



Dermatologic and Ophthalmic Drugs Advisory Committee Meeting  
December 13, 2019

FDA Opening Remarks

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**WELCOME**

# Status of Biologic License Application

- Discipline reviews are ongoing.
- Final determinations have not been made for any discipline.
- Clinical issues will be discussed.
- Manufacturing and Inspection Reviews will not be discussed but are necessary prior to any regulatory action.

# Status of Biologic License Application



- We encourage all comments.



Dermatologic and Ophthalmic Drugs Advisory Committee Meeting  
December 13, 2019

FDA Clinical Review of Teprotumumab  
BLA 761143

Wiley A. Chambers, MD  
Clinical Reviewer

# Discussion and Questions



**DISCUSSION:** Please discuss the expected onset and duration of effect following the administration of teprotumumab. Please also include in your discussion whether there is a potential safety concern with repeated courses of treatment.

**DISCUSSION:** Please discuss any safety limitations or safety labeling that should result from the relatively small database of patients in this orphan indication for teprotumumab.

**DISCUSSION:** Please discuss whether the term “Active” as used in the proposed indication is informative to clinicians and patients considering use of the product.

# Discussion and Questions



**DISCUSSION:** Please discuss the need for glucose monitoring after initiation of teprotumumab administration. If needed, please discuss the recommended timing of any monitoring.

**DISCUSSION:** Please discuss your level of concern with the episodes and frequency of reported:

- muscle spasms
- hypoacusis/loss of hearing
- diarrhea/inflammatory bowel disease
- infection rate
- alopecia

# Discussion and Questions



**VOTE:** Do the potential benefits of using teprotumumab as recommended outweigh the potential risks associated with the use of the drug product for the intended population?

**DISCUSSION:** If teprotumumab is approved, are there specific recommendations for the labeling?



# Product



- Sterile, preservative-free, lyophilized powder for reconstitution
- Active: Teprotumumab 500 mg per vial
- Inactives:

|                     |                               |
|---------------------|-------------------------------|
| L-Histidine         | Buffer                        |
| Trehalose dihydrate | Bulking agent, tonicity agent |
| Polysorbate 20      | Surfactant                    |
- Diluted to teprotumumab concentration of 50 mg/mL.

# Dosing



- Infusions administered every 3 weeks for a total of 8 infusions
- First infusion: 10 mg/kg IV infusion
- Infusions two (2) through eight (8): 20 mg/kg IV infusion

# Key Inclusion

- Clinical diagnosis of Grave's Disease
- Fewer than 9 months since onset of Thyroid Eye Disease (TED)
- Euthyroid or mild hypo or hyperthyroidism
- Active Thyroid Eye Disease

# Active Thyroid Disease

- Defined in Study as Clinical Activity Score of  $\geq 4$  in most severely affected eye:
  1. Spontaneous orbital pain.
  2. Gaze-evoked orbital pain.
  3. Eyelid swelling due to active (inflammatory phase) Graves Ophthalmopathy.
  4. Eyelid erythema.
  5. Conjunctival redness due to active (inflammatory phase) Graves Ophthalmopathy.
  6. Chemosis.
  7. Inflammation of caruncle or plica.

# Questions About Active TED vs. TED



- Will the term “Active Thyroid Eye Disease (TED)” be understood by most physicians who are likely to prescribe the product?
- Is it important to define the term “Active”?
- Is it important to use the term “Active”?
- Is there a better way to identify potential patients?

# Clinical Data

- Safety- derived from all clinical use
  - Clinical trials in the intended population
  - Clinical trials from other potential indications
  - Other clinical use
- Efficacy- derived from adequate and well controlled studies

# Efficacy



- Standard expectation is that efficacy will be demonstrated in at least two adequate and well control studies.
- Study #1      ED01RV                      NCT#01868997
- Study #2      HZNP-TEP-301              NCT#03298867
- Both studies meet the regulatory definition of adequate and well controlled studies.

# Endpoints



- Many endpoints are considered important if they affect how a patient feels, functions, or survives.
- Proptosis is considered important because it can lead to pain, corneal exposure, and diplopia. Appearance is also important to patients.



