Teprotumumab Treatment Effect on Proptosis in Patients with Active Thyroid Eye Disease: Results from a Phase 3, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study

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2. Horizon Pharma USA, Inc.
3. University of Michigan Kellogg Eye Center
4. Johannes Gutenberg University Medical Center
Forward Looking Statement

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Financial Interest: Consultant Horizon Pharma 2019
Treatment of Thyroid Eye Disease

Theory

Reality
The Three Components of Graves’ 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
Inflammation → Fibrosis
How Do Thyroid Eye Disease (TED) Patients Present? Clinical Activity and Severity of TED

Definable and Identifiable Criteria for Moderate-to-Severe TED

- Lid swelling / redness
- Chemosis (swelling of conjunctiva)
- Swelling of plica and caruncle
- Conjunctivitis
- Orbital prolapse of fat tissue
- Proptosis
- Lid retraction
Proptosis (Bulging of Eyes)

Swelling or bulging of the eye that results in:
- Diplopia (double vision)
- Difficulty closing eye (sleep, ulcerations)
- If asymmetric, can cause strabismus (abnormal alignment)
- Compress optic nerve (blindness)

Healthy Eye and Orbital Tissue in Normal Condition
- Eye is well protected by lid
- Thin periorbital muscles
- Optic nerve can easily pass through apex
- Orbit contains a small amount of tissue and fat

In Presence of Severe TED
- Inflamed and enlarged muscles due to fluid accumulation
- Lid retraction
- Compression of the optic nerve at orbital apex
- Eye protrusion
- Lid and conjunctival redness
- Increase in orbital tissue and fat

Source: INDIGO Project.
Diplopia (Double Vision)

- Two images of a single object are seen resulting from unequal action of the eye muscles
- Misalignment of one or both eyes
- Headache
- Nausea

Source: AllAboutVision.com and WebMD.
Thyroid Eye Disease

• Progressive, autoimmune inflammatory disease often with extensive fibrosis

• Proptosis, strabismus and permanent facial disfigurement

• Currently no FDA-approved therapies for TED

• “Standard of Care” watch and wait - then surgery

• Off label therapies used clinically for active TED have not demonstrated improvement in proptosis when compared with placebo in clinical trials
What should treatment target?

<table>
<thead>
<tr>
<th>Short Term Manifestations</th>
<th>Long Term Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>Eye bulging and disfigurement</td>
</tr>
<tr>
<td>Redness</td>
<td>Double vision</td>
</tr>
<tr>
<td>Discomfort</td>
<td>Quality of life</td>
</tr>
<tr>
<td>CAS</td>
<td>Facial changes</td>
</tr>
</tbody>
</table>
Important Considerations for Treatment - THEORY

- Decrease Inflammatory Signs
- Reduce Proptosis
- Reduce Double vision
- Improve Quality of Life
- Minimal Side Effects
- Eliminate or Minimize Surgical Treatment
Current Reality: Steroids / Radiation etc.

• Do **NOT** reverse the underlying alterations of orbital tissue
• Do **NOT** reverse proptosis or strabismus
• Often Substantial side effects
The Path to Treat TED

Personalized Treatment:

- Reduce Risk of development / progression
  - Treatment of thyroid
  - Reduce autoimmunity through diet

- Biologic treatment of TED
  - Molecular targeting of antigen

- Treatment of residual effects of disease
  - Personalized minimally or noninvasive improvement of function and appearance.
What about TED specific therapy???

.....*Not immune based*
Heterogeneous disease

Delineate the common molecular mechanisms to interrupt process
Heterogeneous disease

Delineate the common molecular mechanisms to interrupt process
Antigen specific therapy blocking Insulin-like Growth Factor-1 Receptor (IGF-1R)
TSHR and IGF-1R...

