An Overview of Thyroid Eye Disease (TED) and Teprotumumab Clinical Data

October 4, 2018
Forward-Looking Statements

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Agenda

1. Horizon Pharma: Building an Innovation-Driven Biopharma Company
   - Shao-Lee Lin, M.D., Ph.D.
     EVP, Head of R&D and Chief Scientific Officer
     Horizon Pharma

2. Thyroid Eye Disease (TED): Disease Overview and Current Treatment Landscape
   - Raymond S. Douglas, M.D., Ph.D.
     Professor of Surgery
     Director of Orbital and Thyroid Eye Disease Program
     Cedars Sinai Medical Center

3. Teprotumumab: Phase 2 Trial Design and 24-Week Data
   - Raymond S. Douglas, M.D., Ph.D.
     Professor of Surgery
     Director of Orbital and Thyroid Eye Disease Program
     Cedars Sinai Medical Center

4. Teprotumumab: Phase 2 Trial 72-Week Data Presented at American Thyroid Association
   - George J. Kahaly, M.D., Ph.D.
     Professor of Endocrinology and Chief of Endocrine Outpatient Clinic
     Johannes Gutenberg University Medical Center

5. Teprotumumab: Phase 2 Trial Recap and Phase 3 Trial Design
   - Shao-Lee Lin, M.D., Ph.D.
     EVP, Head of R&D and Chief Scientific Officer
     Horizon Pharma

6. TED: Addressable U.S. Patient Population
   - Vikram Karnani
     EVP, Chief Commercial Officer
     Horizon Pharma

7. Q&A
Key Takeaways for Today’s Call

Thyroid eye disease (TED) is a rare and debilitating autoimmune disease of the orbit (area around the eye); moderate-to-severe TED impacts 15,000 to 20,000 U.S patients annually\(^{(1)}\)

- Estimated U.S. peak net sales potential of >$750M\(^{(2)}\)

No FDA-approved therapies exist; currently used therapies are not disease modifying; teprotumumab is the only medicine in clinical development for TED

Phase 2 data at Week 24 demonstrate that teprotumumab has the potential to be a disease modifying therapy for the treatment of TED\(^{(3)}\)

Phase 2 data at Week 72 (approximately one year off treatment) indicate teprotumumab has a durable response

Phase 3 data from the confirmatory OPTIC trial is expected in 2Q19 with FDA submission expected mid-2019

- Investigating retreatment and length of treatment in OPTIC-X (Phase 3 follow on study)

\(^{(1)}\) Company analysis of claims data and market research.

\(^{(2)}\) Horizon Pharma estimate.

Horizon Pharma: Building an Innovation-Driven Biopharma Company

Shao-Lee Lin, M.D., Ph.D.

EVP, Head of R&D and Chief Scientific Officer
Horizon Pharma
We Have Purposefully and Rapidly Transitioned to a Rare Disease Medicines Company

- Developed a highly successful commercial business, generating attractive growth and cash flows to support BD and growth initiatives
- Built a stable base of rare disease growth assets
- Added high-growth on-market and pipeline rare disease medicines
- Continue the evolution to generate long-term value
  - Commercial execution
  - Expanding our pipeline and building best-in-class R&D organization

Horizon Pharma
Initial Public Offering

July 2011

2011-2014

2014-2016

2016-2017

Continue the evolution to generate long-term value
- Commercial execution
- Expanding our pipeline and building best-in-class R&D organization
Transforming R&D at Horizon Pharma

Driving Horizon Pharma’s next transformation in building a robust pipeline of medicines for sustainable long term growth

Building our Team

- **Head of Development Sciences**
  - Leading critical development functions, including clinical pharmacology, statistics, toxicology and biomarkers

- **Head of External Research and Development**
  - Leading R&D efforts in identifying, evaluating and executing transactions in partnership with commercial, business development and other key functions

- **Rare Disease / Rheumatology Therapeutic Area Heads**
  - Leading the respective therapeutic areas’ clinical development strategies and portfolio management

