CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761143Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA LABELING REVIEW AND EVALUATION

Application number:	761143
Supporting document/s:	SD 1 (new BLA, received 7/08/2019) SD 24 (revised labeling/package insert draft, received 11/22/2019) Pending SD (expect the numbering to be SD 37)
Applicant's letter date:	January 9, 2020
Product:	(b) (4) (Teprotumumab-trbw) for injection
Indication:	Treatment of active thyroid eye disease (TED)
Applicant:	Horizon Pharma Ireland DAC (Horizon)
Review Organization:	Division of Transplant and Ophthalmology (DTOP), Office of Infectious Diseases (OID)
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor:	Lori E. Kotch, PhD, DABT, DTOP
Acting Division Director:	Ozlem Belen, MD, DTOP
Project Manager:	Jacquelyn Smith, DTOP

1 Executive Summary

1.1 Introduction

- Horizon submitted an original Biologic License Application (BLA) 761143 for teprotumumab for injection for the treatment of active thyroid eye disease (TED) on July 8, 2019.
- The Pharmacology/Toxicology (P/T) review discipline has entered the following reviews in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS):
  - PT filing review (McDougal, 8/19/2019)
  - Primary PT review (McDougal, 12/06/2019)
  - Tertiary PT review (McGovern, 12/19/2019)
- The Agency's proposed edits to the Prescribing Information (PI) were sent to the Applicant via email (Smith/Potthast) on 1/08/2020. The Applicant responded via email (Potthast/Smith) on 1/09. This labeling review is based on the emailed MS Word document titled "1.7.20 FDA Revised PI tracked_v1 to FDA Ja 2020 (003).dox" (not yet received by CDER's electronic document room (EDR)).
- The Applicant's submissions to the EDR are available to the review team via: \\CDSESUB1\evsprod\BLA761143\761143.enx

1.2 Brief Discussion of Nonclinical Findings

- Under section 8.1, P/T proposed to describe the intravenous dose of 75 mg/kg given to the monkeys as "([(b) (4)]-fold the maximum recommended human dose (MRHD) based on AUC"
- The Applicant (1/08/2020) suggests changing the exposure multiple to [(b) (4)] with the comment, "Sponsor Comment: The dosing frequency in animals was weekly vs clinical frequency of Q3W, so the correct number is [(b) (4)]-fold." [Comment author is Nicole Potthast]
  - This change is not acceptable; the rationale is not scientifically appropriate.
  - The exposure margin bridges from the clinical AUC for study HZNP-TEP301. Since the clinical study tested the same dosage and administration as is proposed for labeling, no adjustment is needed.
  - Calculating the exposure margin by serum AUC already accounts for potential differences in study design, including: frequency of dosing, rate of intravenous infusion, administered dose, body weight, and body surface area. No adjustment for these factors is needed when bridging by AUC.
  - The 2005 P/T guidance is referenced.[1]
- Note: P/T proposes to adjust the exposure margin from [(b) (4)] to **2.8**.

[1] CDER 2005 Pharmacology and Toxicology Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Accessed via: https://www.fda.gov/media/72309/download

- The AUC margin had been based on the (b) (4) (b) (4), reported in the Applicant's original proposed labeling (section 12.3 Pharmacokinetics)[2].
- The Clinical Pharmacology review, Dr. Abhay Joshi, updated this AUC value. His review is in DARRTS (Joshi, 12/18/2019). The current paragraph (sent to the Applicant 1/09) now reads,

  "The pharmacokinetics of teprotumumab-trbw was described by a two compartment population PK model based on data from 40 patients with Thyroid Eye Disease receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg TEPEZZA every 3 weeks in two clinical trials. Following this regimen, the mean (± standard deviation) estimates for steady-state area under the concentration curve (AUC), peak (C_{max}), and trough (C_{trough}) concentrations of teprotumumab-trbw were 138 (± 34) mg•hr/mL, 632 (± 139) mcg/mL, and 176 (± 56) mcg/mL, respectively."
- For the monkey embryofetal study, the maternal AUC was 385 mg*h/ml.
- The change of the clinical AUC from 131 to 138 mg*h/ml changes the nonclinical exposure margin slightly. Therefore, P/T proposes to incorporate this change into labeling.

- The Applicant proposed to move wording from labeling section 8.1 to 8.3; P/T has no preference.
- P/T and Clinical Pharmacology (McDougal and Joshi, personal communication, 1/10/2020) discussed the Applicant's proposed change to labeling section 12.1 Mechanism of Action, and P/T has no objection.

1.3 Recommendations

1.3.3 Labeling

- The Applicant proposed labeling in the original BLA submission (7/08/2019), proposing (b) (4). From a nonclinical perspective, P/T concurs with this (b) (4). However, P/T defers to the clinical review team, and understands (personal communications, Chambers/review team, 2019) that the clinical team does not consider this (b) (4) supported by current clinical data (b) (4) (b) (4)
- The Applicant proposed (1/09/2020) (b) (4). From a nonclinical perspective, P/T concurs (b) (4). The Clinical review team (personal communication, Chambers/McDougal, 1/10/2020) does not concur, and plans to send revised wording for Highlights of Prescribing Information, and under section 8.3.
- P/T defers to the Clinical review team.
- Review note: the propriety name should be updated from TEPEZZA (b) (4) throughout (not flagged further)

[2] \\cdsesub1\evsprod\bla761143\0001\m1\us\11412-annotated-pi.pdf

Applicant's proposed language (1/10/2019: showing tracked changes)	P/T recommended language & comments
-USE IN SPECIFIC POPULATIONS-- Females of Reproductive Potential: (b) (4) contraception (b) (4) (b) (4) prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA (8.3)	[no recommendation, noted for context]
2.1 (b) (4) (b) (4)	[no recommendation, noted for context]
2 (b) (4) Recommended Dosing The recommended dose of TEPEZZA is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg (b) (4) (b) (4) every three weeks for (b) (4) 7 additional infusions.	[no recommendation, noted for context]
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Risk Summary Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF1R), TEPEZZA may cause fetal harm when administered to a pregnant woman (b) (4) (b) (4). Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes.	[Change is acceptable]

In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*.	[no change]
~~Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA~~. (b) (4) (b) (4)	[P/T concurs with moving this language (b) (4), and understands that the Clinical team plans to edit further] [Note that this (b) (4) (b) (4) should be double-checked for consistency after 8.3 is edited]
If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus. The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.	[no change]

Data *Animal Data* In an abridged pilot EFD study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg ((b) (4)-fold the maximum recommended human dose (MRHD) based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal	In an abridged pilot EFD study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (**2.8**-fold the maximum recommended human dose (MRHD) based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal

growth during pregnancy, decreased fetal size and weight at cCaesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals, and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL). Based on mechanism of action inhibiting IGF1R, postnatal exposure to teprotumumab may cause harm.	size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL). Based on mechanism of action inhibiting IGF1R, postnatal exposure to teprotumumab may cause harm.
8.2 Lactation Risk Summary There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.	[no change]
8.3 Females and Males of Reproductive Potential	
(b) (4)	
Contraception *Females* Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a	

pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.	[P/T concurs]
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** Teprotumumab-trbw's mechanism of action in patients with Thyroid Eye Disease (b) (4) has not been fully characterized. (b) (4) Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.	[P/T concurs] [P/T concurs]
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** *Carcinogenesis* The carcinogenic potential of TEPEZZA has not been evaluated in long-term animal studies. *Mutagenesis* The genotoxic potential of TEPEZZA has not been evaluated. *Impairment of Fertility* Fertility studies have not been performed with TEPEZZA.	[The Applicant added underlines to the three subsection headings (not tracked). P/T's understanding is that these should be italics but not underlined.]
[no section 13.2 Animal Toxicology and/or Pharmacology] .	[P/T proposed to delete this section for the current indication, and the Applicant concurred. (b) (4) (b) (4)]

17 PATIENT COUNSELING INFORMATION **…** Embryo-Fetal Toxicity • Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy. • Educate and counsel females of reproductive potential about the need to use effective contraception during treatment with TEPEZZA and for at least 6 months after the last dose of TEPEZZA.	[P/T notes that the Applicant had previously proposed essentially this exact language (b) (4). P/T understands that the Clinical team plans to delete this wording, and defers.]

