New TEPEZZA Topline Data Underscore Efficacy in Longer Disease Duration, Long-Term Durability and Potential for Retreatment

Horizon Therapeutics plc

July 31, 2020
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TEPEZZA: First and Only FDA-Approved Medicine for Patients with Thyroid Eye Disease (TED)
Growing Body of Evidence Further Supports the Efficacy and Safety of TEPEZZA

**Received early U.S. FDA approval in Jan. 2020 for patients with TED**
- Dramatic OPTIC Phase 3 results: 82.9 percent of TEPEZZA patients experienced ≥2mm proptosis (eye bulging) reduction
- Broad indication for treatment of TED enables treatment of acute (active) and chronic (inactive) TED patients

**TED: A debilitating disease that severely impacts quality of life**
- Vision-threatening, rare autoimmune disease
- Orbital inflammation and tissue expansion severely impacts quality of life
- Prior to TEPEZZA, there was no FDA-approved medicine to address proptosis and diplopia (double vision); patients often had to wait several years before surgical intervention to treat these symptoms

**OPTIC Phase 3 Program: Three components**
- OPTIC Phase 3 confirmatory clinical trial:
  - 24-week placebo-controlled period
  - 48-week off-treatment follow-up period
- OPTIC-X extension trial: Evaluated OPTIC non-responders and relapsed patients

**New positive topline data from OPTIC-X and 48-week OPTIC follow-up add to growing body of evidence supporting TEPEZZA efficacy and safety**
- Underscore TEPEZZA efficacy in longer disease duration, long-term durability and potential for retreatment
Summary of OPTIC-X and OPTIC 48-Week Off Treatment Topline Results
Data Underscore TEPEZZA Efficacy in Longer Disease Duration, Long-Term Durability and Potential for Retreatment

OPTIC-X data support the use of TEPEZZA in patients who have had TED for a longer period of time (12 mos. average) than those in the OPTIC trial (6 mos. average)
• 89 percent of OPTIC placebo patients achieved clinically significant proptosis reduction when treated with TEPEZZA in OPTIC-X

Of the small number of patients who received a full course of TEPEZZA in OPTIC and were non-responders (five), two achieved a >2mm proptosis reduction with an additional course of TEPEZZA

Regarding durability, the majority of TEPEZZA proptosis responders at Week 24 of OPTIC maintained response at Week 72, which was nearly a year off treatment

Of the the small number of TEPEZZA patients who relapsed during off-treatment follow-up in OPTIC, >60 percent experienced >2mm proptosis improvement with additional TEPEZZA treatment in OPTIC-X

There were no new safety concerns in either OPTIC-X or 48-week OPTIC follow-up period, even with the additional TEPEZZA treatment in OPTIC-X

OPTIC Week 24 non-responders: Patients who did not achieve at least a 2mm proptosis improvement from baseline at Week 24 of OPTIC. Relapse is defined as patients who lost at least 2mm of their Week 24 proptosis improvement during the 48-week off-treatment period even if proptosis improvement was substantially better than at OPTIC baseline, or patients who had a substantial increase in the number of inflammatory signs or symptoms without worsening proptosis.
Thyroid Eye Disease

A Rare, Debilitating Eye Disease That Severely Impacts Quality of Life
Thyroid Eye Disease: Rare, Debilitating, Vision-Threatening; Severely Impacts Quality of Life

Inflammation and tissue expansion behind the eye causes **proptosis**, the most disfiguring sign of TED

Can impair ability to close eyes, resulting in **pain**, corneal ulcerations

Associated with **diplopia** (double vision), which is a result of misalignment of eyes

**Impacts quality of life:** Working, driving, reading, sleeping
Patients Living with TED Have Significant Challenges Living a Normal Life

“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.”

“TED has robbed me of a normal life and my looks. I don’t know how much more I can take.”

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

“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.”

Diplopia (Double Vision)

Proptosis (Eye Bulging)

Requires Night Protection

Source: Horizon market research and patient interviews.
OPTIC and OPTIC-X Clinical Trial Designs
OPTIC Phase 3 Pivotal Confirmatory Trial Design

Randomized, Double-Masked and Placebo-Controlled On-Treatment Period

Patient Criteria
- Acute (active) TED
- 18-80 years old
- Within 9 months since onset of active TED with no prior treatment
- CAS ≥4

Dosing: TEPEZZA Patients
- First infusion: 10 mg/kg of body weight
- Subsequent 7 infusions: 20 mg/kg of body weight

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

Q3W: 1 infusion every 3 weeks.