Building our Pipeline

- **Approach to Continue Accelerating Our Momentum**
  - Maximize the value of our existing programs for patients
  - Expand and advance the pipeline to enable sustained growth
  - Build R&D to complement existing strengths and add new capabilities
# Our Pipeline – Today’s Focus on Teprotumumab

<table>
<thead>
<tr>
<th>MEDICINE / CANDIDATE</th>
<th>DESCRIPTION</th>
<th>PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>PHASE 3b / 4</th>
</tr>
</thead>
</table>
| **KRSTEXXA®**        | Immunomodulation Studies:  
  - MIRROR: KRSTEXXA + methotrexate  
  - RECIPE*: KRSTEXXA + mycophenolate mofetil  
  - TRIPLE*: KRSTEXXA + azathioprine |               |         |         |         |            |
| **RAYOS**            | RIFLE trial*: lupus |               |         |         |         |            |
| **RAVICTI®**         | Label expansion: birth to 2 months |               |         |         |         |            |
| **HZN-001 (teprotumab)** | OPTIC trial: Phase 3  
  - OPTIC-X trial: Phase 3 extension |               |         |         |         |            |
| HZN-003              | Optimized uricase and optimized PEGylation for uncontrolled gout |               |         |         |         |            |
| **PASylation**(2)    | Optimized uricase and PASylation for uncontrolled gout |               |         |         |         |            |

(1) Teprotumumab is a fully human monoclonal antibody (mAb) IGF-1R inhibitor in development for moderate-to-severe thyroid eye disease (TED).  
(2) Collaboration agreement.  
MIRROR: Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving KRSTEXXA.  
RECIPE: Reducing Immunogenicity to Pegloticase. TRIPLE: Tolerization Reduces Intolerance to Pegloticase and Prolongs the Urate Lowering Effect.  
TRIPLE: Tolerization Reduces Intolerance to Pegloticase and Prolongs the Urate Lowering Effect.  
RIFLE: RAYOS (delayed release prednisone) Inhibits Fatigue in Lupus Erythematosus.  
OPTIC: Treatment of Graves’ Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study.

= rare disease  
* Investigator-initiated trial

For us, it’s personal  
8
Teprotumumab Exemplifies the Next Phase of Our Strategy: Building a Pipeline for Sustainable Long-Term Growth

<table>
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<tr>
<th>Pipeline Candidate Criteria</th>
<th>Teprotumumab</th>
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| High unmet need with preference for rare diseases | ✓ No FDA-approved therapies exist for thyroid eye disease  
✓ Standard of care proven ineffective; safety concerns  
✓ Surgery is invasive, complex and often ineffective |
| Compelling clinical trial data or proof of concept | ✓ Impressive Phase 2 results published in *The New England Journal of Medicine*  
✓ Phase 3 trial underway; enrollment completed ahead of schedule |
| Key regulatory designations | ✓ U.S. Orphan; Fast-Track; Breakthrough Therapy |
| Compelling IP | ✓ 12-year biologic exclusivity |

*Teprotumumab meets ALL pipeline candidate criteria and has potential to be first therapy for thyroid eye disease (TED)*

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Thyroid Eye Disease (TED)

- **Debilitating** autoimmune inflammatory disease of the orbit (area around the eye)
  - Associated with Graves’ Disease, but TED is a separate and distinct disease
  - Impacts more women than men; typically happens mid-life; smoking worsens severity
- Inflammation behind the eye causes **proptosis** (bulging of the eyes)
  - Over time turns fibrotic causing permanent structural damage
- **Proptosis causes** diplopia (double-vision), strabismus (misalignment), compressed optic nerve (can threaten sight), ulcerations, pain, and can be disfiguring and emotionally debilitating
- Begins as **treatable active TED** and moves to inactive TED
Pathology of TED

- The body **attacks its own orbital cells which overexpress IGF-1R**
- The IGF-1R and TSHR are linked and **form a signaling complex**
- This leads to severe inflammation and **expansion of tissue**, muscle and fat cells behind the eye
- **Causes proptosis** (bulging of the eyes) and optic nerve compression

**IGF-1R**: Insulin-like growth factor-1 receptor.
**TSHR**: Thyroid stimulating hormone receptor.
TED: Disease Overview and Current Treatment Landscape

