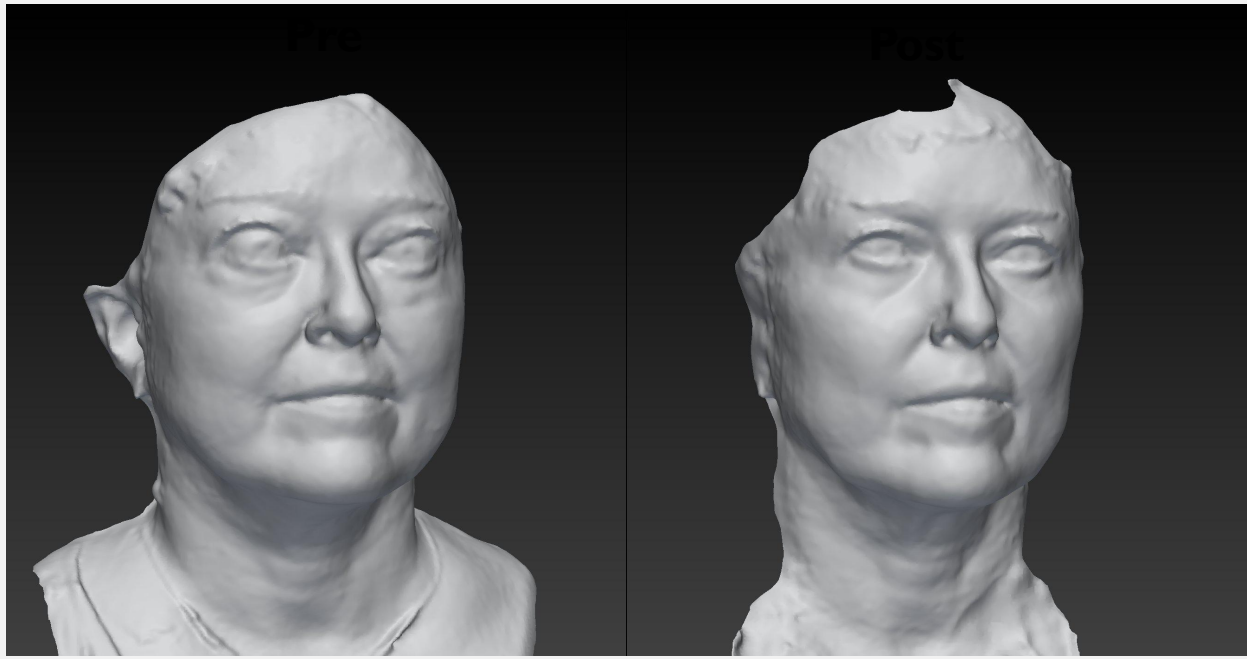
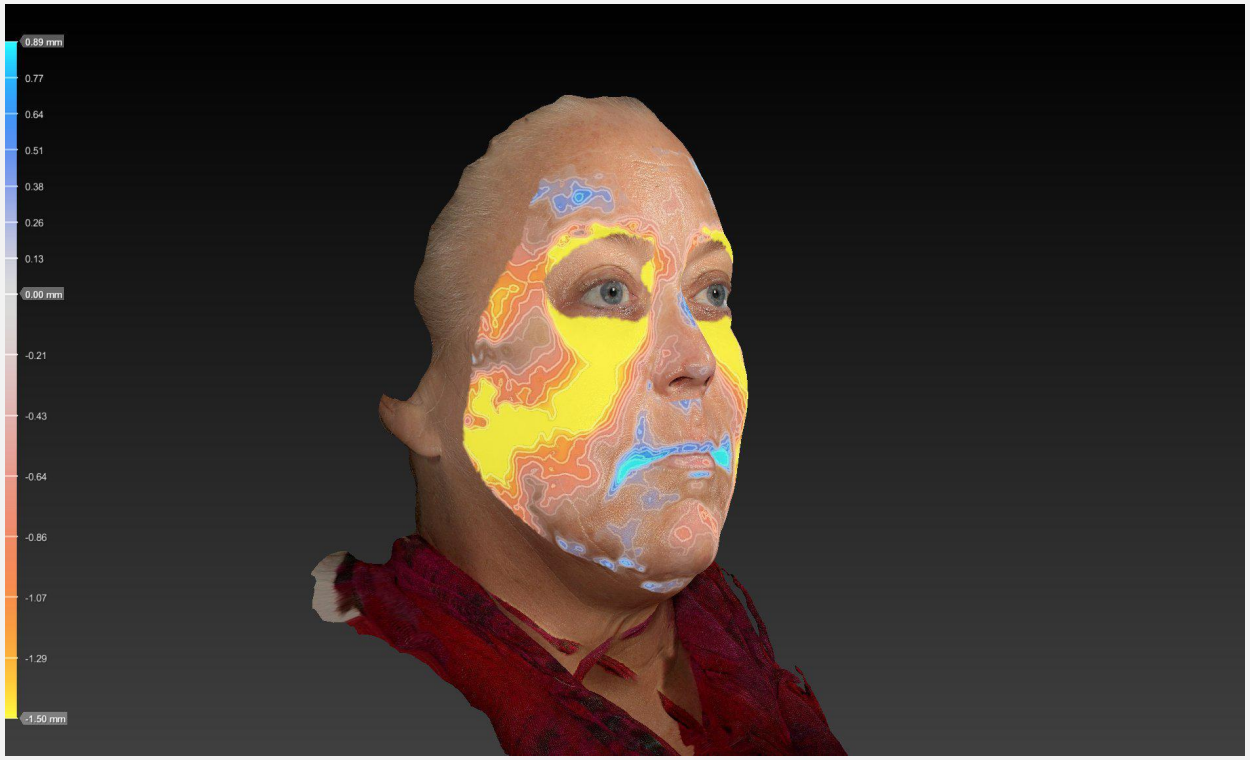