- *Proposed note to convey to the Applicant for section 8.1*: the previous exposure margin of (b) (4) was calculated using the maternal monkey AUC of 385 mg*h/ml, and the clinical AUC of (b) (4) mg*h/ml. Since labeling section 12.3 has updated the clinical AUC from (b) (4) to **138** mg*hr/ml, the exposure margin is updated from (b) (4) to **2.8**. Because clinical study HZNP-TEP301 used the labeled dosage and administration, no adjustment is needed. Bridging from the nonclinical study to the clinical study by AUC accounts for differences in design (e.g. dosing interval, administered dose, rate of intravenous infusion, body weight); further adjustment for these differences is not scientifically appropriate.

2 Drug Information

2.1 Drug

CAS Registry Number	89957-37-9
Generic name	Teprotumumab
Applicant's code name	HZN-001
Previous code names	• RV 001 • RO4858696 • R1507 • huMab IGF-1R • AK18 • Cl.18

Chemical name	Immunoglobulin G1 anti-(human insulin-like growth factor 1 receptor)([redacted] human monoclonal [redacted]
Molecular weight	148 KDa
Biochemical description	• human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass
[redacted]	
Pharmacological Class	Insulin like growth factor 1 receptor (IGF1R) antagonist

11 Exposure Margin Calculation Note

- For the non-GLP monkey EFD study (report # 1035664), pregnant monkeys were dosed by slow intravenous bolus injection with 0 or 75 mg/kg of teprotumumab,

once weekly for 18 doses. For the teprotumumab-treated group, the gestation day 105 maternal AUC = 385 mg*hr/ml.

- The Applicant submitted draft labeling in the original (7/08/2019) BLA submission. The submitted labeling, in section 12.3 Pharmacokinetics, reports clinical steady-state PK AUC = (b) (4) mg/hr/ml. [This is the equivalent of (b) (4).]
- As noted above, the Clinical Pharmacology review calculated a slightly different clinical AUC for labeling, 138 ± 34 mg*hr/mL

Table: Nonclinical exposure margin based on AUC

Dose	Description	AUC		
		Monkey result mg*hr/ml	Exposure margin from the clinical AUC = (b) (4) mg*hr/ml	Exposure margin from the clinical AUC = 138 mg*hr/ml
75 mg/kg	Maternal NOAEL (report # 1035664)	385	(b) (4)	2.7898 x

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/s/

ANDREW J MCDOUGAL
01/10/2020 03:08:22 PM

LORI E KOTCH
01/10/2020 03:13:56 PM

Tertiary Pharmacology/Toxicology Review

From: Timothy J. McGovern, Ph.D., Office Associate Director for Pharmacology and Toxicology, OND IO
BLA: 761143
Agency receipt date: July 8, 2019
Drug: (b) (4) (Teprotumumab) for injection
Sponsor: Horizon Pharma Ireland DAC

Indication: Treatment of active thyroid eye disease (TED)

Reviewing Division: Division of Transplant and Ophthalmology Products

The pharmacology/toxicology reviewer and supervisor concluded that the nonclinical data support approval of (b) (4) for the indication listed above.

Teprotumumab is a human monoclonal antibody inhibitor of human insulin-like growth factor-1 receptor (IGF1R). It is formulated as a lyophilized powder to be reconstituted in sterile water for injection. It is intended to be administered intravenously at a dose of 10 mg/kg for the initial infusion followed by infusions of 20 mg/kg every three weeks for a total of 8 infusions.

The nonclinical program consisted primarily of primary and safety pharmacology studies, intravenous toxicity studies in monkeys (up to 39 weeks), and a non-GLP embryo-fetal dose range-finding study in monkeys. Drug administration was associated with cessation of weight gain, decreased serum alkaline phosphatase, and thymic atrophy.

Genetic toxicity and carcinogenicity studies with teprotumumab were not conducted or considered necessary for approval.

Teprotumumab was associated with reduced fetal growth and was teratogenic in the non-GLP monkey study. The published literature is mixed regarding the potential for IGF1R inhibition to adversely affect fertility. No adverse signals were identified regarding reproductive tissues in general toxicity studies. The product label will address the potential for fetal harm based on the observed findings and mechanism of action.

Conclusion:
I agree with the Division pharmacology/toxicology conclusion that teprotumumab can be approved from the nonclinical perspective. I have reviewed the proposed text for the nonclinical sections of the product label and agree with the Division recommendations.

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/s/

TIMOTHY J MCGOVERN
12/19/2019 12:37:36 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761143
Supporting document/s:	SD 1 (new BLA, received 7/08/2019) SD 5 (response to nonclinical information request, received 8/26/2018) SD 8 (response to nonclinical information request, received 9/04/2019) SD 24 (revised labeling/package insert draft, received 11/22/2019)
Applicant's letter date:	July 6, 2019
CDER stamp date:	July 8, 2019
Product:	(b) (4) (Teprotumumab-trbw) for injection
Indication:	Treatment of active thyroid eye disease (TED)
Applicant:	Horizon Pharma Ireland DAC
Review Organization:	Division of Transplant and Ophthalmology (DTOP), Office of Infectious Diseases (OID)
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor:	Lori E. Kotch, PhD, DABT, DTOP
Acting Division Director:	Ozlem Belen, MD, DTOP
Project Manager:	Jacquelyn Smith, DTOP

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1 Executive Summary

1.1 Introduction

- In accordance with section 351a of the Public Health Service Act and 21 CFR 601.2, Horizon Pharma Ireland Ltd. submitted an original Biologic License Application (BLA) 761143 for teprotumumab for injection for the treatment of active thyroid eye disease (TED) on July 8, 2019.
    - The Applicant changed the corporate name of record to Horizon Therapeutics Ireland DAC on November 22, 2019.
- Teprotumumab is a human monoclonal antibody inhibitor of human insulin-like growth factor-1 receptor (IGF1R).
- The Applicant's initial proposed proprietary name (trade name) of Tepezza was not accepted. The proprietary name of [redacted] (b) (4) was accepted. For the nonproprietary name, a suffix of *trbw* was assigned.
- Teprotumumab was developed under IND 112952.
- The nonclinical Pharmacology/Toxicology (P/T) review of the BLA is complete, and P/T recommends approval. From a P/T perspective, no safety or regulatory issues were identified that would preclude approval.
- The BLA was submitted electronically, and is available to the review team via: \\CDSESUB1\evsprod\BLA761143\761143.enx

1.2 Brief Discussion of Nonclinical Findings

Teprotumumab is an antagonist, binding with high affinity and selectivity to the IGF-1R via the extracellular α-subunit. Teprotumumab inhibits the endogenous ligands, IGF-1 and IGF-2, from binding to IGF-1R. IGF1R is known to be expressed on the surface of most cells. The Applicant's tissue cross-reactivity studies detected IGF1R primarily on epithelial and endothelial cells.