Raymond S. Douglas, M.D., Ph.D.
Professor of Surgery
Director of Orbital and Thyroid Eye Disease Program
Cedars Sinai Medical Center
Epidemiology and Risk Factors of TED

TED is Not Merely a Complication of Graves’ Disease (GD)

- TED is a separate and distinct disease although it is commonly associated with GD (hyperthyroidism)

- TED can occur before, during or after diagnosis of GD; can occur without thyroid disease
  - TED can present with hyperthyroid, hypothyroid or euthyroid
  - Phase 2 and Phase 3 trial patients had/have well-controlled thyroid disease

TED: Disease Progression

Active TED

Inflammation

Up to 3 Years

Inactive TED

Fibrosis

Beyond 3 Years

How Do TED Patients Present?

Clinical Activity and Severity of TED

Moderate-to-Severe Active TED

Normal

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

Source: Hearst Digital Media.
Conjunctiva: The mucous membrane that covers the front of the eye and lines the inside of the eyelids.
Plica: A small fold of bulbar conjunctiva on the medial canthus of the eye.
Caruncle: Small, pink, globular nodule at the inner corner (the medial canthus) of the eye.
Proptosis (Bulging of the Eye)

Swelling or bulging of the eye that can result in:

- Diplopia (double vision)
- Difficulty closing eye (sleep, ulcerations)
- Strabismus (misalignment)
- Optic nerve compression and potentially blindness

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

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

Source: INDIGO Project (indigo-iapp.eu).
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.
Testimonials of Patients Living with TED

“My social life has basically been non-existent since the bulging started.”

“You would think, ‘Oh, not being able to close your eye, that's not a big deal,’ but it was a big deal. It was so easy to irritate. I had to wear sunglasses to sleep; it felt like I was in a stupor.”

“I keep trying to be strong – but I feel that TED has robbed me of a normal life and my looks. I don’t know how much more I can take.”

“My colleagues know about the condition but it’s difficult talking to an acquaintance about it, or someone I just met...it can be kind of embarrassing.”

Source: Horizon Pharma market research and patient interviews.
Who Diagnoses TED and How is TED Treated?

Physicians Involved in Treatment and Diagnosis

- Primary Care
- Endocrinologist
- Ophthalmologist
- Oculoplastic Surgeon

How Is TED Treated Today?

- Active TED → Treat with Medicine
- Inactive TED → Treat with Surgery
## Active TED: Unapproved Treatments Are Suboptimal

**Pathogenic Mechanisms of Disease Not Targeted**

<table>
<thead>
<tr>
<th>Current Treatment</th>
<th>Steroids</th>
<th>Surgery (Emergency Basis)</th>
</tr>
</thead>
</table>
| **Deficiencies**  | • Do not reverse underlying alterations of orbital tissue  
        • Do not reverse proptosis or strabismus  
        • Significant side effects  |
|                   | • Performed during active TED only if optic nerve is threatened by proptosis, which could lead to blindness  
        • Complex procedure that usually requires multiple surgeries per eye  |

### UNMET NEED

There is a significant unmet need for a disease modifying treatment that can prevent the progression of the disease and prevent surgery.

**Strabismus:** Eye misalignment.
Inactive TED: Surgery Becomes Only Option

• Once TED becomes inactive, long-term damage is done

• Surgery becomes only option (1)
  – Complex with mixed results
  – Often requires multiple surgeries per eye because accumulation of fibrotic tissue complicates operations
  – Tens of thousands of dollars per surgery
  – While corrective for some, can result in permanent eye misalignment, double vision, lazy eye or blindness

(1) Surgical treatment can include decompression surgery, eyelid surgery and corrective vision surgery.
Potential Impact of Disease Modifying Therapy

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Up to 3 Years</th>
<th>Beyond 3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active TED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive TED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment during active TED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ideal Therapy</td>
<td></td>
<td></td>
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</tbody>
</table>

Pathology of TED

- The body **attacks its own orbital cells which overexpress IGF-1R**
- The IGF-1R and TSHR are linked and **form a signaling complex**
- This leads to severe inflammation and **expansion of tissue**, muscle and fat cells behind the eye
- **Causes proptosis** (bulging of the eyes) and optic nerve compression