WHERE DID THE CHANGES OCCUR?



Region	Volume Change
Upper Face	-0.69 ml (0.8)
Orbit	-1.7 ml (1)
Temples	-0.16 ml (0.5)
Midface	-1.8 ml (2)
Lower Face	-2.6 ml (4.2)
Full Face	-8.4 ml (8.5)

IMPORTANT POINTS

- For all patients, there was no relationship between change in total body weight and facial volume ($p = 0.6$)

Volumetrics from Imaging

- Facial fat correlated best with overall soft tissue volume change
- The buccal fat pad showed the greatest change across the face

CONCLUSIONS

- Steroids do NOT reverse the underlying alterations of orbital tissue or reverse proptosis or strabismus and have substantial side effects

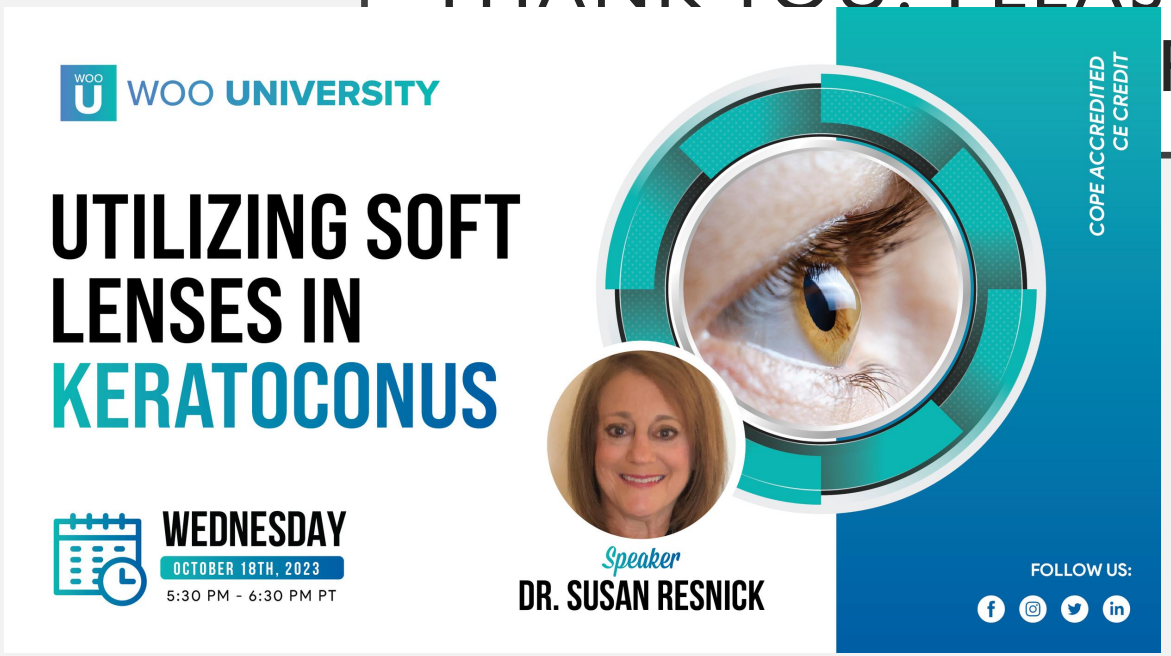
- *Teprotumumab*
  - Phase 3, placebo-controlled study of teprotumumab demonstrated a significant reduction in proptosis
  - Teprotumumab is highly effective in reducing proptosis, supporting a positive benefit/risk profile in the treatment of TED, with apparent disease-modifying activity
  - Teprotumumab is FDA approved for TED
  - Appears to be specific to diseased tissue
  - Has proven efficacy in chronic TED