Active thyroid eye disease (TED) is also described as thyroid-associated ophthalmopathy, Graves' ophthalmopathy, and Graves' orbitopathy. The Applicant reports that it is a rare, serious, debilitating and painful disease associated with major morbidities, including risk of blindness. The Applicant hypothesizes that activation of orbital fibroblasts by autoantibodies contributes to the pathophysiology of TED.

Teprotumumab Nonclinical Safety

- GLP toxicology studies in cynomolgus monkeys administered teprotumumab once weekly by intravenous (IV) bolus or slow IV bolus injection. Adult monkeys have been dosed for up to 39 weeks. Juvenile monkeys were tested in two separate studies (both 13 weeks).
- For adults, the low-dose (3 mg/kg/week IV) is the lowest adverse effect level (LOAEL), and a no observed adverse effect level (NOAEL) was not identified. Teprotumumab was active at all dose levels (3, 15, 75 mg/kg) and exhibited pharmacological activity, causing:
    - Cessation of weight gain during the dosing window. Resumption of weight gain was observed for recovery animals after the last dose. This effect

correctly predicts the slight reduction in body weight for treated patients ([redacted](b) (4) discussed in section 11 of the this review, below)
    - Decreased serum alkaline phosphatase (ALP) during the window, with partial recovery apparent. This effect also correctly predicted the slight decrease in ALP observed clinically.
    - Thymus diffuse atrophy (also described as thymic lymphoid depletion, and thymic involution). No correlate was observed for other endpoints in the monkeys (e.g., blood cell counts, other lymphoid tissues). The observed thymus atrophy in monkeys did not have an observed clinical correlate.
    - Because the treatment-related thymus atrophy is distinct from normal physiological thymus involution, P/T concludes that the thymus atrophy is adverse.
- For juveniles, the low-dose (3 mg/kg/week IV) is the lowest adverse effect level (LOAEL), and no NOAEL was identified.
    - As in the adults, teprotumumab blocked weight gain and affected the thymus (decreased size and weight, diffuse atrophy) at all dose levels. The magnitude of the effect, compared to controls, is more dramatic in juvenile monkeys than in adults. Comparing between the two juvenile studies, the younger monkeys (in report # 103784) were more sensitive. Based on the importance of normal growth and normal thymus, these effects are considered adverse.
    - Treatment reduced juvenile spleen weight in both studies.
    - The first 13-week study included two juvenile monkeys arms (0 and 15 mg/kg/day). Serum bone-specific ALP (BAP) assessment was included, and the 15 mg/kg dose decreased BAP.
    - The second 13-week study was a stand-alone juvenile study (0, 3, 15, 75 mg/kg). The design included in-life radiography of long bones (humerus, radius, ulna, femur, tibia, fibula). Teprotumumab decreased bone growth. Additionally, femur and tibia density were evaluated at necropsy: all dose levels were shown to reduce bone density. The cortical bone of the tibial diaphysis showed thinning.
- The proposed labeling has three clinical warnings and precautions for: infusion reactions, exacerbation of inflammatory bowel disease, and hyperglycemia.
    - The monkey toxicology studies did not predict these effects.
    - Teprotumumab's target is IGF1R; IGF1R and insulin receptor are members of the same family, and insulin is an endogenous ligand for IGF1R. Retrospectively, P/T hypothesizes that the clinically observed hyperglycemia might be due to off-target activity against the insulin receptor (e.g. increased circulating IGF1R).
- The BLA includes a non-GLP IV monkey embryofetal (EFD) dose range-finding (DRF) study. One dose level of teprotumumab was tested, 75 mg/kg/week. Teprotumumab reduced fetal growth (measured by ultrasound in-life; body weight and measurements at C-section) and was clearly teratogenic in all 5/5 fetuses. The laboratory mainly focused on cranial/skull malformations. The 75 mg/kg dose was not maternally toxic.

- The published literature are unclear regarding the potential for IGF1R inhibition to adversely affect human male and female fertility.
    - No fertility studies were conducted with teprotumumab; no basis for concern for reproductive tissues was identified in the general toxicology studies (i.e. NOAEL for reproductive tissues is 75 mg/kg/week).
    - The Applicant provided published literature regarding IGF1R function; its role in fertility varies across mammalian species, but it is consistently central to healthy ovarian and testes function.
- Based on mechanism of action, teprotumumab may affect peri/postnatal development (PPND).
    - No PPND study was submitted to the BLA.
    - The Applicant provided published literature regarding IGF1R function in normal development, and in conditional IGF1R knock out mice.

TED: disease background

Active thyroid eye disease (TED) is also described as thyroid-associated ophthalmopathy, Graves' ophthalmopathy, and Graves' orbitopathy. The Applicant reports that it is a rare, serious, debilitating and painful disease associated with major morbidities, including risk of blindness. The Applicant hypothesizes that activation of orbital fibroblasts by autoantibodies contributes to the pathophysiology of TED.

In IND 112952 (incorporated into this BLA by cross-reference[1]), the Applicant previously reported: "*In the US, the annual incidence rate of TED has been estimated to be 16 cases per 100,000 population for women and 2.9 cases for men." "While TED appears to affect females more frequently than men, severe cases occur more often in men than in women. Patients aged between 30-50 years are most frequently affected, with severe cases occurring more frequently in those older than 50 years. TED is strongly associated with smoking, which appears to increase the risk of development of more severe ophthalmopathy."*

In deciding to grant breakthrough therapy designation to IND 112952, the Clinical reviewer (Wadhwa, 7/29/2016, IND 112952) explained that:

- "*TED is an autoimmune condition most commonly associated with Graves' hyperthyroidism, but also found in a small proportion of euthyroid and hypothyroid patients. Active TED is a local inflammatory condition, typically lasting between 1 to 3 years*."
- "*The autoimmune inflammation then spontaneously resolves to leave the permanent sequelae of expanded, fibrotic orbital tissues and dysfunctional orbital muscles, which constitutes what is termed inactive (or stable) TED*."
- "*TED is a painful, debilitating, and potentially vision-threatening condition. Protrusion of the eyeball from the socket, termed proptosis, is a hallmark of the disease and can cause sight-threatening optic neuropathy. Proptosis also impairs the ability of patients to close their eyes, resulting in corneal ulceration.*

[1] BLA module 1.4.4 Cross-reference to previously submitted information, accessed via: \\cdsesub1\evsprod\bla761143\0001\m1\us\cross-reference-to-other-application.pdf

Diplopia is also a common symptom, causing difficulty with working, driving and other activities of daily living. In addition, TED symptoms cause marked psychosocial distress for patients due to profound changes in appearance."