Primary Endpoint at Week 24:
Percentage of patients with ≥2 mm reduction in proptosis
OPTIC Trial: 82.9 Percent of Patients Achieved Primary Endpoint of Proptosis Response

Throughout the 24-week treatment period, patients treated with TEPEZZA had an average proptosis reduction of 2.82 mm compared with 0.54 mm for those who received placebo (p<0.001).

(1) 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.
TEPEZZA 8 infusions (Q3W)

Placebo 8 infusions (Q3W)

Q3W: 1 infusion every 3 weeks.
OPTIC and OPTIC-X Clinical Trial Designs

Assessment of TEPEZZA on Patients with Longer Disease Duration

1. **Does longer disease duration impact response?**

Patients who received placebo in OPTIC were able to enter OPTIC-X and receive a course of TEPEZZA.
OPTIC and OPTIC-X Clinical Trial Designs

Assessment of An Additional Course of TEPEZZA on Non-Responders

Can non-responders benefit from an additional course of TEPEZZA?

OPTIC Week 24 non-responders: Patients who did not achieve at least a 2mm proptosis improvement from baseline at Week 24 of OPTIC.

Q3W: 1 infusion every 3 weeks.

Patients who received TEPEZZA in OPTIC but did not have a proptosis response were able to enter OPTIC-X and receive an additional course of TEPEZZA.
**What is the long-term durability of response to TEPEZZA?**

**OPTIC and OPTIC-X Clinical Trial Designs**

**Assessment of Long-Term Durability of Response to TEPEZZA**

 Patients who responded to TEPEZZA in OPTIC entered a 48-week off-treatment follow-up period and were evaluated for maintenance of response.
Can relapsed patients benefit from an additional course of TEPEZZA?

Patients who relapsed during the 48-week off-treatment follow-up period were able to enter OPTIC-X and receive an additional course of TEPEZZA.
Summary of Topline Results from OPTIC-X and OPTIC 48-Week Off-Treatment Follow-Up Period
Topline Results from OPTIC-X and OPTIC 48-Week Follow-Up Period

TEPEZZA Was Similarly Effective in Patients Who Had TED for a Longer Period of Time

**OPTIC and OPTIC-X Clinical Trial Topline Results**

| Day 1 | Week 24
|-------|----------------|
| TEPEZZA (n=41) | Placebo (n=42)
| 8 infusions (Q3W) | 8 infusions (Q3W)

**OPTIC Primary Endpoint**

1. **Does longer disease duration impact response?**
   - Results were similar to the shorter disease duration results in OPTIC
   - **89 percent** (33/37) of OPTIC placebo patients who entered OPTIC-X became proptosis responders when treated with TEPEZZA

**Patients who received placebo in OPTIC were able to enter OPTIC-X and receive a course of TEPEZZA**

Q3W: 1 infusion every 3 weeks.
OPTIC-X Patients Had Longer Duration of TED Since Diagnosis than OPTIC Patients

Average of 12 Months in OPTIC-X (as Long as 16 Months) Compared to 6 Months in OPTIC

<table>
<thead>
<tr>
<th></th>
<th>OPTIC-X (Received Placebo in OPTIC and TEPEZZA in OPTIC-X)</th>
<th>OPTIC (Received TEPEZZA in OPTIC)</th>
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<tbody>
<tr>
<td></td>
<td>n=37</td>
<td>n=41</td>
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<tr>
<td>Age, Mean (SD)</td>
<td>48.5 (13.5)</td>
<td>51.6 (12.6)</td>
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<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27 (73.0)</td>
<td>29 (70.7)</td>
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<tr>
<td>Male</td>
<td>10 (27.0)</td>
<td>12 (29.3)</td>
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<td>Race, n (%)</td>
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<tr>
<td>White</td>
<td>33 (89.2)</td>
<td>35 (85.4)</td>
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<tr>
<td>Black</td>
<td>1 (2.7)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.7)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (5.4)</td>
<td></td>
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<tr>
<td>Years Since Diagnosis of Graves’ Disease</td>
<td></td>
<td></td>
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<tr>
<td>Mean (range)</td>
<td>2.7 (0.58 – 15.29)</td>
<td>3.5 (0.26 – 28.24)</td>
</tr>
<tr>
<td>Months Since Diagnosis of Thyroid Eye Disease</td>
<td></td>
<td></td>
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<tr>
<td>Mean (range)</td>
<td>12.3 (7.01 – 15.86)</td>
<td>6.2 (0.92 – 9.67)</td>
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<tr>
<td>Smoking Status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>29 (78.4)</td>
<td>32 (78.0)</td>
</tr>
<tr>
<td>Smoker</td>
<td>8 (21.6)</td>
<td>9 (22.0)</td>
</tr>
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**OPTIC-X: Response Rate and Proptosis Reduction Similar to OPTIC**