- autoantigens, central to disease process
- circulating stimulating antibodies
Autoantibodies to the TSHR

- Endocrine abnormalities
- Incomplete explanation of disease
- Fails to explain orbital manifestations
- TSHR auto-immunity alone does not recapitulate disease 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

Thyroid Eye Disease: Mechanism

- Cytokines (e.g. IL-16, RANTES)
- T-Cell / Monocyte Infiltration
- Inflammation
- Proliferation
- Adipogenesis
- Tissue Edema
- Hyaluronan

GD-IgG connects to GO Orbital Fibroblast
IGF-1R and TSHR – “kissing cousins”

- Is autoimmunity to TSHR and IGF-1R mutually exclusive?
- Many examples where multiple autoantigens are necessary for full manifestation of disease.
- But what if these receptors were related?
Muscle

Fibroblast

TSI
GD-IgG

IGF-1R

TSHR
Teprotumumab

- Fully human monoclonal antibody inhibitor of IGF-1R
- Targeted binding to 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
Thyroid Eye Disease: Disease Time Course

Disease Activity

1.5 → 2

3 → 6

years

Active

Inactive

Teprotumumab

Untreated

Efficacious therapy

Smith & Douglas (2011)
Teprotumumab Phase 2 Results Published in The New England Journal of Medicine

“In conclusion, a 24-week course of teprotumumab therapy provided clinical benefit in patients with active, moderate-to-severe thyroid-associated ophthalmopathy by reducing proptosis and the Clinical Activity Score and by improving the patients’ quality of life.” (1)

Clinical Activity Score (CAS): A 7-point scale that measures change in orbital inflammation and pain; a score of >3 indicates active TED. Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Phase 3 24-week randomized, double-masked, placebo-controlled treatment trial of Teprotumumab

Active TED
- 18 to 80 years
- ≤ 9 mo. since active TED onset with no prior treatment
- CAS ≥ 4
- FT4 and FT3 <50% above or below normal limits

Teprotumumab
Infusions q3w (total of 8)

Placebo
Infusions q3w (total of 8)

Screening
Randomization

Off Treatment
Follow Up Period

24 week Treatment Phase
(last dose at Week 21)

Follow Up

Primary Endpoint:
≥2 mm improvement in proptosis at Week 24
**Measures Utilized**

### Clinical activity Score (CAS)

**7-item CAS was used**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Spontaneous orbital pain</td>
</tr>
<tr>
<td>2</td>
<td>Gaze evoked orbital pain</td>
</tr>
<tr>
<td>3</td>
<td>Eyelid swelling that is considered to be due to active GO</td>
</tr>
<tr>
<td>4</td>
<td>Eyelid erythema</td>
</tr>
<tr>
<td>5</td>
<td>Conjunctival redness that is considered to be due to active GO</td>
</tr>
<tr>
<td>6</td>
<td>Chemosis</td>
</tr>
<tr>
<td>7</td>
<td>Inflammation of caruncle or plica</td>
</tr>
</tbody>
</table>

For initial CAS, only score items 1-7

Patients assessed after follow-up (1-3 months) can be scored out of 10 by including items 8-10

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>8</td>
<td>Increase of &gt;2 mm in proptosis</td>
</tr>
<tr>
<td>9</td>
<td>Decrease in uniocular ocular excursion in any one direction of &gt;5°</td>
</tr>
<tr>
<td>10</td>
<td>Decrease of acuity equivalent to 1 Snellen line</td>
</tr>
</tbody>
</table>


### Exophthalmometer

- **Proptosis**

### Diplopia Score

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no diplopia</td>
</tr>
<tr>
<td>1</td>
<td>intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening</td>
</tr>
<tr>
<td>2</td>
<td>inconstant, i.e. diplopia at extremes of gaze</td>
</tr>
<tr>
<td>3</td>
<td>constant, i.e. continuous diplopia in primary or reading position</td>
</tr>
</tbody>
</table>
Phase 3  Subject Disposition

83 underwent randomization
83 received study drug (ITT population)

42 randomized to received placebo
- 2 subjects discontinued early
  - Adverse event (1; “visual field defect”)
  - Withdrew consent (1)
- 40 completed double-masked treatment period