IGF1R: background on the target

Considered from the perspective of insulin receptor (IR), the insulin receptor family has three members: IR and insulin like growth factor (IGF)-1 receptor (IGF1R, IGF-1R), and IGF2R[2]. Considered from the perspective of IGF1R, the IGF receptor family has multiple members, including IR, IGF2R, the IGF binding proteins (IGFBP1-6), and IGFBP-related proteins (IGFBprP)[3]. Human IGF1R shares 60% homology with human insulin receptor (IR).

The physiology of IGF1R is well understood. IGF1R is a tyrosine kinase cell surface receptor, with two extracellular alpha units (N-terminal), and an intracellular tyrosine kinase domain. Downstream signaling includes the PI3K-AKT and the RAF-MAPK pathways. IGF1R has three known endogenous ligands: insulin, insulin like growth factor 1 (IGF1) and insulin like growth factor 2 (IGF2). Activation of IGF1R by ligand binding results in rapid autophosphorylation, ubiquitination, and internalization of IGF1R. Activation of IGF1R stimulates cell proliferation, cell differentiation, and inflammatory responses, and inhibits apoptosis. IGF-1R activation is associated with proliferation of adult fibroblasts, epithelial cells, and bone marrow.

The normal hormonal regulation of IGF-1 and IGF1R is well understood. Growth hormone (GH) is produced in the anterior pituitary gland in response to somatostatin and growth-hormone-releasing hormone (GHRH). Additionally, paracrine regulation of IGF1R (stromal-epithelial interactions) and autocrine regulation (tumor cell self-stimulation) of IGF-1R has been reported. The availability of unbound IGF1 for interaction with IGF1R is also modulated by IGFBP1-6 expression.

P/T review and labeling issue: mechanism of action

- For the oncology clinical trials, the rationale for teprotumumab was direct pharmacology (i.e. inhibition of IGF1R stimulated tumor growth).
- For the TED indication, the rationale is indirect and hypothetical. Teprotumumab is not intended to directly target the thyroid or the eye.
    - TED is an autoimmune disorder; the primary causes are thought to be autoantibodies against thyroid-stimulating hormone receptor (TSHR) and IGF1R.
    - The Applicant hypothesizes that autoantibodies against IGF1R activate the IGF1R signaling pathway and contribute to the pathophysiology of Graves' disease and TED. By blocking activation of IGF1R (by

[2] Hernandez-Sanchez C, Mansilla A, de Pablo F, Zardova R. 2008. Evolution of the insulin receptor family and receptor isoform expression in vertebrates. Mol. Biol. Evol. 25(6):1043-1053. Accessed online via: https://www.ncbi.nlm.nih.gov/pubmed/18310661

[3] Boon DN, Lee AV. 2012. Targeting the insulin-like growth factor receptor: developing biomarkers from gene expression profiling. Crit. Rev. Oncog. 17(2):161-173. Accessed online via: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3926653/pdf/nihms398362.pdf

endogenous ligands and autoantibodies) on orbital fibroblasts, teprotumumab is intended to reduce the severity of the active phase of TED.

- The BLA lacks direct proof of mechanism of action.
  - No nonclinical pharmacodynamics (PD) studies were submitted to demonstrate that teprotumumab blocks autoantibody activation of IGF1R.
  - With deference to the Clinical and Clinical Pharmacology review teams, this reviewer found no mention in the BLA of measuring patient anti-IGF1R levels.
  - However, the Applicant prospectively (in 2011, when IND 112952 was opened) proposed this mechanism of action for TED. Therefore, the demonstration of clinical efficacy is (from a scientific perspective) strong support for the proposed mechanism of action.
  - Considering the overall weight of evidence (detailed in section 4.1.2 of this review, below), this reviewer concludes that the Applicant's hypothesis may be accurate, but has not been demonstrated at the level usually expected for Investigator Brochure claims or labeling.
  - The mechanism of action section of labeling (section 12.1) was discussed internally at the December 4, 2019 internal meeting.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, P/T recommends approval of BLA 761143 for (b) (4) (teprotumumab-trbw) for injection.

1.3.2 Additional Non Clinical Recommendations

1. We recommend empirical verification that teprotumumab blocks IGF1R activation by autoantibodies from patients with thyroid eye disease (TED), to support labeling section 12.1 Mechanism of Action.

1.3.3 Labeling

The Applicant proposed labeling in the original BLA submission (7/08/2019), proposing (b) (4). From a nonclinical perspective, P/T concurs with this contraindication. However, P/T defers to the clinical review team, and understands (personal communications, Chambers/review team, 2019) that the clinical team does not consider this contraindication supported by current clinical data.

Revised labeling was submitted 11/22/2019[4], without the previously-proposed contraindication. Notably, the draft included comments but not full annotation.

[4] Proposed labeling text with tracked changes:
\\cdsesub1\evsprod\bla761143\0024\m1\us\11413-proposed-pi-tracked.pdf

Review note: the propriety name should be updated from TEPEZZA (b) (4) throughout (not flagged further)

Applicant's proposed language (11/22/2019)	P/T recommended language:
2.1 (b) (4) (b) (4)	[no recommendation, noted for context]
2 (b) (4) **Recommended Dosing** The recommended dose of TEPEZZA is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks. (b) (4)	[no recommendation, noted for context]
5 WARNINGS AND PRECAUTIONS	

(b) (4)

[redacted] (b) (4)

8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** <u>Risk Summary</u> Based on findings in animals and its mechanism of action, TEPEZZA may cause fetal harm when administered to a pregnant woman [redacted] (b) (4). Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes.	Based on findings in animals and its mechanism of action **inhibiting IGF1R**, TEPEZZA may cause fetal harm when administered to a pregnant woman [redacted] (b) (4) [redacted] (b) (4). Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes.
In utero TEPEZZA exposure in cynomolgus monkeys dosed once weekly with TEPEZZA throughout pregnancy resulted in external and skeletal abnormalities. TEPEZZA exposure may	*[These sentences should use the non-proprietary name, teprotumumab]* In utero **teprotumumab** exposure in cynomolgus monkeys dosed once weekly

lead to an increase in fetal loss [see Data].	with **teprotumumab** throughout pregnancy resulted in external and skeletal abnormalities. **Teprotumumab** exposure may lead to an increase in fetal loss *[see Data]*.
Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus. The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.	[no recommendation]

Data *Animal Data* (b) (4)	*Animal Data* In an abridged pilot EFD study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (b) (4)-fold the maximum recommended human dose (MRHD) based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at Caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals, and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL). Based on mechanism of action inhibiting IGF1R, postnatal exposure to teprotumumab may cause harm.
8.2 Lactation Risk Summary There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.	[P/T concurs with the Applicant's proposed language.]
8.3 Females and Males of Reproductive Potential (b) (4)	

(b) (4)	
Contraception *Females* Based on its mechanism of action, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.	Based on its mechanism of action **inhibiting IGF1R**, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA. [P/T infers that the 6-month recommendation is based on the recovery period of the 9-month monkey toxicology study. This duration was adequate to allow for recovery from the treatment-related pharmacological effects of teprotumumab.]
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action**	
(b) (4)	**Teprotumumab-xxxx's mechanism of action in Thyroid Eye Disease patients has not been fully characterized.** (b) (4) blocks IGF-1R activation.