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.
Teprotumumab. Prescribing Information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761143s000lbl.pdf

If you have any questions, you may send an email to

raymonddouglasmd@gmail.com

THANK YOU! PLEASE JOIN US FOR OUR P



Date: October 18, 2023
Time: 5:30 PM - 6:30 PM PT

Date: October 19, 2023
Time: 5:30 PM - 6:30 PM PT

METHODS – STUDY DESIGN

- *Prospective Longitudinal Study*

  - **Inclusion:** Consecutive patients over the age of 18 with GD related TAO, who were scheduled to receive teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions) every 3 weeks with the intention to complete 8 infusions over 24 weeks.

  - **Exclusion:** Anyone on any other medical therapy for TED or those that had received rituximab or tocilizumab in the past. Furthermore, patients who had any plans to embark on a weight loss regime, or medications that might cause weight loss were also excluded

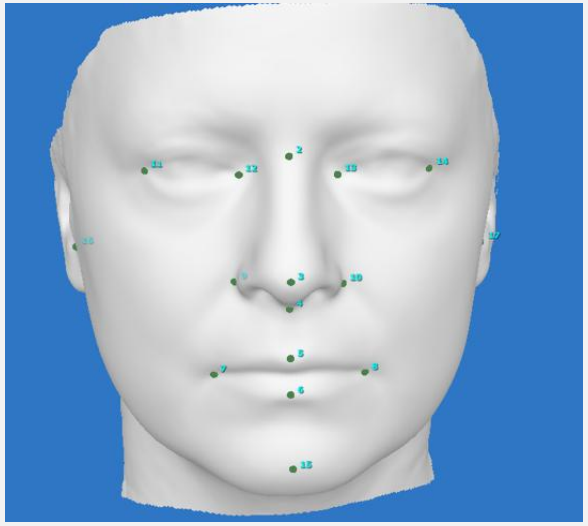
OUTCOME MEASURES

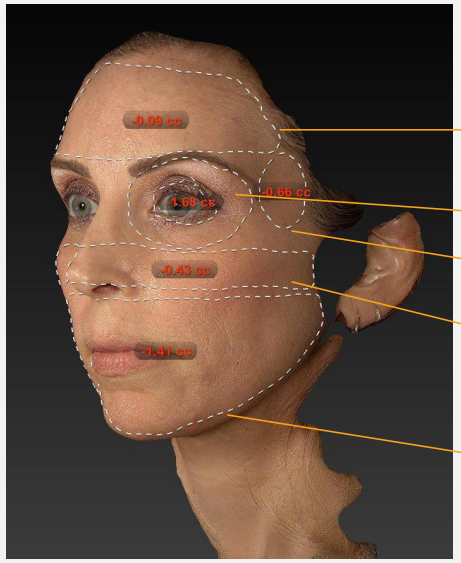
- **Primary Outcome:** To quantify facial soft-tissue changes following treatment with teprotumumab in patients with TED

- Secondary outcomes included characterization of eyelid changes
  - MRD1, MRD2, Intercanthal Distance of the same orbit
  - CAS, Proptosis and body weight

3D STEREOPHOTOGRAMMETRIC IMAGING

- H2 Vectra 3D imaging system (Canfield Scientific, Fairfield, N.J.) used to capture 3d facial imaging at each visit
- Standard landmarks used to register images to compare pre and post conditions