41 randomized to receive teprotumumab
- 2 subjects discontinued early
  - Adverse event (1; “infusion reaction”)
  - Withdrew consent (1)
- 39 completed double-masked treatment period
## Phase 3: Key Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=42)</th>
<th>Teprotumumab (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>48.9 (12.96)</td>
<td>51.6 (12.63)</td>
</tr>
<tr>
<td><strong>Gender, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26.2%</td>
<td>29.3%</td>
</tr>
<tr>
<td>Female</td>
<td>73.8%</td>
<td>70.7%</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88.1%</td>
<td>85.4%</td>
</tr>
<tr>
<td>Black</td>
<td>4.8%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Asian</td>
<td>2.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Other</td>
<td>4.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Years Since Diagnosis of Graves’ Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.905 (0.09 - 14.81)</td>
<td>1.040 (0.26 - 28.24)</td>
</tr>
<tr>
<td><strong>Months Since Diagnosis of Thyroid Eye Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.830 (1.05 - 10.33)</td>
<td>6.320 (0.92 - 9.67)</td>
</tr>
<tr>
<td><strong>Smoking Status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>81.0%</td>
<td>78.0%</td>
</tr>
<tr>
<td>Smoker</td>
<td>19.0%</td>
<td>22.0%</td>
</tr>
</tbody>
</table>
Phase 3  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≤0.001)
  • 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 one 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
Phase 2

Clinical Activity Score

![Graph showing change from baseline over weeks for Placebo and Teprotumumab]

- Placebo: P < 0.001
- Teprotumumab: P < 0.001

Proptosis Response (Reduction of ≥2 mm)

**Phase 2**
- **Teprotumumab (N=42)**
- **Placebo (N=45)**

**Phase 3**
- **Teprotumumab (N=41)**
- **Placebo (N=42)**

\[ \text{Difference}^{\dagger} = 73.45\% \\
95\%CI 58.89\%, 88.01\% \]

\[ ^\dagger \text{Stratified Difference in Response Rates. Estimates from the two strata (tobacco user, tobacco non-user) are combined with Cochran-Mantel-Haenszel weights.} \]
Proptosis Reductions in the Phase 2 and 3 Trials

**Phase 2**
- Teprotumumab (N=42)
- Placebo (N=45)

**Phase 3**
- Teprotumumab (N=41)
- Placebo (N=42)

Difference: -2.79
(95%CI -3.40, -2.17)

Change from baseline in proptosis as a continuous variable is based on Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline score, tobacco use status (non-user, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions.
## Overall Average Proptosis Reduction over the Treatment Period

<table>
<thead>
<tr>
<th>Proptosis (mm)</th>
<th>Baseline$^a$</th>
<th>Change from Baseline$^b$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=45)</td>
<td>23.1 ± 2.9</td>
<td>−0.15 ± 0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Teprotumumab (n=42)</td>
<td>23.4 ± 3.2</td>
<td>−2.46 ± 0.20</td>
<td></td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=42)</td>
<td>23.2 ± 3.2</td>
<td>−0.54 ± 0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Teprotumumab (n=41)</td>
<td>22.6 ± 3.3</td>
<td>−2.82 ± 0.19</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Mean ± standard deviation

$^b$Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline score, tobacco use status (non-user, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean ± standard error
Phase 2

Individual Patient Plots

Placebo: Proptosis Change From Baseline

Teprotumumab: Proptosis Change From Baseline

*1 patient in placebo received a single dose of teprotumumab in error at week 15. Data from week 24 is not included for this patient.

Phase 2
Proptosis Reductions

Smokers

- Placebo
- Teprotumumab

Non Smokers

- Placebo
- Teprotumumab

Change from Baseline (mm)

Weeks

0 6 12 18 24

Change from Baseline (mm)

Weeks

0 6 12 18 24

Teprotumumab, N= 11 11 11 9
Placebo, N= 17 16 16 15

Teprotumumab, N= 29 29 28 29
Placebo, N= 25 25 25 24

p=0.002  p<0.001  p<0.001  p<0.001
p<0.001  p<0.001  p<0.001  p<0.001

Phase 2 Teprotumumab – effective regardless of baseline proptosis

Mean Reduction = 3.7

Mean Reduction = 2.6
Overall Responders– Proptosis + CAS

**Phase 2**
- Teprotumumab (N=42)
- Placebo (N=45)

**Phase 3**
- Teprotumumab (N=41)
- Placebo (N=42)

Overall responders: Reduction of ≥2 mm proptosis + ≥2 points CAS improvement

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

Difference†: 70.82%
(95% CI 55.89%, 85.75%)
No Acute Disease Recurrence 7 Weeks Off Treatment at Week 28