(b) (4)	
12.3 Pharmacokinetics The pharmacokinetics of TEPEZZA was described by a two compartment model based on data from (b) (4) patients with (b) (4) Thyroid Eye Disease receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg every 3 weeks in two clinical trials (b) (4) (b) (4). Following this regimen the mean (± standard deviation) steady-state area under the concentration curve (AUC), peak (C_{max}) and trough (C_{trough}) concentrations were (b) (4) (b) (4) (b) (4), respectively. (b) (4) (b) (4)	[no recommendation; language noted for context]
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** The carcinogenic potential of TEPEZZA has not been evaluated in long-term animal studies. The genotoxic potential of TEPEZZA has not been evaluated. Fertility studies have not been performed with TEPEZZA.	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** *Carcinogenesis* The carcinogenic potential of TEPEZZA has not been evaluated in long-term animal studies. *Mutagenesis* The genotoxic potential of TEPEZZA has not been evaluated. *Impairment of Fertility* Fertility studies have not been performed with TEPEZZA.
(b) (4)	

(b) (4)	
17 PATIENT COUNSELING INFORMATION **…** <u>Embryo-Fetal Toxicity</u> • Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy (b) (4) (b) (4)	[no recommendation; language noted for context]

• Educate and counsel females of reproductive potential about the need to use effective contraception during treatment with TEPEZZA and for at least 6 months after the final dose of TEPEZZA (b) (4) (b) (4)	

These labeling recommendations considered:

- The 2012 Guidance for Industry ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals[5]
- The 2014 Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format[6]
- The CDER/CBER 2009 Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information[7]
- The CDER 2018 Manual of Policy and Procedures (MAPP) 7400.13 Determining the Established Pharmacologic Class for Use in the Highlights of Prescribing Information[8]
- The current EPC Text phrase table[9]

2 Drug Information

2.1 Drug

CAS Registry Number	89957-37-9
Generic name	Teprotumumab
Applicant's code name	HZN-001
Previous code names	• RV 001 • RO4858696

[5] ICH S6(R2) accessed via https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals
[6] The guidance was accessed via: https://www.fda.gov/media/90160/download
[7] The guidance was accessed via: https://www.fda.gov/media/77834/download
[8] MAPP accessed via: https://www.fda.gov/media/86437/download
[9] https://www.fda.gov/media/90321/download

	• R1507 • huMab IGF-1R • AK18 • Cl.18
Chemical name	Immunoglobulin G1 anti-(human insulin-like growth factor 1 receptor) (b) (4) human monoclonal (b) (4)
Molecular weight	148 KDa
Biochemical description	• human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass
(b) (4)	
Pharmacological Class	Insulin like growth factor 1 receptor (IGF1R) antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 112952	The Applicant cross-referenced their own Investigational New Drug Application (IND) 112952 for teprotumumab for TED.
Other teprotumumab INDs	The Applicant did not explicitly cross-reference the withdrawn Roche INDs (b) (4) for teprotumumab. Notably, IND 112952 includes a letter of authorization (LOA) from Roche to IND (b) (4)[10]
Drug Master Files	The BLA includes LOAs for DMF (b) (4), (b) (4).
Competitor INDs	Information regarding other investigational anti-IGF1R products has been published (e.g. ClinicalTrials.gov). The Applicant did not cite any other INDs; none are listed herein to maintain confidentiality. No data from the other INDs was used in this review.

2.3 Drug Formulation

BLA module 2.3.P (Quality Overview Summary – Drug Product)[11]:

- "The drug product (DP) is a sterile, preservative-free, lyophilized powder for reconstitution and dilution for infusion, which is presented as a white to off-white powder cake. Each vial delivers 500 mg of teprotumumab formulated in (b) (4) histidine, (b) (4) trehalose and (b) (4) polysorbate 20, pH 5.5."
- "At time of use, the product is reconstituted with 10 mL of sterile water for injection, which is supplied by the pharmacy, to a final teprotumumab concentration of 50 mg/ml. The reconstituted solution for infusion is a clear to opalescent, nearly colorless to slightly brown liquid and practically free of visible particles."

Table 1: Teprotumumab drug product formulation

Material	Concentration after reconstitution		Amount per vial	Function
	(various units)	(per ml)		
Teprotumumab	50 mg/ml	50 mg/ml	500 mg	Active
L-Histidine, USP/Ph. Eur./JP	(b) (4)		7.45 mg	Buffer

[10] \\cdsesub1\evsprod\ind112952\0000\m1\us\14-ref\loa-ind1(b) (4).pdf
[11] \\cdsesub1\evsprod\bla761143\0001\m2\23-qos\qos-dp.pdf

L-Histidine hydrochloride, monohydrate, Ph. Eur.	(b) (4)	31.8 mg	Buffer
α, α – Trehalose dihydrate, NF/Ph. Eur./JP		946 mg	Bulking agent, tonicity agent
Polysorbate 20, NF/Ph. Eur./JPE		1 mg	Surfactant

NF=National Formulary; Ph. Eur.=European Pharmacopeia; USP=United States Pharmacopeia; JP = Japanese Pharmacopeia: JPE = Japanese Pharmaceutical Excipients

- The BLA (module 2.3.P, section 2.3.P.2.1.1) reports that the actual concentration variability is 50 ± 5 mg/ml
- The Applicant reports that:
  - The trehalose is important (b) (4) (b) (4).
  - The polysorbate surfactant protects (b) (4).
  - The use of histidine and histidine hydrochloride monohydrates allows for pH balancing.

2.4 Comments on Novel Excipients

Each excipient has adequate previous qualification for intravenous injection at/above the proposed concentrations.

2.5 Drug Product Formulation History

- The Applicant (2.3.P.2.2.1.1) reports that the initial monkey toxicology studies tested a formulation of (b) (4) teprotumumab in (b) (4) histidine/HCl at pH (b) (4) with (b) (4) NaCl and (b) (4) polysorbate 20.
  - α,α-trehalose dihydrate (CAS # 6138-23-4) is a disaccharide, consisting of two glucose molecules joined by a 1-1 alpha bond. It is produced naturally by bacteria, yeast, plants, and some invertebrates.
  - The Applicant reports that original Sponsor was concerned about the use of trehalose dihydrate exceeding the maximum tolerated dose in monkeys. Therefore, the initial monkey studies, including the 13-day study (report # 1020097) and the GLP 7-week study (report # 1016123) used the sodium chloride formulation instead.
  - The Applicant reports that the sodium chloride formulation was stable for 3 months storage, but did not meet acceptance criteria at 6 months (b) (4) (b) (4)). The solution was (b) (4) prior to dosing, (b) (4) (b) (4).
- This issue is obviated, since the subsequent GLP monkey toxicology studies (13-week, 39-week), as well as the EFD DRF study used the clinical IV formulation.
- For the initial GLP toxicology studies through the end of the Phase 1 clinical oncology trials, the drug substance was produced in mouse SP2/0 cells. For the

Phase 2 oncology trials, and for the entire TED clinical program, the drug substance was produced by Chinese hamster ovary (CHO) cells.
  - Several of the nonclinical pharmacodynamic (PD) studies compared the SP2/0 and the CHO products (see below).