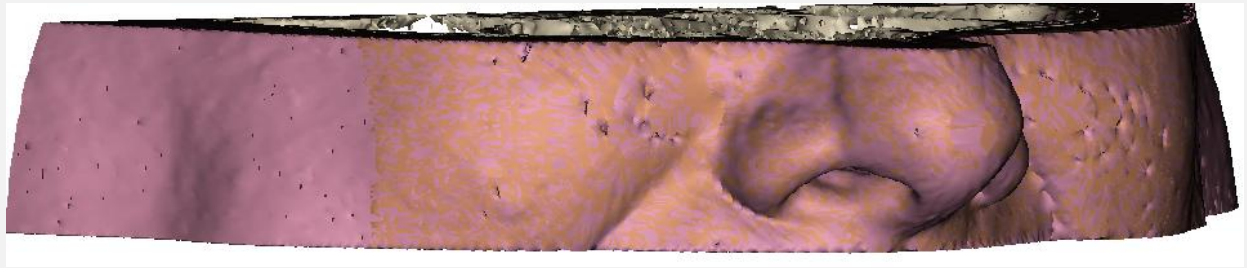


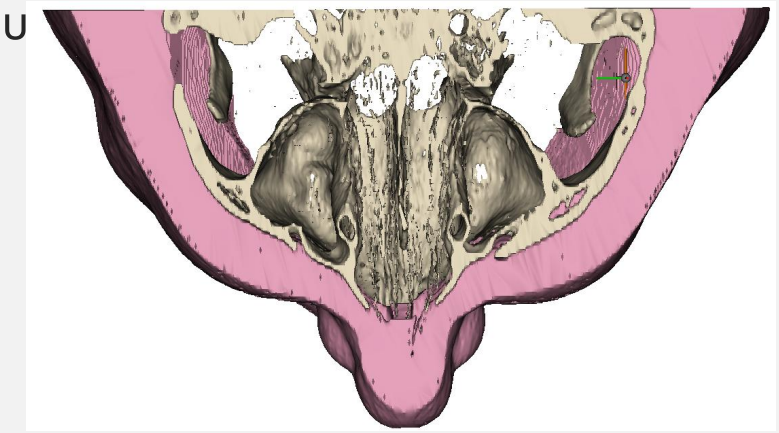
VOLUMETRIC STUDY

- CT / MR scans from each patient at baseline and final visit were analyzed using previously validated MIMICS Materialise software MIMICS (Materialise, Leuven, Belgium).

- 3D Reconstructions of each scan were created, using the program's AI to define: skin, muscle, fat and bone – previously validated[1]

- Using previously defined regions of the face, volumes of each tissue constituent were calculated and subtracted from bone, thereby allowing calculation of soft tissu





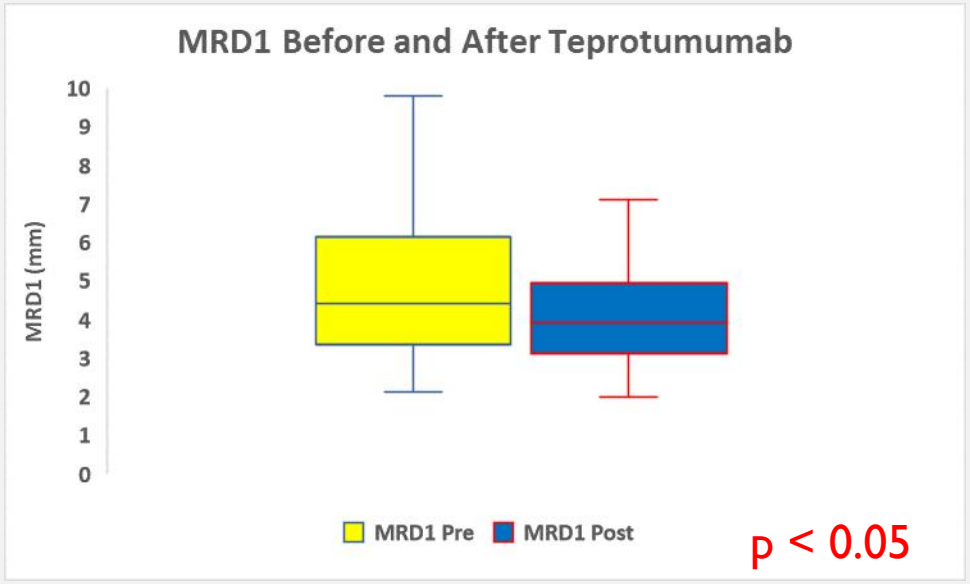
1. Regensburg NI, Kok PHB, Zonneveld FW, Baldeschi L, Saeed P, Wiersinga WM, et al. A new and validated CT-Based method for the calculation of orbital Soft tissue volumes. Investig. Ophthalmol. Vis. Sci. 2008; 49(5): 1758–1762.