# Clinical Activity Score (CAS)



The 7-point CAS scale is comprised of 2 patient-reported outcomes and 5 clinician-reported outcomes. For each item present, 1 point was given. The sum of these points was the total score.

1. Spontaneous orbital pain.
2. Gaze-evoked orbital pain.
3. Eyelid swelling that was considered to be due to active (inflammatory phase) Graves Ophthalmopathy.
4. Eyelid erythema.
5. Conjunctival redness that was considered to be due to active (inflammatory phase) Graves Ophthalmopathy (ignore “equivocal” redness).
6. Chemosis.
7. Inflammation of caruncle or plica.

# Clinical Activity Score (CAS)



- Problematic as primary endpoint to established efficacy
  - Disagree with equal weighting of scores
  - Pain should be considered more important than chemosis
  - Redness/erythema scores very subjective
  - Eyelid swelling and chemosis very subjective
  - Eyelid swelling and chemosis of questionable significance
  - Impact on cornea not included
  - Diplopia not included

# Phase 2 Endpoints



- Agency encourages exploration of multiple clinical endpoints during Phase 2, whether or not they may ultimately support efficacy.
- Discussion of primary endpoints often occurs at an End of Phase 2 meeting with Agency.

# Study 1 Primary Endpoint



The primary efficacy endpoint was whether the subject was a responder or not (yes or no) at Week 24. A responder was defined as a subject with the following:

- A decrease in overall CAS  $\geq 2$  points AND
- A reduction in proptosis  $\geq 2$  mm, AND
- No deterioration of CAS in the Non-Study Eye (i.e., increase of CAS  $\geq 2$  points OR increase in proptosis  $\geq 2$  mm) at the 24-week evaluation.



# Discussion of Study 1

- Agency disagreed with inclusion of CAS score in the primary endpoint. However, the study had already been completed.
  - Agency agreed that a 2 millimeter change in proptosis was clinically significant and was willing to accept a re-analysis if it demonstrated:
    - Either statistically significant difference in number of patients with a 2 millimeter decrease in proptosis
- OR
- Mean difference in proptosis of at least 2 millimeters.

# Changes in Endpoints



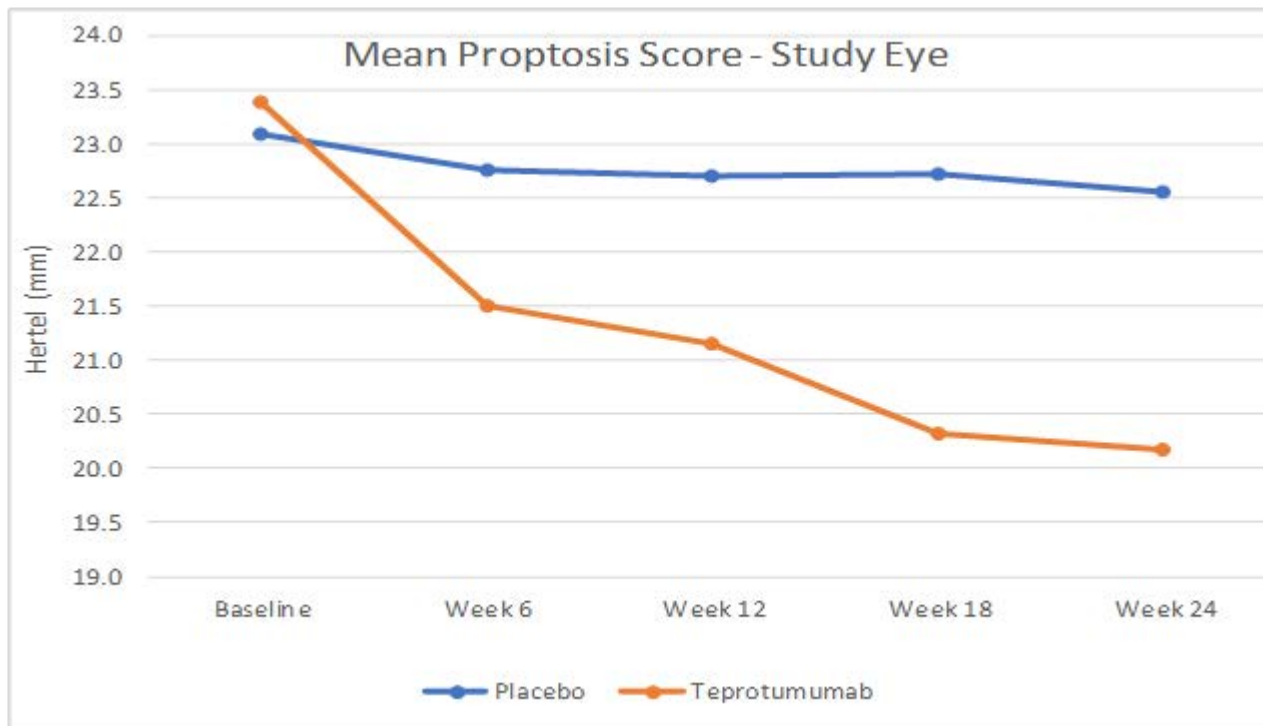
- Applicants required to provide the analysis described in the protocol.
- It is not uncommon for the US and the EU to ask for different endpoints in ophthalmology.
- If Agency disagrees with endpoint, the Agency will request an additional analysis(es) using the Agency's preferred endpoint.
- Agency may treat the analysis using the Agency preferred endpoint as the primary analysis for the purposes of establishing efficacy.