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant proposed (in the original BLA, submitted 7/08/2019):

- Indication: DRUG NAME is indicated for the treatment of Active Thyroid Eye Disease.
- Dosage and Administration: The recommended dose of DRUG NAME is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks. The recommended course of therapy is 8 infusions.
- Administration: Administer the diluted solution as an intravenous solution over 90 minutes for the first two infusions. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes. Do not administer as an intravenous push or bolus. DRUG NAME should not be infused concomitantly with other agents.

2.7 Regulatory Background

IND (b) (4)	This was the first IND for teprotumumab
	• DARRTS does not record the submission date of the original IND.
	  o In January 2006, the CDER/OND review division was the Division on Biologic Oncology Products (DBOP)
	  o When the Oncology Office reorganized, the IND was assigned to the Division of Oncology 2 (DOP2)
	• Sponsor: Hoffman La Roche Inc.
	• Product: RO4858696, expressed in the (b) (4) cell line
	• Indication: (b) (4) (b) (4)
	• The last protocol change was submitted in 2011.
	• The IND was formally withdrawn in December 2011, “because there are no plans for additional clinical development of RO4858696 using the SP2/0 formulation” (Sickafuse, 12/29/2011, IND (b) (4)).

	(b) (4)

	(b) (4)
IND (b) (4)	This is the second IND for teprotumumab • As for IND (b) (4), it was originally submitted to DBOP, and reassigned to DOP2 • Sponsor: Hoffman La Roche Inc. • Product: RO4858696, expressed in Chinese hamster ovary (CHO cells) • Indication: (b) (4) malignancies • The IND was submitted 10/15/2007 • The last protocol information was submitted in 2011. • The IND was formally withdrawn in August 2011 "because the clinical development program for RO4858696 has been discontinued." (Sickafuse, 8/11/2014, IND (b) (4)) (b) (4)
IND 112952	This is the third IND for teprotumumab, and is the parent IND for this BLA 761443. • New IND submitted to DTOP 11/18/2011 • Original Sponsor: River Vision, LLC • Product: RV 001 (teprotumumab) • Indication: active moderate-to-severe thyroid eye disease (TED) • The Division was notified of a change in sponsor on 5/23/2017, to Horizon Pharma USA, Inc. • Meetings include:

	o a type B End of Phase 2 meeting held August 19, 2016 o A type B pre-BLA meeting was held May 14, 2019
	• A type B End of Phase 2 (EOP2) meeting was held August 19, 2016. P/T recommended: o "The overall nonclinical program conducted to date appears adequate to support registration, with the following recommendations…" o "The BLA should include an integrated summary and a copy of all published literature used to support a role of IGF/IGF-1R in fertility and any adverse effects related to IGF/IGF-1R inhibition" o "Please submit formal waiver requests to the Division to omit fertility and peripostnatal studies. They should include your rationale, a summary of all safety data to support your rationale, and a copy of all literature referenced in the summaries." o "If you believe that carcinogenicity studies are not needed, you should also submit a formal waiver to the Division for review providing your rationale to omit the studies." • A type B pre-BLA meeting was held May 14, 2019. The Applicant did not submit nonclinical questions for the meeting, and nonclinical topics were discussed.

3 Studies Submitted

3.1 Studies Reviewed

Table 2: Primary pharmacology study reports

Report #	Report title
1019200	Characterization of Human anti IGF-1-Receptor Antibody RO4858696-000 and FITC- RO4858696-000 by Immunocytochemistry and Confocal Laser Scanning Microscopy
1019483	Affinity of RO4858696 to IGF-1R
1027532	Affinity of RO4858696 from CHO and SP2/0 cells to the human and cynomolgus monkey IGF-1R
1019598	Cynomolgus monkey as IGF-IR cross-reactive species for RO4858696
1019991	Cross-reactivity of RO4858696 with IGF-1R from mouse and rat
1019287	Inhibition of ligand binding to IGF-1R by RO4858696
1027507	Functional assay to assess inhibition of IGF-1R autophosphorylation

1019219	Downregulation of surface IGF-1R by human anti-IGF-1 receptor antibody RO4858696 in H322M tumor cells *in vitro*
1019078	Inhibition of IGF- 1 Mediated Proliferation by Human anti-IGF- 1 - Receptor Antibody RO4858696 in Human Tumor Cell Lines *in vitro*
101449	Acute effect of treatment with rhu anti-IGF-IR antibody <18> (R04858696-000) on IGF-IR expression of H322M lung tumor xenografts

Table 3: Secondary pharmacology study reports

Report #	Report title
1019286	Cross-reactivity of RO4858696 with human Insulin Receptor
1019183	Lack of Cross reactivity of Human anti-IGF-1-Receptor Antibody RO4858696-000 to Human Insulin Receptor analyzed by Immunocytochemistry and Confocal Laser Scanning Microscopy
1018657	RO4858696/F01-01 (huMAb-IGF-1R): Hemolytic Potential and Blood Compatibility Study
1026030	*In Vitro* Evaluation of the Influence of RO4858696 on Human and Cynomolgus Monkey Whole Blood Hemolysis and Plasma Flocculation
1019288	Antibody dependent cellular cytotoxicity (ADCC) by RO4858696

Table 4: Pharmacokinetic study reports (TK and tissue-cross reactivity studies)

Report #	Report title
1033803	Comparison of IGF-1R expression in formalin fixed normal human and normal Cynomolgus monkey tissue (TMAs)
1019357	RO4858696/F01-01 (huMAb-IGF-1R): Cross-Reactivity Study of RO4858696 with Normal Human Tissues
1019358	RO4858696/F01-01 (huMAb-IGF-1R): Cross-Reactivity Study of RO4858696 with Normal Cynomolgus Monkey Tissues
1018220	RO4858696-000-009 (IGF-1R): A Single Intravenous Dose Pharmacokinetic Study in Male Rats
1016690	RO4858696 (huMab-IGF-1R): Single Dose Pharmacokinetic Study of RO4858696 Following Intravenous Administration to Monkeys
AGD00037	A Single-Dose Intravenous Comparative Pharmacokinetic and Pharmacodynamic Study of RO4858696 Administered to Male Cynomolgus Monkeys

Table 5: Repeat-dose intravenous (IV) toxicology studies in cynomolgus monkeys

Report #	Report title
2136-005	RO4858696: 13 - Days Intravenous Pilot Toxicity and Toxicokinetic Study in the Cynomolgus Monkey
6131-477	Ro 485-8696/F01-01(huMAb-IGF-1R): A 7-Week Intermittent Intravenous Toxicity, Toxicokinetic, and Immunogenicity Study with Ro 485-8696/F01-01 (huMAb-IGF-1R) in Cynomolgus Monkeys with an 8-Week Recovery Period
AGD00022	RO4858696: A 13-Week Toxicity and Toxicokinetic Study Administered Once Weekly by Intravenous Injection to Cynomolgus Monkeys, with a 12-Week Recovery Period
AGD00061	A 39-Week Toxicity Study of RO4858696 Administered Once Weekly by Intravenous Injection to Cynomolgus Monkeys, with a 24-Week Recovery Period
1037684	RO4858696: A 13-Week Toxicity Study of RO4858696 Administered by Intravenous Injection to Juvenile Cynomolgus Monkeys, with a 13-Week Recovery Period

Table 6: Repeat-dose intravitreal (ivt) toxicology study in cynomolgus monkeys

Report #	Report title
8250539	Ocular Tolerance Study of Teprotumumab Following Intravitreal Administration in Cynomolgus Monkeys

Table 7: Study of embryofetal development (EFD)

Report #	Report title
AGD00065	Embryo-Fetal Development Study of RO4858696 Administered by Intravenous Injection to Pregnant Cynomolgus Monkeys

3.2 Studies Not Reviewed

Four pharmacokinetic analytical methods and validation reports were submitted (BLA module 4.2.2.1). Full review of these study reports is not documented herein.