RESULTS

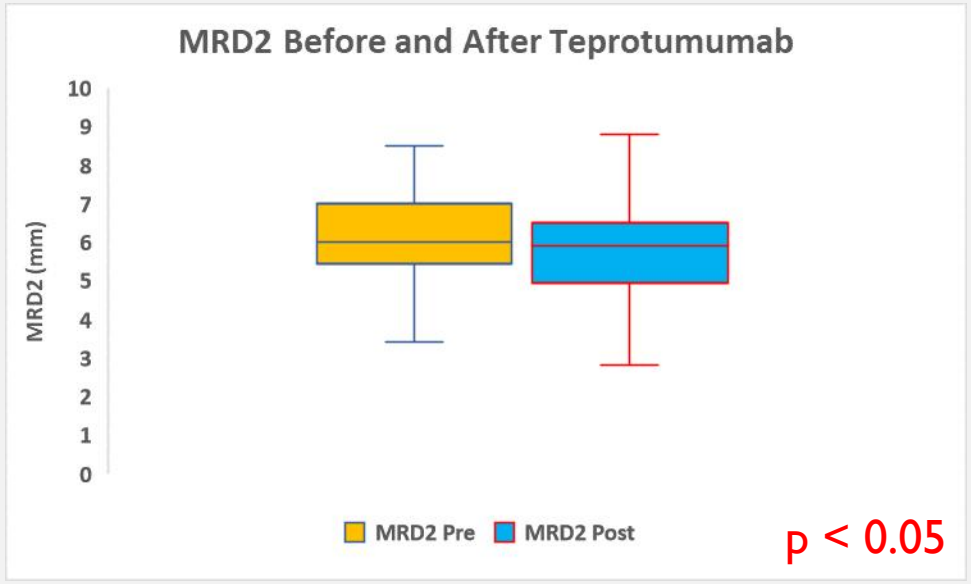
- 43 Pati

- The mean duration of TED prior to therapy was 30 months (34)
- Mean (SD) weight prior to therapy was 74 kg (9) and 71 kg (7) following therapy ($p < 0.05$)