Overall and Proptosis Responders remained statistically significant at Week 28

- 73.8% [N = 31] of Teprotumumab treated were Responders and Proptosis Responders at Week 28 vs 13.3% [N = 6] in the placebo group, P<0.001

Phase 2  Maintenance of Proptosis Response with Teprotumumab: One Year Off Drug at Week 72

Subjects electing for additional TED therapy were counted as non-responders.
Important Considerations for Treatment

- Decrease Inflammatory Signs
- Reduce Proptosis
- Reduce Double vision
- Improve Quality of Life
- Minimal Side Effects
- Eliminate or Minimize Surgical Treatment
Phase 2  Subjective Diplopia Response

![Bar chart showing placebo and Teprotumumab results over weeks with significance levels](image)

Phase 2  Diplopia Improvement One Year Off Drug

- 38 subjects who received teprotumumab had any diplopia at baseline
- 26 subjects had improved diplopia (≥1 grade improvement from baseline) Week 24

69.2%
(18/26)

% with Week 24 Diplopia Improvement Who Maintained Improvement at End of Follow-Up
Phase 2

GO-QOL Visual-Functioning Improvement

Change from Baseline

Weeks

Placebo

Teprotumumab

P < 0.001

P = 0.006

P = 0.009

Important Considerations for Treatment

- Decrease Inflammatory Signs
- Reduce Proptosis
- Reduce Double vision
- Improve Quality of Life
- Minimal Side Effects
- Eliminate or Minimize Surgical Treatment
Table 3. Adverse Events and Serious Adverse Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Teprotumumab (N=43)</th>
<th>Placebo (N=44)</th>
<th>Summary Details of Adverse Events in Teprotumumab Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event during intervention†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (19)</td>
<td>4 (9)</td>
<td>Generally mild and reported after first and second infusions</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>8 (19)</td>
<td>2 (5)</td>
<td>Intermittent, 2 of 8 patients had muscle spasms for &gt;1 wk and received muscle relaxants</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (14)</td>
<td>2 (5)</td>
<td>Treatment occurred in 2 of 6 patients, 1 case designated as a serious adverse event (see below)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5 (12)</td>
<td>2 (5)</td>
<td>Mechanism-based adverse event</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>All mild and no treatment necessary</td>
</tr>
<tr>
<td>Dry skin</td>
<td>3 (7)</td>
<td>0</td>
<td>All mild, 1 patient used topical dry-skin cream</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 (7)</td>
<td>0</td>
<td>In 2 of 3 patients, a transient “metallic” taste reported on days 1–2</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>Generally mild, 1 patient took paracetamol</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (7)</td>
<td>0</td>
<td>“Tingling” reported in nose, feet, or chest; variable onset and in 2 of 3 patients occurred on 1 day</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>3 (7)</td>
<td>0</td>
<td>Disparate symptoms, onset, and duration (i.e., one case of unilateral hearing impairment with onset 16 wk after end of therapy; one case of mild bilateral hearing impairment that resolved, and one case of tinnitus in a patient with a history of tinnitus)</td>
</tr>
</tbody>
</table>

### Safety Overview

- Safety profile similar to Phase 2 with no new safety observations
- Drop-out rate was low (<5%) and balanced across arms
- No deaths

<table>
<thead>
<tr>
<th>Number of subjects (%)</th>
<th>Placebo (N=42)</th>
<th>Teprotumumab (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Emergent Adverse Events</td>
<td>29 (69.0%)</td>
<td>35 (85.4%)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>1 (2.4%)(^a)</td>
<td>2 (4.9%)(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Placebo: visual field defect requiring orbital decompression surgery (patient discontinued study)