**OPTIC-X Patients Had Longer Duration of TED Since Diagnosis than OPTIC Patients**

First-time treatment in patients with ~1 year avg (up to 16 months) diagnosis of TED led to responder rates consistent with OPTIC

Proptosis Responders

![Proptosis Responders Graph](image)

- TEPEZZA Responders in OPTIC (n=41)
- Placebo Patients in OPTIC Who Received TEPEZZA in OPTIC-X (n=37)

First-time treatment in patients with ~1 year avg (up to 16 months) diagnosis of TED led to proptosis reduction consistent with OPTIC (-3.3)

Proptosis Change (mm)

![Proptosis Change Graph](image)
Topline Results from OPTIC-X and OPTIC 48-Week Follow-Up Period

Potential Benefit with an Additional Course of TEPEZZA in the Small Number of OPTIC Non-Responders

<table>
<thead>
<tr>
<th>OPTIC</th>
<th>Placebo (n=42)</th>
<th>8 infusions (Q3W)</th>
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<tbody>
<tr>
<td>TEPEZZA (n=41)</td>
<td></td>
<td>8 infusions (Q3W)</td>
</tr>
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**OPTIC Week 24 non-responders:** Patients who did not achieve at least a 2mm proptosis improvement from baseline at Week 24 of OPTIC.

Q3W: 1 infusion every 3 weeks.

**OPTIC-X Clinical Trial Topline Results**

- TEPEZZA non-responders may benefit from additional course of TEPEZZA
- Of the five OPTIC TEPEZZA non-responders in OPTIC-X, two benefitted from an additional course of TEPEZZA

**Can non-responders benefit from an additional course of TEPEZZA?**

- Patients who received TEPEZZA in OPTIC but did not have a proptosis response were able to enter OPTIC-X and receive an additional course of TEPEZZA
Topline Results from OPTIC-X and OPTIC 48-Week Follow-Up Period

Response to TEPEZZA Was Durable in Majority of Patients

OPTIC and OPTIC-X Clinical Trial Topline Results

What is the long-term durability of response to TEPEZZA?

- The majority of OPTIC TEPEZZA responders maintained response

Patients who responded to TEPEZZA in OPTIC entered a 48-week off-treatment follow-up period and were evaluated for maintenance of response

Sustained responders for the 48-week follow-up period: Patients with ≥2mm proptosis improvement from OPTIC baseline at Week 24, ≥2mm proptosis improvement from OPTIC baseline at Week 72, and no additional TED treatment.

OPTIC Week 24 non-responders: Patients who did not achieve at least a 2mm reduction in proptosis from baseline at Week 24 of OPTIC.

Relapse: Patients who lost at least 2mm of their proptosis improvement during the 48-week off-treatment period even if the proptosis was substantially better than at OPTIC baseline, or patients who had a substantial increase in the number of inflammatory signs or symptoms without worsening proptosis. Q3W: 1 infusion every 3 weeks.
Topline Results of OPTIC 48-Week Off-Treatment Follow-Up Period

**Durable Response Observed with TEPEZZA**

The majority of TEPEZZA proptosis responders at Week 24 of OPTIC maintained response at Week 72, approximately one year off treatment.

### OPTIC 48-Week Follow-Up Results

- **56 percent** (19/34) of patients maintained proptosis response, defined as:
  - ≥2mm proptosis improvement from OPTIC baseline at Week 24,
  - ≥2mm proptosis improvement from OPTIC baseline at Week 72, and
  - No additional TED treatment

- Similar durability was also seen for other endpoints including diplopia and Clinical Activity Score (CAS)

- Of the 15 patients who did not qualify as maintaining response, 8 patients had at least a 2mm proptosis improvement from baseline at the time of their last assessment in the OPTIC follow-up period

- **15 patient detail:**
  - 4 patients prematurely discontinued the study
  - 2 patients had worsened slightly but not enough to qualify as relapsed for OPTIC-X
  - 9 patients met the OPTIC-X criteria for relapse prior to Week 72 of the off-therapy follow-up period

  - 8 entered OPTIC-X for retreatment; 1 did not enroll into OPTIC-X

One additional patient qualified for relapse at Week 72 and entered retreatment in OPTIC-X.