Table 8: Analytical methods and validation reports

Report #	Report title
09009	RO4858696: Method Validation Bioanalytical Report for Analysis of RO4858696 in Monkey Serum by ELISA

1028362	Method for determination of Anti-R04858696 (CHO1 material) in Cynomolgus Monkey Serum by ECLIA
10338	Bioanalytical Method Validation Report for the Quantification of RO4858696 (CHO Material) in Monkey Serum by ELISA
10405	RO4858696 (IGF-1R): Bioanalytical Method Validation Report for Analysis of Anti-RO4858696 Antibodies (CHO Material) in Monkey Serum by ECLIA

3.3 Previous P/T Reviews Referenced

The P/T reviews for teprotumumab conducted under IND are referenced:

Table 9: previous P/T reviews for teprotumumab (conducted under IND) referenced

IND (b) (4)[a]	McDougal 7/26/2011 McDougal 8/31/2011
IND	McDougal 11/20/2007 McDougal 1/14/2009 McDougal 12/23/2010 McDougal 12/30/2010 McDougal 8/23/2011 McDougal 8/15/2011
P/T reviews for entered for both IND (b) (4) and IND (b) (4)	McDougal 5/18/2011 McDougal 8/24/2011 McDougal 12/15/2011
IND 112952	Rivera 9/26/2011 Rivera 12/13/2011 Rivera 8/18/2016

[a] Note: the initial P/T review for IND (b) (4) by Dr. Lei Zhang (undated) was available (in paper format) from DBOP archives in 2007 (cited among the reviews listed above), but was no longer available to support this review.

4 Pharmacology

Table 10: Summary of teprotumumab primary and secondary pharmacology

Binding to human IGF1R	K_D = 2.2 to 2.38 nM
Binding to cynomolgus monkey IGF1R	K_D = 2.54 to 2.69 nM
Inhibits binding of human IGF-1 to human IGF1R	IC_{50} = 0.44 to 1.3 nM
Inhibits binding of human IGF-2 to IGF1R	IC_{50} = 0.28 to 2.8 nM
Inhibits binding of human IGF-1 to monkey IGF1R	IC_{50} = 0.63 nM

Inhibits binding of human IGF-1 to rat and mouse IGF1R	No specific binding detected
Inhibited autophosphorylation of human IGF1R	IC_{50} = 0.96 nM
Causes internalization of human IGF1R from the cell surface	Activity observed ≥ 0.1 µg/ml (equivalent to 0.67 nM)
Inhibited proliferation of IGF1R-expressing human cell lines stimulated to growth with IGF-1	IC_{50} = 2.0 to 29.7 nM
Inhibition of tumor growth (IGF1R-expressing cells, xenografted into nude mice)	No apparent activity for a single intraperitoneal (ip) dose of 6 mg/kg teprotumumab
Cross-reactivity to insulin receptor	No activity detected (tested up to 1 µM)
Human and monkey whole blood tests for blood compatibility, hemolysis, and flocculation	No concerns (tested up to 12.5 mg/ml)
Antibody dependent cellular cytotoxicity (ADCC) assay	No activity (tested up to 10 µg/ml)

4.1 Primary Pharmacology

4.1.1 Species selection notes

- Teprotumumab binds cynomolgus monkey IGF1R and human IG1R with similar potency, and inhibits their binding by IGF1. *In vivo* toxicology studies to support safety were performed in the cynomolgus monkey.
- Teprotumumab does not bind to mouse or rat IGF1R.
    - The parent antibody for temprotumumab was raised in transgenic mice (report # 1019598), and cross-reactivity against rodent IGF1R was not expected (due to immunological self-tolerance)

4.1.2 Primary review of submitted reports

Report title	**Characterization of Human anti IGF-1-Receptor Antibody RO4858696-000 and FITC- RO4858696-000 by Immunocytochemistry and Confocal Laser Scanning Microscopy**
Report #s	• Applicant's #: 1019200 • Study laboratory's #: A84860
Key findings	• This was an early research and development (R&D) study to support further research. • Microscopy experiments verified that teprotumumab binds the outer cell membrane of cells expressing IGF1R (as expected). • Teprotumumab binding could be blocked with excess soluble extracellular domain of IGF1R.

Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019200\1019200.pdf
	Study laboratory	(b) (4)
	Report date	November 13, 2003
Method notes	• Cell lines: o 3T3 mouse fibroblasts stably transfected to express human IGF1R o R-cells (from a IGF1R-deficient mouse stain) • Antibodies used: o Teprotumumab (RO4858696) o Fluorescent-labeled teprotumumab (FITC-RO4858696) o αIR3 (a commercially-available mouse anti-IGF1R reference antibody) • Microscopy: a confocal laser scanning microscope was used	

Report title	**Affinity of RO4858696 to IGF-1R**	
Report #s	• 1019483 (Applicant's report #) • Laboratory report #: 4860	
Key findings	For teprotumumab, K_D for binding to human IGF1R = 2.38 nM (by *in vitro* SPR assay)	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019483\1019483.pdf
	Study laboratory	(b) (4)
	Report date	August 30, 2005
Method notes:	• Surface plasmon resonance (SPR) assays were conducted using a Biacore 2000 instrument. • Teprotumumab (RO4858696) was immobilized on the chip, and washed with recombinant human IGF1R in the injection phase. • Three toxicology batches were measured. Four earlier batches were also measured (eleven measurements total)	
Results notes	• For the toxicology batches, K_D = 2.38 ± 0.128 nM (mean ± standard deviation) o The authors rounded this to 2.4 nM	

	• For the eleven R&D batches, K_D = 2.970 ± 2.08 nM (mean ± standard deviation)

Report title	**Affinity of RO4858696 from CHO and SP2/0 cells to the human and cynomolgus monkey IGF-1R**	
Report #	1027532	
Key findings	Comparable potency demonstrated for temprotumumab binding recombinant human IGF1R (K_D = 2.2 nM) and cynomolgus monkey IGF1R (K_D = 2.54 to 2.69 nM)	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1027532\1027532.pdf
	Study laboratory	(b) (4)
	Report date	November 15, 2017
Method notes:	• SPR assays were conducted using a Biacore 200 instrument. • Recombinant cynomolgus monkey IGF1R was harvested from transfected HEK293F cells (a transformed human cell line) • Two batches of teprotumumab were tested: o RO4858696(SP2/0) GMP batch G002.01E ▪ Produced in SP2/0 mouse cells ▪ Same process as was used for the initial GLP toxicology studies o RO4858696(CHO) GMP batch G002.02E ▪ Newer process using CHO cells • As with the previously reviewed study, teprotumumab (RO4858696) was immobilized on the chip, and washed with recombinant human IGF1R or recombinant monkey IGF1R in the injection phase	
Results:	**Table 11: K_D binding affinity comparing CHO and SP2/0 batch temprotumumab to recombinant monkey IGF1R (report # 1027532)**	

