Teprotumumab Clinical Development Program

Teprotumumab is an investigational medicine being developed for the treatment of thyroid eye disease (TED).

Teprotumumab is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor-1 receptor (IGF-1R). The clinical development program for teprotumumab includes positive results from the Phase 3 OPTIC confirmatory clinical trial and positive Phase 2 results, which were published in *The New England Journal of Medicine*.

OPTIC: Treatment of Graves’ Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study

Phase 3 Confirmatory Study (NCT03298867)

Trial Design

OPTIC investigated the efficacy, tolerability and safety of teprotumumab in patients with Active TED. Patients were assigned to receive teprotumumab or placebo in eight intravenous infusions (10mg/kg for their first infusion followed by 20mg/kg for the remaining seven infusions) every three weeks for 21 weeks. Eighty-three subjects enrolled in OPTIC. The characteristics of the population were consistent with the Phase 2 clinical study.

Inclusion Criteria

See clinical trial site for full inclusion criteria.

- Aged 18–80 years
- TED diagnosis ≤ 9 months since the onset of symptoms
- Previous steroid use was limited to low doses with no use at least 4 weeks prior to study entry

Results

OPTIC met its primary endpoint, with significantly more patients achieving a reduction in proptosis – a major cause of morbidity in TED – with teprotumumab compared to placebo. The study also demonstrated significant differences versus placebo in all secondary endpoints, demonstrating potential benefits on important measures of the patient experience with this disfiguring disease.
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
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<tr>
<td>Responder rate of ≥ 2 mm reduction of proptosis in the study eye (without deterioration in the fellow eye) at Week 24.</td>
<td>In the intent-to-treat population, 34/41 (82.9%) patients receiving teprotumumab and 4/42 (9.5%) patients receiving placebo were proptosis responders at Week 24 (p&lt;0.001).</td>
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<td><strong>Secondary Endpoints</strong></td>
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<td>Average change in proptosis throughout 24 weeks of treatment (average of the improvements seen at weeks 6, 12, 18 and 24).</td>
<td>Throughout the 24-week treatment period, patients treated with teprotumumab had an average proptosis reduction of 2.82 mm compared with 0.54 mm for those who received placebo (p&lt;0.001). After the full course of therapy, there was a 3.32 mm reduction from baseline for the teprotumumab group vs 0.53 mm reduction for placebo at Week 24 (p&lt;0.001).</td>
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<td>Overall responder rate at Week 24: Percent of participants with ≥2-point reduction in Clinical Activity Score (CAS) and ≥2 mm reduction in proptosis from baseline, provided there is no corresponding deterioration (≥2-point/mm increase) in CAS or proptosis in the fellow eye.</td>
<td>Patients treated with teprotumumab had an overall responder rate of 78% compared with 7.1% in the placebo group at week 24 (p&lt;0.001). Overall response rate to teprotumumab was significantly different from placebo from baseline at all study time points: Week 6 (43.9% vs. 4.8%), Week 12 (63.4% vs. 11.9%), Week 18 (73.2% vs 11.9%) and Week 24 (78.0% vs. 7.1%).</td>
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<td>Percentage of participants with a CAS value of 0 or 1 at Week 24 in the study eye.</td>
<td>At Week 24, more patients achieved a CAS value of 0 or 1 with teprotumumab treatment (58.5% vs 21.4% of placebo participants) (p&lt;0.001).</td>
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<td>Percentage of patients with a change from baseline of at least one grade in diplopia (double vision).</td>
<td>At Week 24, 67.9% of patients receiving teprotumumab had a change from baseline of at least one grade in diplopia, compared to 28.6% of patients receiving placebo (p=0.001). This endpoint measured the percentage of patients who reported at least some diplopia at baseline in the study eye and who had a reduction of ≥ 1 grade with no corresponding deterioration (≥ 1 grade worsening) in the fellow eye at Week 24.</td>
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<td>Average change in Graves’ Ophthalmopathy Quality of Life (GO-QoL) from baseline to Week 24.</td>
<td>Patients receiving teprotumumab had a mean change of 13.79 on the GO-QoL scale compared with a change of 4.43 for patients receiving placebo (p&lt;0.001). These scores indicate a statistical and clinically meaningful improvement over placebo in these QoL measures.</td>
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*CAS is a 7-point scale that quantifies the pain, redness and swelling of various eye tissues. A score of zero represents no swelling or activity, and a change in score of 2 points is considered to be clinically relevant.*

*The GO-QoL scale consists of two subscales to evaluate the quality of life of TED (Graves’ Ophthalmopathy) patients, including impacts on visual function and self-assessment of appearance. A change of 6 points is considered clinically relevant.*
Safety

The safety profile of teprotumumab in the double-blind treatment period of OPTIC was similar to that seen in the previously conducted Phase 2 study with no new safety observations.