Week 72: The last TEPEZZA infusion was administered at Week 21 in the OPTIC 24-week placebo-controlled period, with assessments performed at Week 24. The final visit for patients who completed the 48-week off-treatment follow-up period at Week 48 was 51 weeks after their last TEPEZZA infusion.

Patients who subsequently enrolled in OPTIC-X and received additional TED therapy were counted as non-responders in 48-week follow-up period.

Failure to maintain response: Patient discontinued, relapsed or did not meet criteria of relapse during the follow-up period.
Topline Results from OPTIC-X and OPTIC 48-Week Follow-Up Period

**TEPEZZA Benefit Also Seen in Small Number of Patients Who Relapsed**

**OPTIC and OPTIC-X Clinical Trial Topline Results**

**OPTIC**
- TEPEZZA 8 infusions (Q3W)
- Placebo 8 infusions (Q3W)

**OPTIC-X**
- Non-responders Placebo
- TEPEZZA 8 infusions (Q3W)

**Week 24**
- OPTIC Primary Endpoint

**Week 72**
- End of OPTIC Follow-Up Period

**Day 1**
- Week 24

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

If relapse, then retreat (n=9)\(^{(1)}\)

*Can relapsed patients benefit from an additional course of TEPEZZA?*

- For the small number of TEPEZZA patients who relapsed after OPTIC, **>60 percent** experienced at least 2mm of proptosis improvement with additional TEPEZZA treatment in OPTIC-X.

\(^{(1)}\) Includes 8 of the 15 TEPEZZA patients who did not meet the durability response and one additional patient who met the durability response but qualified as a relapsed patient at Week 72. All 9 patients enrolled in OPTIC-X.

OPTIC Week 24 non-responders: Patients who did not achieve at least a 2mm proptosis improvement from baseline at Week 24 of OPTIC.

Relapse: Patients who lost at least 2mm of their Week 24 proptosis improvement during the 48-week off-treatment period even if proptosis was substantially better than at OPTIC baseline, or patients who had a substantial increase in the number of inflammatory signs or symptoms without worsening proptosis.

Q3W: 1 infusion every 3 weeks.

**Patients who relapsed during the 48-week off-treatment follow-up period were able to enter OPTIC-X and receive an additional course of TEPEZZA**
Topline Results from OPTIC-X and OPTIC 48-Week Follow-Up Period

Safety

No new safety concerns in either OPTIC-X or the OPTIC 48-week off-treatment follow-up period, including patients who received additional TEPEZZA treatment in OPTIC-X
Summary of OPTIC-X and OPTIC 48-Week Off Treatment Topline Results

*Data Underscore TEPEZZA Efficacy in Longer Disease Duration, Long-Term Durability and Potential for Retreatment*

**OPTIC-X data support the use of TEPEZZA in patients who have had TED for a longer period of time (12 mos. average) than those in the OPTIC trial (6 mos. average)**

- **89 percent** of OPTIC placebo patients achieved clinically significant proptosis reduction when treated with TEPEZZA in OPTIC-X

- Of the small number of patients who received a full course of TEPEZZA in OPTIC and were non-responders (five), two achieved a >2mm proptosis reduction with an additional course of TEPEZZA.

- Regarding durability, the majority of TEPEZZA proptosis responders at Week 24 of OPTIC maintained response at Week 72, which was nearly a year off treatment.

- Of the the small number of TEPEZZA patients who relapsed during off-treatment follow-up in OPTIC, >60 percent experienced >2mm proptosis improvement with additional TEPEZZA treatment in OPTIC-X.

- There were no new safety concerns in either OPTIC-X or 48-week OPTIC follow-up period, even with the additional TEPEZZA treatment in OPTIC-X.

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OPTIC Week 24 non-responders: Patients who did not achieve at least a 2mm proptosis improvement from baseline at Week 24 of OPTIC.

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Perspectives from a TED Treating Physician
TEPEZZA Decreased Proptosis and Reduced Orbital Swelling

- At Week 24, patient had a 5mm reduction in proptosis, no inflammatory signs and symptoms of TED, and a decrease in the Gorman diplopia score from 3 to 0
- Orbital fat volume was reduced; inferior rectus muscle size decreased by 49 percent, and medial rectus muscle volume decreased by 41 percent

MRI: Magnetic resonance imaging.
Source: Horizon Therapeutics FDA Advisory Committee Presentation.
“Before and After” selfies of one of my patients who completed full course of TEPEZZA therapy.
Q&A