# Teprotumumab Program



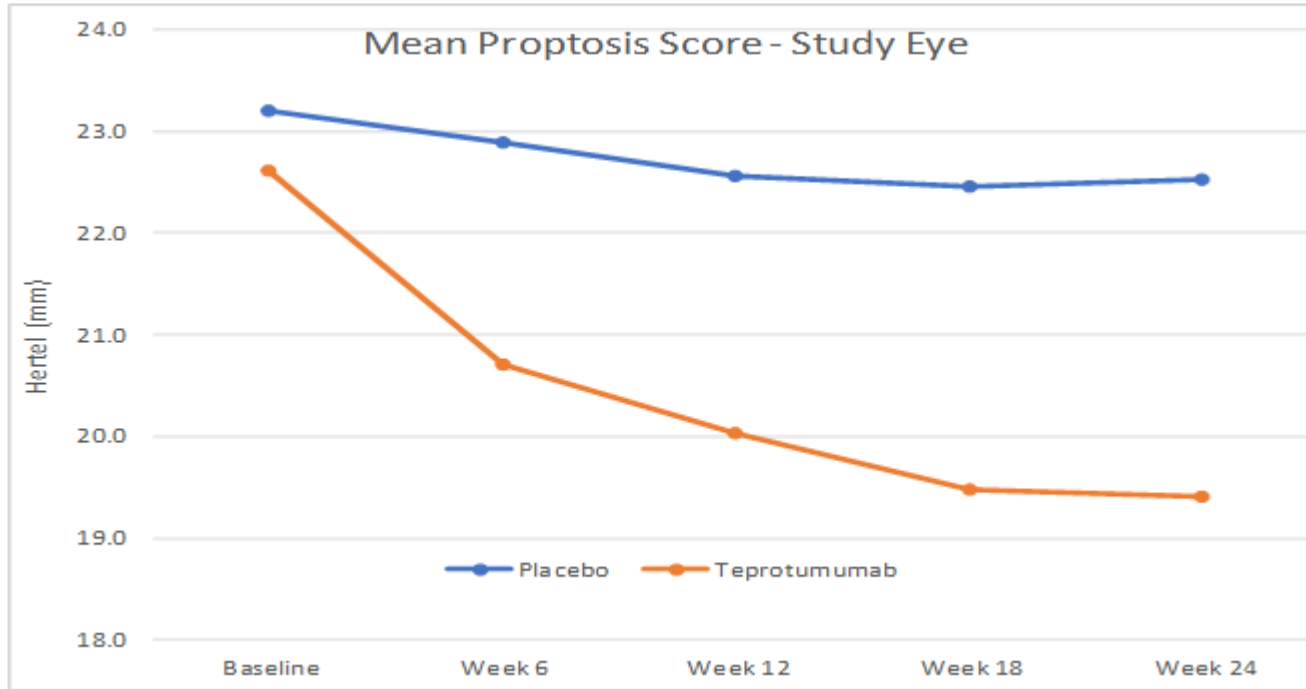
- Agency asked for a re-analysis using only a reduction in proptosis by  $\geq 2$  millimeters as the endpoint for Study 1.
- Applicant agreed to use a reduction in proptosis by  $\geq 2$  millimeters as the endpoint for Study 2.