IGF-1R: Insulin-like growth factor-1 receptor. TSHR: Thyroid stimulating hormone receptor.
Mechanism of Action of Teprotumumab in TED

- Fully human monoclonal antibody inhibitor of IGF-1R
- Blocks IGF-1R and turns off signaling complex at the source of the disease
- Intended to reduce inflammation and prevent excessive cell growth behind the eye

Teprotumumab “may result in a disease-modifying reduction in the volume of orbital fat, muscle or both”

IGF-1R: Insulin-like growth factor-1 receptor. TSHR: Thyroid stimulating hormone receptor.
Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Teprotumumab: Phase 2 Trial Design and 24-Week Data

Raymond S. Douglas, M.D., Ph.D.
Professor of Surgery
Director of Orbital and Thyroid Eye Disease Program
Cedars Sinai Medical Center
Phase 2 Trial Design

Patient Criteria

- Active TED
- 18 to 75 years
- <9 months since active TED onset with no prior treatment
- CAS ≥4
- FT4 and FT3 <50 percent above or below normal limits

Primary endpoint at Week 24
Percentage of participants with >2 mm reduction in proptosis and >2 point reduction in Clinical Activity Score (CAS)

Teprotumumab (N=42)
8 infusions: 1 every three weeks

Placebo (N=45)
8 infusions: 1 every three weeks

CAS: Clinical Activity Score, a 7-point scale that measures change in orbital inflammation and pain; a score of >3 indicates active TED.
FT4: Free thyroxine.
FT3: Free triiodothyronine.
Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
# Phase 2 Trial Measures Used

### Clinical Activity Score (CAS)

<table>
<thead>
<tr>
<th>No.</th>
<th>Measure</th>
</tr>
</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>

### Diplopia Score

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</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>


GO: Graves’ Orbitopathy, also known as thyroid eye disease, or TED.

Chemosis: Swelling of conjunctiva, which is the mucous membrane that covers the front of the eye and lines the inside of the eyelids.

Caruncle: Small, pink, globular nodule at the inner corner (the medial canthus) of the eye.

Plica: A small fold of bulbar conjunctiva on the medial canthus of the eye.

Diplopia: Double vision.
Teprotumumab: Early and Continued Response

Primary Endpoint Results (CAS and Proptosis)

Week 6

- Teprotumumab (N=42): 42.9% responders
- Placebo (N=45): 4.4% responders

Week 24

- Teprotumumab (N=42): 69.0% responders
- Placebo (N=45): 20.0% responders

Note: One placebo responder received a single dose of teprotumumab at Week 15 and became a responder at Week 18 through Week 72.

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.

Proptosis Improvement: Week 24

71.4 Percent of Teprotumumab Patients Responded


Note: One placebo responder received a single dose of teprotumumab at Week 15 and became a responder at Week 18 through Week 72. Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Diplopia Improvement: Week 24

61.9 Percent of Teprotumumab Patients Improved

61.9% of Teprotumumab patients improved at Week 24, compared to 22.2% of placebo patients. This difference is statistically significant, with a p-value of <0.001.

Note: One placebo responder received a single dose of teprotumumab at Week 15 and became a responder at Week 18 through Week 72. Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Safety Overview: 24-Week Treatment Period

• Most adverse events were mild, transient and did not require treatment
  – The most frequent adverse events reported (≥5 percent of teprotumumab and greater than placebo) were nausea, muscle spasms, diarrhea, alopecia, hyperglycemia, dry skin, dysgeusia, headache, paresthesia, hearing impairment and weight loss

• Hyperglycemia (grade 2 or 3) occurred in some diabetics receiving teprotumumab, and it was well controlled after adjustment of diabetes medication

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=45)</th>
<th>Teprotumumab (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>32 (72.7%)</td>
<td>32 (74.4%)</td>
</tr>
<tr>
<td>SAEs(^1)</td>
<td>1 (2.3%)</td>
<td>5 (11.6%)</td>
</tr>
</tbody>
</table>

SAE: Serious adverse event. TEAE: Treatment emergent adverse event.
\(^1\)SAE (placebo): Optic neuropathy.
\(^1\)SAEs (teprotumumab; severe diarrhea in a patient with history of UC; IBD; E coli infection treated with IV antibiotics; Hashimoto’s encephalopathy (Provisional diagnosis after episodic mental confusion with no other neurologic symptoms); urinary retention (after patient had inguinal herniorrhaphy).