\(^b\) Teprotumumab: pneumothorax (considered not related to study drug; patient had history of throat cancer with radiation treatment), infusion reaction (during first infusion; patient discontinued study)
**Phase 3** Safety Overview

- Specific Events of Interest based on Phase 2:

<table>
<thead>
<tr>
<th>Number of subjects (%):</th>
<th>Placebo (N=42)</th>
<th>Teprotumumab (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential infusion-related reaction</td>
<td>4 (9.5%)</td>
<td>6 (14.6%) *</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>4 (9.5%)</td>
<td>13 (31.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (11.9%)</td>
<td>4 (9.8%)</td>
</tr>
<tr>
<td>Hearing Impairment †</td>
<td>0</td>
<td>4 (9.8%)</td>
</tr>
</tbody>
</table>

* Includes 1 SAE of infusion reaction; †2 hypoacusis (resolved), 1 deafness (resolved), 1 tinnitus (occurred concurrent with sore throat, ongoing)

- Events were mild to moderate in intensity and no non-serious events led to discontinuation. Majority of events had resolved by the time of data cut.
### Safety Overview

- **Treatment Emergent Adverse Events occurring in >5% of Patients:**

<table>
<thead>
<tr>
<th>Number of subjects (%)</th>
<th>Placebo (n=42)</th>
<th>Teprotumumab (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Spasm</td>
<td>4 (9.5)</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (11.9)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (9.5)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2.4)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (11.9)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (9.5)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>0 (0.0)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0 (0.0)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (2.4)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>0 (0.0)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0.0)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (7.1)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>3 (7.1)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Influenza</td>
<td>3 (7.1)</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

- Vast majority of treatment-emergent adverse events were mild to moderate in intensity and no non-serious events led to discontinuation.
## Phase 2

### Orbital Surgeries During Off-Treatment Follow-Up

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Subject 1 § ¥</td>
<td>3 orbital surgeries</td>
</tr>
<tr>
<td>Placebo Subject 2 §</td>
<td>2 orbital surgeries</td>
</tr>
<tr>
<td>Placebo Subject 3 §</td>
<td>1 orbital surgery (bilateral)</td>
</tr>
<tr>
<td>Placebo Subject 4</td>
<td>2 orbital surgeries</td>
</tr>
<tr>
<td>Placebo Subject 5</td>
<td>1 orbital (bilateral) and 1 lid surgery</td>
</tr>
<tr>
<td>Teprotumumab Subject 1 §</td>
<td>1 orbital surgery</td>
</tr>
<tr>
<td>Teprotumumab Subject 2</td>
<td>2 orbital and 2 lid surgeries (elective)</td>
</tr>
</tbody>
</table>

§ = received corticosteroids  ¥ = received rituximab

One additional subject who had received placebo received corticosteroids

Two additional subjects who had received teprotumumab received corticosteroids
Important Considerations for Treatment -

**IN SUMMARY**

- Decrease Inflammatory Signs
- Reduce Proptosis
- Reduce Double vision
- Improve Quality of Life
- Minimal Side Effects
- Eliminate or Minimize Surgical Treatment
Patient Photographs from the Phase 2 Trial

Note: Photos provided with permission from Ray Douglas and Terry Smith as presented at the 48th Cambridge Ophthalmological Symposium and the 88th Annual Meeting of the American Thyroid Association.
Conclusions

• This pivotal phase 3, placebo-controlled study of teprotumumab demonstrated a significant reduction in proptosis, confirming the phase 2 study results seen with this targeted IGF-1R inhibitor for the treatment of TED.

• These results confirm teprotumumab is highly effective in reducing proptosis, supporting a positive benefit/risk profile in the treatment of TED.
If approved, how might Teprotumumab be used?

First Line agent
- Only agent to reduce proptosis
- Reduced double vision
- Reduction of CAS quickly

Who will administer therapy?

Does it replace surgery?
- Scenario 1 – Moderate disease patients with improved double vision, CAS and proptosis
- Scenario 2 – Moderate to Severe disease- reduced surgery needed reduced complication rate