# Study 1

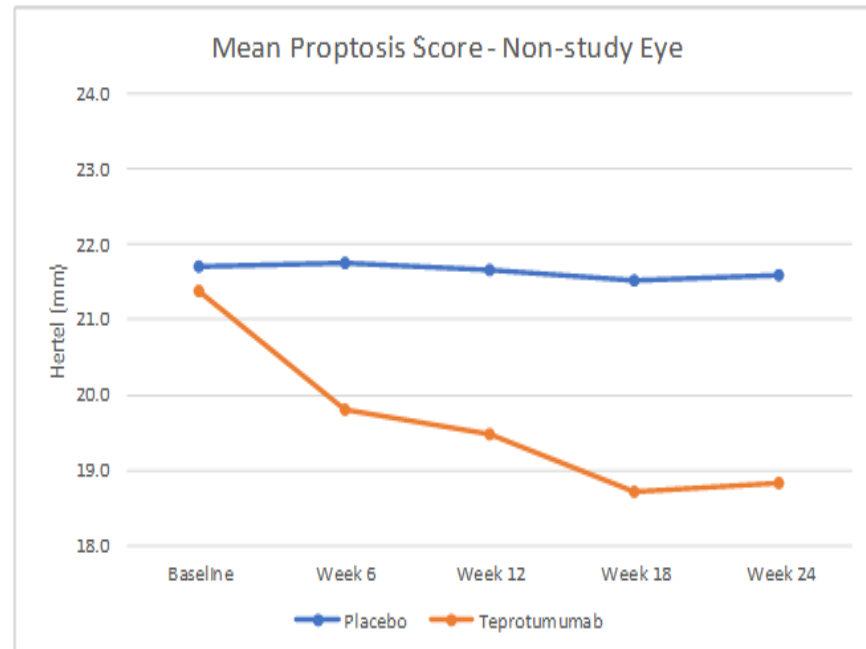
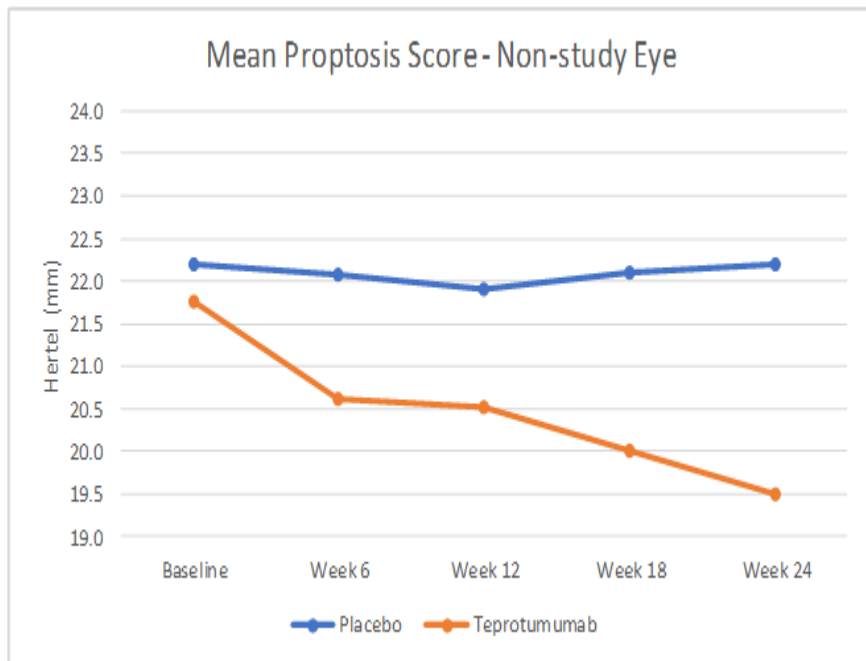