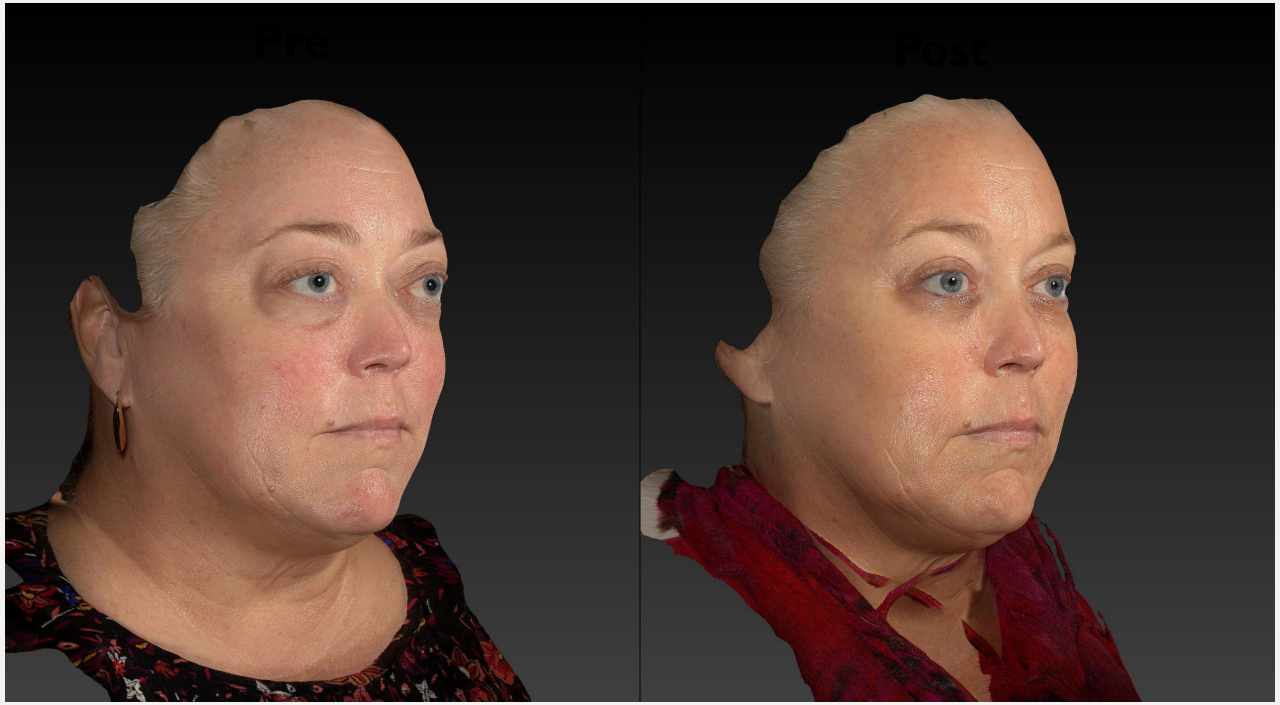
MRD1

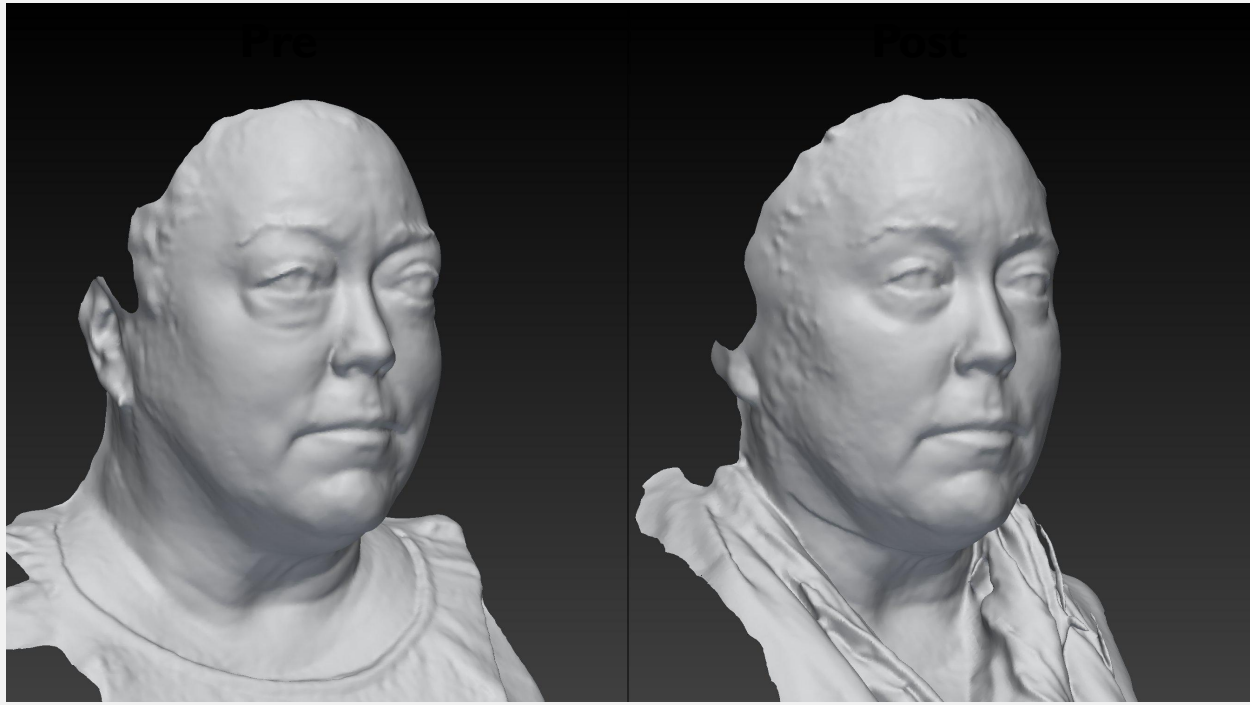


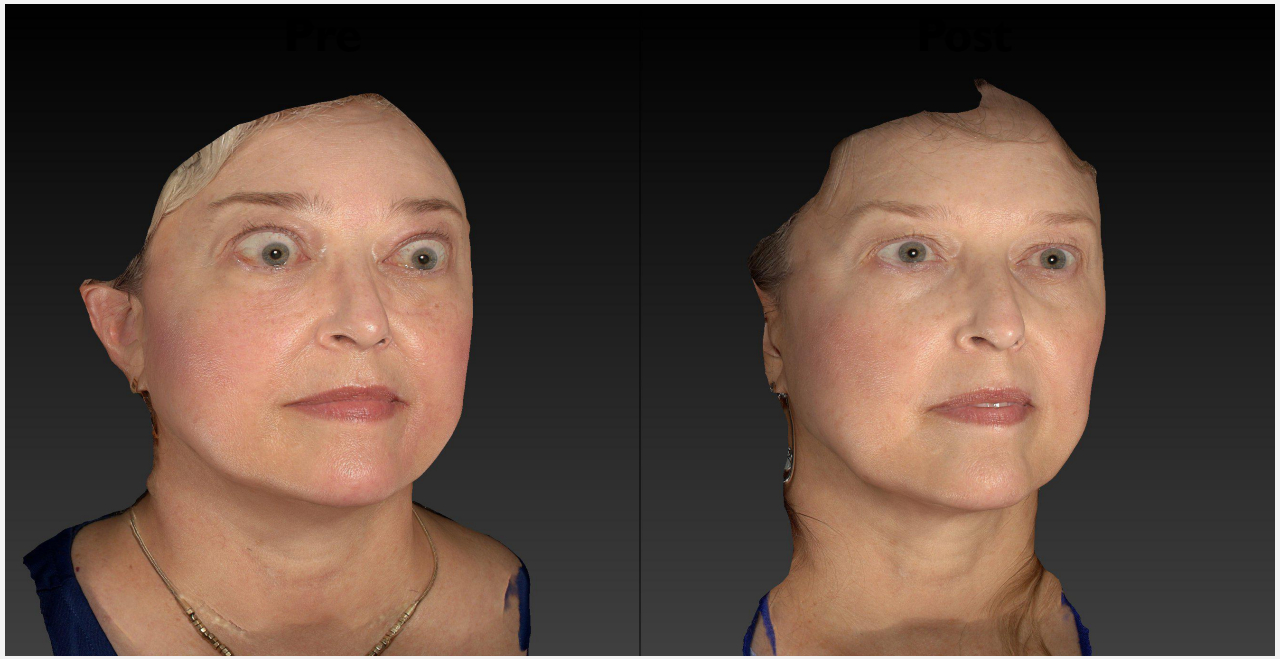
MRD2

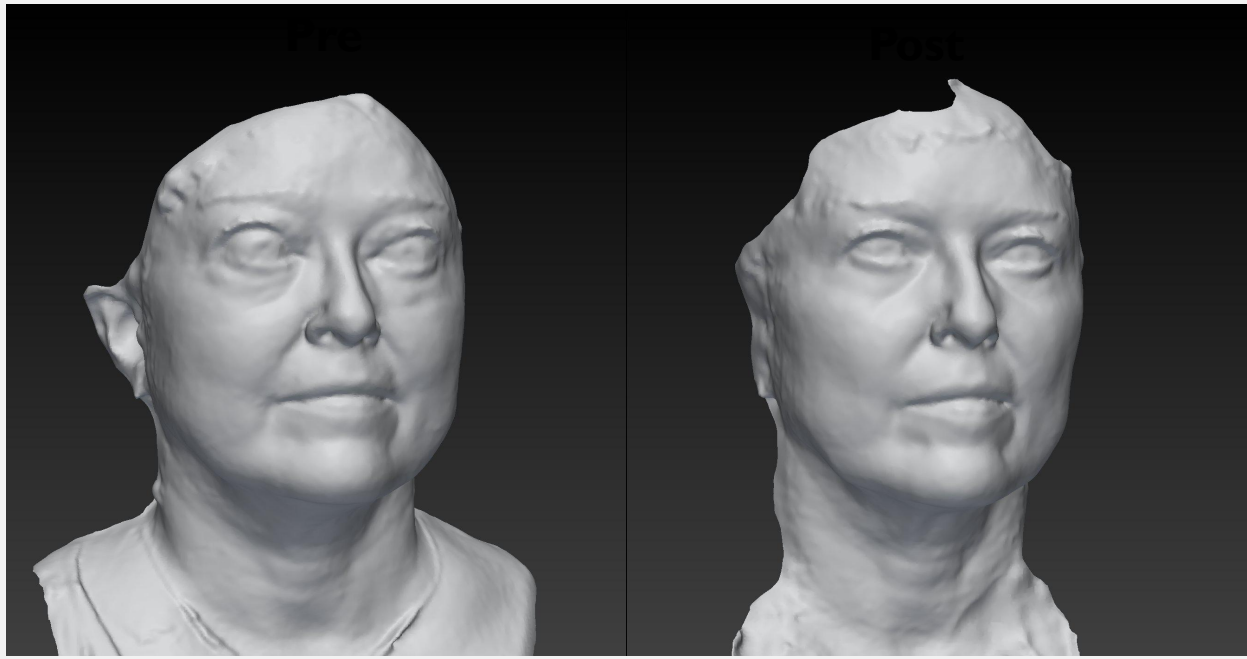


FACIAL VOLUME

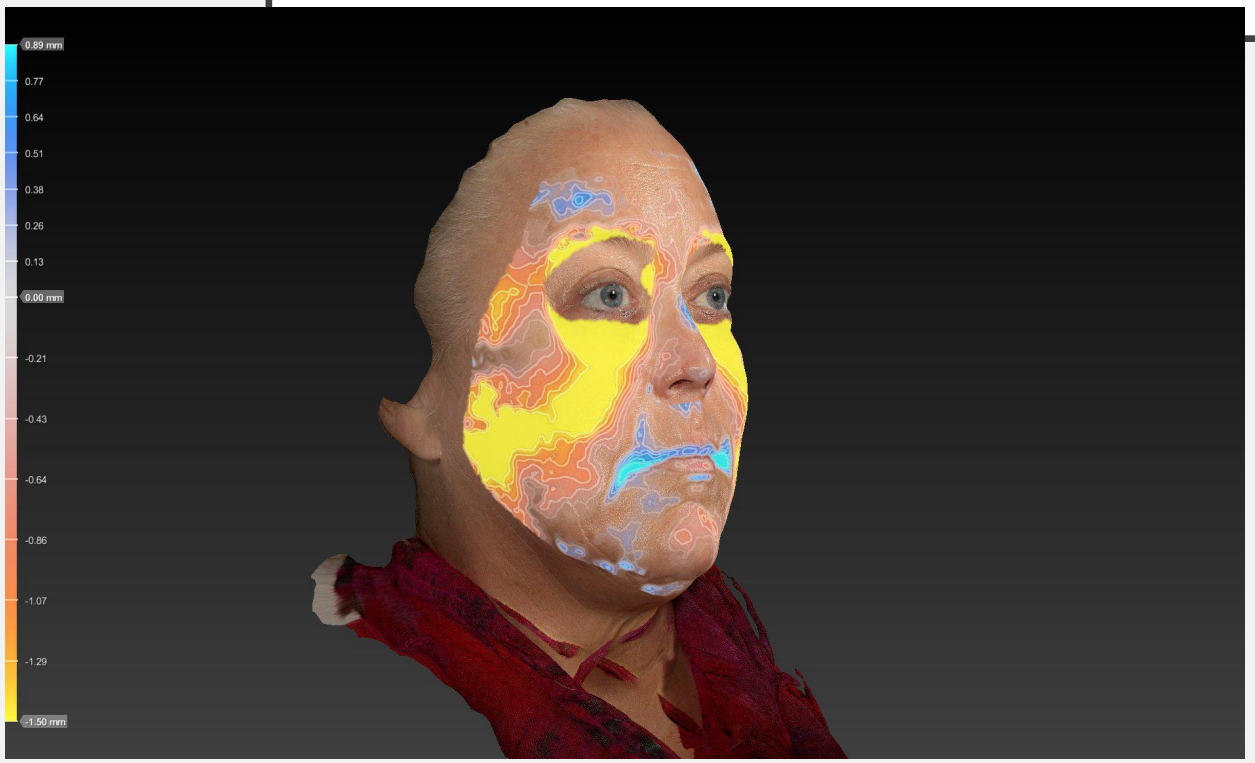





Pre
Post


Pre
Post

WHERE DID THE CHANGES OCCUR?



Region	Volume Change
Upper Face	-0.69 ml (0.8)
Orbit	-1.7 ml (1)
Temples	-0.16 ml (0.5)
Midface	-1.8 ml (2)
Lower Face	-2.6 ml (4.2)
Full Face	-8.4 ml (8.5)

IMPORTANT POINTS FORM THE DATA

Subgroup Analysis

- 18 patients had used steroids at some point in disease course (none within preceding 6 weeks). There was no difference between the steroid group and non steroid group for facial volume change ($p = 0.1$) or MRD1 ($p = 0.6$) and MRD2 ($p = 0.4$).