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
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.

Teprotumumab: Phase 2 Trial
72-Week Data Presented at
American Thyroid Association

George J. Kahaly, M.D., Ph.D.
Professor of Endocrinology and Chief of Endocrine Outpatient Clinic
Johannes Gutenberg University Medical Center
**Phase 2 Trial Design**

**48-Week Follow-Up After Patients Off Treatment**

**Patient Criteria**
- Active TED
- 18 to 75 years
- <9 months since active TED onset with no prior treatment
- CAS ≥4
- FT4 and FT3 <50% above or below normal limits

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**Screening**

**Randomization**

**Week 24**

**Teprotumumab**
8 infusions: 1 every three weeks

**Placebo**
8 infusions: 1 every three weeks

24-week treatment phase with last dose at Week 21

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**48-Week Off-Treatment Follow-Up Period**

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**Week 72**

(1) Per the Phase 2 clinical trial protocol, elective treatments were to be avoided during the first 3 months of the follow up period. Subjects who received treatment for TED and/or surgery were counted as non-responders.

CAS: Clinical Activity Score, a 7-point scale that measures change in orbital inflammation and pain; a score of >3 indicates active TED.

FT4: Free thyroxine.

FT3: Free triiodothyronine.

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Teprotumumab Phase 2 Trial Goals

1. Efficacy and safety of treatment at 24 weeks
2. Assessment of possible acute disease recurrence off treatment at 28 weeks
3. Durability of teprotumumab effect off treatment at 72 weeks
Proptosis Response at Week 28

No Acute Disease Recurrence 7 Weeks After Last Dose

**Teprotumumab Responders at Week 24 and Week 28**

* *p<0.001 vs. placebo.*

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Majority of Teprotumumab Patients Maintain Proptosis Response Approximately One Year Off Treatment

Potential to Change the TED Treatment Landscape

Note: Patients who received additional TED therapy were counted as non-responders. Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Safety Overview: Week 72

• No new safety signals with patients off treatment for approximately one year.

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Teprotumumab: Phase 2 Trial Recap and Phase 3 Trial Design

Shao-Lee Lin, M.D., Ph.D.
EVP, Head of R&D and Chief Scientific Officer
Horizon Pharma
Phase 2 Trial Key Takeaways

**Early and Continued Response**

- At Week 24, percentage of patients with reduction of ≥2 mm of proptosis and ≥2 points in CAS with p<0.001:
  - **Teprotumumab patients:** 69 percent
  - Placebo patients: 20 percent
- At Week 24, percentage of proptosis responders with p<0.001:
  - **Teprotumumab patients:** 71 percent
  - Placebo patients: 20 percent

**Durable Response**

- At Week 28, 74 percent of patients were proptosis responders
- At Week 72, 53 percent of proptosis responders maintained response approximately one year off treatment

**Well Tolerated**

**Additional information on length of treatment and potential retreatment will be provided with OPTIC and OPTIC-X**

CAS: Clinical Activity Score, 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.
**Biologics in Other Inflammatory Disease States**

(1) SILIQ (brodalumab) product insert. SILIQ is a registered trademark of Bausch Health. “Response” was sPGA of 0 or 1. Data from Trial 1 (randomised withdrawal study).

(2) HUMIRA (adalimumab) professional website, accessed Sept. 8, 2018. HUMIRA is a registered trademark of AbbVie. “Response” was ACR Pedi 30 from trial DE038 (week 16 calculated from week 16 responders from ITT population randomized to HUMIRA + MTX [=80/85]).

(3) ENTYVIO (vedolizumab) product insert. ENTYVIO is a registered trademark of Takeda. “Response” was clinical response, defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. Week 6 from UC Trial I; off treatment from UC Trial II.