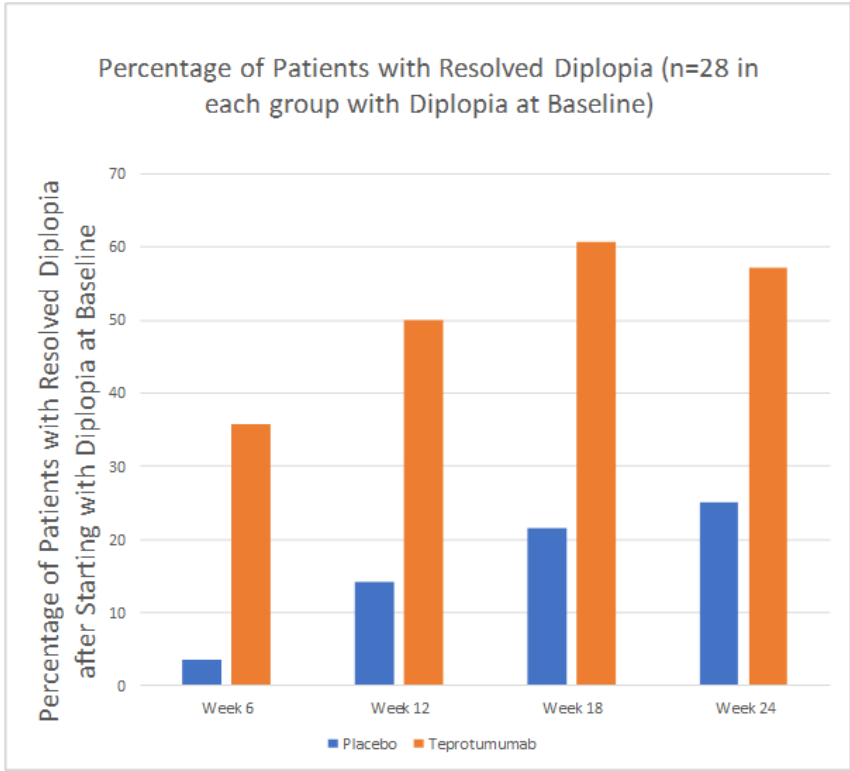
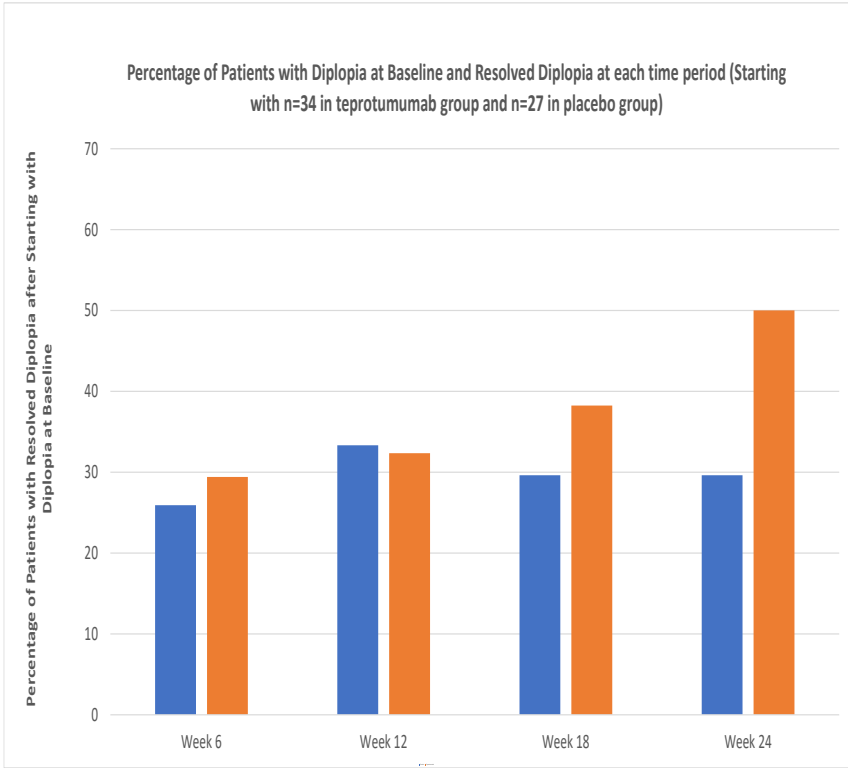
# Study 2