- The dropout rate was low (<5%) and balanced across placebo and treatment arms.
- There were no deaths during the study and a total of three serious adverse events: in the placebo arm, one patient had a visual field defect and received orbital decompression surgery and discontinued the study; in the teprotumumab arm, one patient had pneumothorax (considered not related to study drug), and another had an infusion reaction that led to discontinuation of study drug.
- The vast majority of treatment-emergent adverse events were mild to moderate in intensity and no other adverse events resulted in discontinuation.

The OPTIC trial was conducted at leading centers in the U.S., Germany and Italy, with co-principal investigators Raymond Douglas, M.D., Ph.D., Cedars-Sinai Medical Center; and George Kahaly, M.D., Ph.D., Johannes Gutenberg University Medical Center.

**OPTIC-X: Assessing teprotumumab retreatment and extended treatment**

Open-label extension study (NCT03461211)

**Trial Design**

The OPTIC-X trial, which is currently ongoing, is designed to better understand whether certain patients may benefit from retreatment or longer treatment (more than six months) with teprotumumab. OPTIC-X is a 48-week, open-label extension study in which patients who participated in the OPTIC Phase 3 clinical trial may receive up to eight additional infusions of teprotumumab. The primary endpoint is proptosis responder rate (the percentage of participants with ≥2 mm reduction in proptosis in the study eye) without deterioration (≥2 mm increase) of proptosis in the fellow eye.

**Inclusion Criteria**

- Patient must have completed the OPTIC 24-week double-masked treatment period
- Patient must meet one of the following two criteria:
  - Proptosis non-responder (<2 mm reduction in proptosis in the study eye) at Week 24 of the OPTIC Study, or
  - Proptosis responder at Week 24 who relapsed during the OPTIC follow-up period (48 weeks)
  > Increase in proptosis of ≥2 mm in the study eye since Week 24 of OPTIC, or
  > An absolute CAS of ≥4 following Week 24 of OPTIC

**Phase 2 Clinical Study: Teprotumumab treatment in patients with active thyroid eye disease**

Pivotal Phase 2 clinical study (NCT01868997)

**Trial Design**

The multicenter, double-blind, randomized, placebo-controlled Phase 2 trial was conducted to determine the efficacy and safety of teprotumumab in patients with Active TED. A total of 88 patients were randomly assigned to receive teprotumumab or placebo administered intravenously (10mg/kg for their first infusion followed by 20mg/kg for the remaining seven infusions) once every three weeks for a total of eight infusions.

**Inclusion Criteria**

- Aged 18-75 years
- TED diagnosis ≤ 9 months since the onset of symptoms
- No prior treatment except for low-dose oral glucocorticoids and not received within 6 weeks of enrollment
Results

The Phase 2 clinical trial demonstrated positive findings for the primary composite endpoint, reducing a combination of proptosis and CAS score. These data were reported in the *New England Journal of Medicine*.

- At week 24, 69% of teprotumumab-treated patients showed reductions in both proptosis and CAS score; 71% of teprotumumab-treated patients achieved the target reduction in proptosis.
- Response was defined as a reduction of 2 points or more in the CAS and a reduction of 2 mm or more in proptosis at week 24.
- Treatment effect occurred as early as week 6 (in 43% of teprotumumab-treated patients).
- The treatment was well tolerated. The majority of adverse events experienced with teprotumumab treatment were graded as mild to moderate and were managed in the trials, with few discontinuations. Adverse events included hyperglycemia, nausea, diarrhea, muscle spasms, hearing impairment and inflammatory bowel disease in a patient with a recent diagnosis of ileitis and colitis. No deaths occurred during the trial.