(4) HUMIRA (adalimumab) product insert. HUMIRA is a registered trademark of AbbVie. “Response” was clinical response, defined as decrease in CDAI ≥70. Week 4 and off treatment from CD-III trial.

(5) Phase 2 clinical trial results.

JIA: Juvenile idiopathic arthritis.

Note: Comparisons across studies, indications and therapies are limited. Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Teprotumumab Phase 3 Clinical Trial Design (OPTIC)
Enrollment Completed Ahead of Schedule

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

24-Week treatment period

Teprotumumab (N=38)
8 infusions: 1 every three weeks

Placebo (N=38)
8 infusions: 1 every three weeks

Primary endpoint at Week 24
- Proptosis responder rate defined as percentage of participants with >2 mm reduction in study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye
  - Proptosis selected as primary endpoint because it is objective, measurable and agreed upon by the FDA

Secondary endpoints at Week 24
- Percentage of participants with ≥2 point reduction in Clinical Activity Score (CAS) AND >2 mm reduction in proptosis in the study eye without deterioration in fellow eye
- Percentage of participants with CAS of 0 or 1
- Mean change in proptosis from baseline
- Mean change in QoL questionnaire overall score from baseline

Estimated Milestones
- 2Q 2019: Data anticipated
- Mid 2019: BLA submission anticipated
- 2020: Potential FDA approval

OPTIC: Treatment of Graves’ Orbitopathy (TED) to reduce Proptosis with Teprotumumab Infusions in a randomized, placebo-controlled Clinical study.

For us, it’s personal
OPTIC: Treatment of Graves’ Orbitopathy (TED) to reduce Proptosis with Teprotumumab Infusions in a randomized, placebo-controlled Clinical study.

Q3W: Once every 3 weeks

Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Phase 2 Diplopia Data Off Treatment Follow Up at Week 72 Presented at AAO

October 26 - 30, 2018
Chicago, IL
TED: Addressable U.S. Patient Population

Vikram Karnani
EVP, Chief Commercial Officer
Horizon Pharma
Expect Annual Addressable TED Patient Population of 15,000 to 20,000\(^{(1)}\) and U.S. Peak Net Sales Potential of >$750M\(^{(2)}\)

**Annual U.S. Treatable Population**
- 15,000 to 20,000 patients eligible for treatment\(^{(1)}\)
- Active disease lasts up to 3 years

**Epidemiology**
Bottoms-up market model uses patient-level data
- Multi-year
- Hospital admissions, diagnostic, insurance claims

Literature informative, however
- Limited data
- Varies widely

**U.S. Peak Net Sales Potential of >$750M\(^{(2)}\)**
- No FDA-approved therapies exist
- Current treatment paradigm is suboptimal
- Teprotumumab can potentially be disease modifying\(^{(3)}\)

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\(^{(1)}\) Company analysis of claims data and market research.
\(^{(2)}\) Horizon Pharma estimate.
Teprotumumab is an investigational candidate, and safety and efficacy have not been established.
Key Takeaways for Today’s Call

Thyroid eye disease (TED) is a rare and debilitating autoimmune disease of the orbit (area around the eye); moderate-to-severe TED impacts 15,000 to 20,000 U.S patients annually\(^{(1)}\)

- Estimated U.S. peak net sales potential of >$750M\(^{(2)}\)

No FDA-approved therapies exist; currently used therapies are not disease modifying; teprotumumab is the only medicine in clinical development for TED

Phase 2 data at Week 24 demonstrate that teprotumumab has the potential to be a disease modifying therapy for the treatment of TED\(^{(3)}\)

Phase 2 data at Week 72 (approximately one year off treatment) indicate teprotumumab has a durable response

Phase 3 data from the confirmatory OPTIC trial is expected in 2Q19 with FDA submission expected mid-2019

- Investigating retreatment and length of treatment in OPTIC-X (Phase 3 follow on study)

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\(^{(1)}\) Company analysis of claims data and market research.
\(^{(2)}\) Horizon Pharma estimate.
Q&A
An Overview of Thyroid Eye Disease (TED) and Teprotumumab Clinical Data

October 4, 2018