# Non-Study Eye Proptosis



# Diplopia



## Endpoints Noted But Not Included to Support Efficacy

- Clinical Activity Score (CAS)
  - 0-7 points scale
- Disagree with equal weighting of scores
- Redness/erythema scores very subjective
- Eyelid swelling and chemosis very subjective
- Eyelid swelling and chemosis of questionable significance
- Impact on cornea not included
- Diplopia not included

# Endpoints Noted But Not Included to Support Efficacy

- Graves' Ophthalmopathy Quality of Life (GO QOL)
  - Visual Functioning – 8 Questions
  - Appearance- 8 Questions
- Questions raised concerning the choice of questions
- Questions raised concerning equal weighting of questions
- Agency has provided a Guidance Document for the Development of Quality of Life measures
  - Sponsors of applications are encouraged to follow this Guidance Document

# Endpoints Noted But Not Included to Support Efficacy

- Motility
  - Monocular excursion in horizontal and vertical directions of gaze
- Diplopia is used as a clinically important alternative to motility
- In the absence of using diplopia, methodology is needed to establish the minimum change considered clinically significant



# Endpoints Noted But Not Included to Support Efficacy

- Clinical Measures of Severity
  - Lid aperture
  - Swelling of the eyelids
  - Redness of the conjunctiva
  - Inflammation of the caruncle or plica
  - **Subjective diplopia**
  - Eye muscle involvement
  - Corneal involvement
  - Optic nerve involvement
  
- How much of a change is clinically significant?



# Outcomes After Week 28

- Study #1
  - Approximately 60% had not relapsed
- Study #2
  - Ongoing
- Based on the results from Study #1, a significant portion may consider a second series of infusions.



# Safety



- Common events
- Rare serious events

# Safety Evaluations Are a Balance



- All effective products cause adverse events.
- There is a need to balance the availability of an effective product versus the utility in having more safety information available.
- Number of evaluable patients needed
  - Rule of 3s
  - 300 patients needed to have 95% confidence that one event would occur in the database if the true incidence rate of the event is 1%



# Commonly Reported Adverse Events- Controlled Trials

(in which Teprotumumab events are more frequently reported than placebo)

| <b>System Organ Class</b>                       | <b>Study 1<br/>Placebo<br/>(N=44)</b> | <b>Study 2<br/>Placebo<br/>(N=42)</b> | <b>Study 1<br/>Teprotumumab<br/>(N=43)</b> | <b>Study 2<br/>Teprotumumab<br/>(N=41)</b> |
|---|---------------------------------------|---------------------------------------|--|--|
| <b>Preferred Term</b>                           | <b>n (%)</b>                          | <b>n (%)</b>                          | <b>n (%)</b>                               | <b>n (%)</b>                               |
| Gastrointestinal Disorders                      | 6 (14%)                               | 9 (21%)                               | 16 (37%)                                   | 18 (44%)                                   |
| Nausea  | 4 (9%)                                | 4 (10%)                               | 8 (19%)                                    | 6 (15%)                                    |
| Infections and Infestations                     | 9 (21%)                               | 10 (24%)                              | 13 (30%)                                   | 16 (40%)                                   |
| Skin and Subcutaneous Tissue Disorders          | 9 (20%)                               | 11 (26%)                              | 11 (26%)                                   | 15 (37%)                                   |
| Alopecia  | 2 (5%)                                | 5 (12%)                               | 3 (7%)                                     | 8 (20%)                                    |
| Musculoskeletal and Connective Tissue Disorders | 7 (16%)                               | 5 (12%)                               | 12 (28%)                                   | 16 (39%)                                   |
| Muscle spasms                                   | 2 (5%)                                | 4 (10%)                               | 8 (19%)                                    | 13 (32%)                                   |
| Nervous System Disorders                        | 9 (20%)                               | 8 (19%)                               | 10 (23%)                                   | 14 (34%)                                   |
| Dysgeusia                                       | 0                                     | 0                                     | 3 (7%)                                     | 4 (10%)                                    |
| Metabolism and Nutrition Disorders              | 2 (5%)                                | 0                                     | 10 (23%)                                   | 0  |
| Hyperglycemia                                   | 2 (5%)                                | 0                                     | 5 (12%)                                    | 2 (5%)                                     |

# Limited Number of Patients Treated



- 84 patients treated with teprotumumab in the intended population.
- $3/84=3.6\%$  Adverse events with frequencies of occurrence less than 3.6% would not be expected to have been observed in the clinical trials.