- For all patients, there was no relationship between change in total body weight and facial volume ($p = 0.6$)

Volumetrics from Imaging

- Facial fat correlated best with overall soft tissue volume change
- The buccal fat pad showed the greatest change across the face
- Good correlation between Imaging and 3D stereophotogrammetric
    - Bland Altman Analysis – limit of agreement for volume was between 0.9 ml and 1.4 ml (95% of values for both methods lies between these figures) for the full face
- Finally, ICC between 0.97 and 0.99 for measurements across the face for volume in different facial regions.

CONCLUSIONS

- Treatment with Teprotumumab was associated with:
  - Weight loss of about 3kg (6)
  - Reduction in total facial volume of 8.4 ml (Lower face > midface >orbit)
  - Reduction of MRD1 and MRD2

- TAO may only be the most striking sign of GD on the face, but the whole face is generally involved
- Teprotumumab reverses these changes
- We may need to start thinking about the concept of this condition in terms of a thyroid facial disease, rather than just an orbitopathy – important psychosocial implications.

CONCLUSIONS

- Overexpression of IGF-1R is hallmark of disease
- Teprotumumab blocks the IGF-1R and IGF-1R/TSHR signalling cascade in Active and Chronic disease
- Reduced inflammation, and extracellular matrix deposition
- Durable clinical improvement in TED