# Safety Database in Other Indications

- Majority of patients were treated in clinical trials of patients with a variety of cancer indications.
- Efficacy in the cancer indications was poor, and therefore treatment was limited.
- Reported adverse events were often associated with the cancer under treatment or ancillary cancer therapies.

# Safety Data Clinical Trials



| <u>Study</u> | <u># of Subjects</u> | <u>Patient Population</u>     | <u>Treatment Duration</u>   |
|--------------|----------------------|-------------------------------|-----------------------------|
| Study 1      | 42                   | Thyroid Eye Disease           | 8 infusions                 |
| Study 2      | 41                   | Thyroid Eye Disease           | 8 infusions                 |
| DME01RV      | 5                    | Diabetic Macular Edema        | 3 infusions                 |
| NO21161      | 6                    | Breast Cancer                 | Up to 24 weeks              |
| NO2202       | 8                    | Breast Cancer                 | Single dose                 |
| NO21884      | 11                   | Advanced Solid Tumors         | Repeated until progression  |
| NO21746      | 34                   | Lung Cancer                   | Up to 24 month              |
| NO21200      | 34                   | Advanced Solid Tumors         | Limited number of infusions |
| BO19373      | 97                   | Solid tumors and lymphoma     | Various schedules           |
| NO22068      | 104                  | Advanced malignancies         | Repeated until progression  |
| NO21160      | 116                  | Lung Cancer                   | Repeated until progression  |
| NO21157      | 317                  | Recurrent/refractory sarcomas | Repeated until progression  |

# Adverse Events in Cancer Chemotherapy Trials (1)



|                    | NO21157 | NO21160  | BO19373  | NO21746  |
|--------------------|---------|----------|----------|----------|
| Adverse Event      | N=310   | N=116    | N=36     | N=34     |
| DIARRHEA           | 12 (4%) | 62 (53%) |          | 15 (44%) |
| RASH               | 4 (1%)  | 74 (64%) | 4 (11%)  | 5 (15%)  |
| NAUSEA             | 21 (7%) | 39 (34%) | 5 (14%)  | 6 (18%)  |
| FATIGUE            | 11 (4%) | 45 (39%) | 12 (34%) | 2 (6%)   |
| DECREASED APPETITE | 9 (3%)  | 35 (30%) |          | 14 (41%) |
| VOMITING           | 17 (5%) | 21 (18%) | 3 (8%)   | 7 (21%)  |
| MUSCLE SPASMS      | 3 (<1%) | 20 (17%) | 5 (14%)  | 9 (26%)  |
| COUGH              | 2 (<1%) | 19 (16%) | 5 (14%)  | 8 (23%)  |
| ASTHENIA           | 4 (1%)  | 12 (10%) |          | 18 (52%) |
| WEIGHT DECREASED   | 1 (<1%) | 24 (21%) | 3 (8%)   |          |

# Adverse Events in Cancer Chemotherapy Trials (2)



|                           | NO21157 | NO21160  | BO19373  | NO21746 |
|---------------------------|---------|----------|----------|---------|
| Adverse Event             | N=310   | N=116    | N=36     | N=34    |
| DYSPNEA                   | 1 (<1%) | 18 (16%) | 4 (11%)  | 2 (6%)  |
| HEADACHE                  | 11 (4%) | 10 (9%)  |          |         |
| CONSTIPATION              | 3 (<1%) | 13 (11%) |          | 4 (12%) |
| INFUSION RELATED REACTION | 18 (6%) |          |          |         |
| ANAEMIA                   |         | 7 (6%)   | 10 (28%) |         |
| CREATININE INCREASED      |         | 8 (7%)   | 6 (17%)  |         |
| HYPERGLYCEMIA             |         | 7 (6%)   | 5 (14%)  | 2 (6%)  |
| PRURITUS                  | 1 (<1%) | 12 (10%) |          |         |
| PYREXIA                   | 7 (2%)  |          | 4 (11%)  |         |
| ARTHRALGIA                | 1 (<1%) | 8 (7%)   |          |         |



# Safety Update



| Event                   | Patients | (%)    | Events |
|-------------------------|----------|--------|--------|
| Muscle spasms           | 39       | ( 32%) | 75     |
| Alopecia                | 18       | ( 15%) | 21     |
| Nausea                  | 15       | ( 12%) | 24     |
| Diarrhea                | 15       | ( 12%) | 20     |
| Fatigue                 | 12       | (10%)  | 15     |
| Dry skin                | 12       | (10%)  | 12     |
| Dysgeusia               | 10       | (8%)   | 15     |
| Headache                | 8        | (7%)   | 10     |
| Rash                    | 8        | (7%)   | 10     |
| Ear discomfort          | 8        | (7%)   | 9      |
| Urinary tract infection | 7        | (6%)   | 7      |

# Topics for Consideration/Discussion (1)



- Efficacy in reducing Proptosis has been demonstrated in two adequate and well controlled studies.
- Treatment does not result in a cure. Some patients will consider additional treatment beyond that observed in the clinical trial. Repeated courses of treatment have not been studied.

## Topics for Consideration/Discussion (2)



**DISCUSSION:** Please discuss the expected onset and duration of effect following the administration of teprotumumab. Please also include in your discussion whether there is a potential safety concern with repeated courses of treatment.

# Topics for Consideration/Discussion (3)



- Adverse events with frequencies of occurrence less than 3.6% may not have been observed in the clinical trials.
- While additional patients were treated, the utility of the safety database in patients being treated for recurrent cancers is of questionable value.

# Topics for Consideration/Discussion (4)



**DISCUSSION:** Please discuss any safety limitations or safety labeling that should result from the relatively small database of patients in this orphan indication for teprotumumab.

# Topics for Consideration/Discussion (5)



**DISCUSSION:** Please discuss whether the term “Active” as used in the proposed indication is informative to clinicians and patients considering use of the product.

# Topics for Consideration/Discussion (6)



- Teprotumumab is a fully human IgG1 monoclonal antibody specific for insulin-growth factor receptor 1.
- Diabetic patients have needed additional therapy to maintain control of the blood glucose levels.
- Glucose monitoring may be potentially important in diabetic individuals as well as non-diabetic individuals.

# Topics for Consideration/Discussion (7)



**DISCUSSION:** Please discuss the need for glucose monitoring after initiation of teprotumumab administration. If needed, please discuss the recommended timing of any monitoring.



# Topics for Consideration/Discussion (8)



- A number of adverse events have repeatedly been identified in patients administered teprotumumab.
- While a temporal association with the administration of teprotumumab has been observed, a direct causal relationship has not been established.

# Topics for Consideration/Discussion (9)



- At least five patients reported hypoacusis/loss of hearing. In addition, patients have reported tinnitus.
  - A 32-year-old female, experienced an adverse event of *Hypoacusis* on Day 75 that spontaneously resolved the following day.
  - In other subjects, the event did not resolve until after completion of treatment with teprotumumab.

# Topics for Consideration/Discussion (10)



- Muscle spasms were reported in 32% of patients treated with teprotumumab compared to 9.5% of patients in the placebo group.
- Gastrointestinal complaints were reported in clinical trials by 36% of patients. Nausea and diarrhea were each reported in 12% of patients. Abdominal pain was reported in 5% of patients.

# Topics for Consideration/Discussion (11)



- The reported infection rate associated with teprotumumab was 33%, and higher than that of the placebo control in both studies. No specific site of infection was identified and the potential contribution of teprotumumab to this infection rate is not known.
- In Clinical Trials of TED, alopecia was reported in 13% of patients treated with teprotumumab, but only 8% of the patients in the placebo groups.

# Topics for Consideration/Discussion (12)



- **DISCUSSION:** Please discuss your level of concern with the episodes and frequency of reported:
  - muscle spasms
  - hypoacusis/loss of hearing
  - diarrhea/inflammatory bowel disease
  - infection rate
  - alopecia

# Questions



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