Teprotumumab test article	IGF1R test article	K_D value (nM)
CHO batch	Human	2.20
	Cynomolgus monkey	2.54
SP2/0 batch	Cynomolgus monkey	2.69

Report title	**Cynomolgus monkey as IGF-IR cross-reactive species for RO4858696**	
Report #s	• Applicant's report #: 1019598 • Laboratory report #: 4860	
Key findings	• Competitive binding assays were used to investigate the pharmacological relevance of marmoset monkey and cynomolgus monkey for teprotumumab o Cynomolgus monkey is a relevant species by two assays (immunoprecipitation of monkey IGF1R from brain tissue, and competitive binding) o Weak binding was observed in marmoset tissues (not clearly relevant, not investigated further and not used as a toxicology model)) • In competitive binding assays, teprotumumab exhibited similar potency inhibiting IGF1 binding to human IGF1R (IC_{50} = 0.49 nM) and cynomolgus monkey IFR1R (IC_{50} = 0.63 nM)	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019598\1019598.pdf
	Study laboratory	(b) (4)
	Report date	August 8, 2005
Initial experiment: tissue lysate immune-precipitation	Methods	• Four tissues from marmoset monkey (liver, kidney, skin, pancreas) and one tissue from cynomolgus monkey (brain) were used. • Tissues were snap-frozen immediately after collection, ground to powder frozen, and lysed. • The authors report previous data that teprotumumab (RO4858696) binds cynomolgus monkey IGF1R, but not marmoset IGF1R. Another investigational antibody RO4594410, humanized IgG against human IGF1R, reportedly binds to both cynomolgus monkey and marmoset monkey IGF1R. • Immunoprecipitation assays were conducted with teprotumumab, RO4594410, or αIR3 (a commercial mouse antibody against human IGF1R). • Specificity was verified by Western blotting, using C20, a commercial pan-specific IGF1R antibody
	Results	• Strong immunoprecipitation was observed from cynomolgus monkey brain; and shown to be IGF1R (by Western blotting)

		• Marmoset brain was not investigated (a minor study limitation). Weak immunoprecipitation from marmoset kidney and pancreas was detected
Second experiment: competitive binding	Methods:	• Cell types used: o Human HT29 cancer cells o Cynomolgus monkey kidney cells (no details on whether these were primary or cultured cells) • Cells were treated with ^{125}I-labeled IGF-1 and teprotumumab (over a range of concentrations from 1 pM to > 100 nM) for 3.5 hours at 4°C, then isolated from media (via centrifugation and resuspension), and incubated with excess (1 µM) unlabeled IGF-1. • Radioactivity was measured by gamma counting.
	Results:	Teprotumumab inhibition of IGF1 binding: • Human cell line IC_{50} = 0.49 nM • Cynomolgus monkey cells IC_{50} = 0.63 nM • Graphs for both experiments showed the expected sigmoidal response curve with increasing antibody concentration.

Report title	**Cross-reactivity of RO4858696 with IGF-IR from mouse and rat**	
Report #s	1019991	
Key findings	Neither the mouse nor the rat are pharmacologically relevant models for teprotumumab primary pharmacology • No specific binding was observed for either species by immunoprecipitation. • Competitive binding showed weak specific binding for rat IGF1R (not quantified; mouse IGF1R not tested).	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019991\1019991.pdf
	Study laboratory	(b) (4)
	Report date	November 14, 2002
Immuno-precipitation	Methods	Same methods as described for report # 1019598 (reviewed above)

assay		• Fresh brain and heart tissue from rat and mouse (strains not reported) were snap-frozen, and lysates prepared. • Teprotumumab, RO4594410, and αIR3 were used for immunoprecipitation. The c20 antibody was used for Western blotting (to investigate specificity of binding)
	Results	• No specific binding of rat or mouse IGF1R by teprotumumab or RO4594410 was detected. • IGF1R in the tissues was detected (by c20), indicating that the methods were adequate
Competitive binding assay	Methods	Methods similar to those described for report # 1019598 (reviewed above). • Cell lines tested: o Human H460 tumor cells o Rat primary astrocytes
	Results	• 50 nM teprotumumab inhibited binding of labeled IGF1 to human cells by 96% (IC_{50} value not calculated). • 200 nM teprotumumab inhibited binding of labeled IGF1 to rat cells by 6.7%. This suggests weak binding (not further quantified).

Report title	**Inhibition of ligand binding to IGF-1R by RO4858696**	
Report #s	1019287	
Key findings	Teprotumumab (RO4858696) inhibition of IGF1R binding to its endogenous ligands (IGF-1 and IGF-2) was measured in two cell lines. • HT29 human cancer cells: o IGF-1 binding to IGF1R IC_{50} = 0.44 ± 0.13 nM o IGF-2 binding to IGF1R IC_{50} = 0.28 ± 0.33 nM • i24 cells (transfected to overexpress recombinant human IGF1R): o IGF-1 binding to IGF1R IC_{50} = 1.3 nM o IGF-2 binding to IGF1R IC_{50} = 2.8 nM	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019287\1019287.pdf
	Study laboratory	(b) (4)
	Report date	July 11, 2005

Rationale	• Teprotumumab is directed against the extracellular α domain of human IGF1R. • The authors report that IGF-1 and IGF-2 bind different but overlapping regions on the extracellular domain of IGF1R. • The authors report that a goal of these experiments was to reveal whether teprotumumab "*is able to prevent the ligands from binding to the IGF-IR either by direct competition for the same binding site or by sterical hinderance after binding to a distinct epitope*." o However, no discussion of steric hinderance was provided. This reviewer is unable to ascertain from the results provided whether teprotumumab's activity is direct or indirect.
Methods	• Cell lines: o Human cancer cell line (HT29) o Mouse fibroblasts expressing recombinant human IGF1R (3T3-IGF-IR cells; i24 cells) • Antibodies: o Teprotumumab (RO4858696) o αIR-3 (a commercially available mouse anti-IGF1R, known to block IGF-1 but not IGF-2 binding to IGF1R) • Assay: cells were treated with [^{125}I]-IGF-1 or with [^{125}I]-IGF-2 (concentration not reported) and a range of antibodies for 3.5 hours at 4^{o}C, then pelleted and resuspended. After washing with excess unlabeled protein (IGF-1 or IGF-2, respectively). • Radioactivity was measured by gamma counting.
Results:	• For HT29 cancer cells, inhibition of IGF1R binding to: o Teprotumumab ▪ IGF-1 IC_{50} = 0.4 nM ▪ IGF-2 IC_{50} = 0.28 nM o Positive control (αIR-3) ▪ IGF-1 IC_{50} = 2.5 nM ▪ IGF-2 IC_{50} not calculable (no specific binding)\ • For the i24 cells, teprotumumab: ▪ IGF-1 IC_{50} = 1.3 nM ▪ IGF-2 IC_{50} = 2.8 nM ▪ [Review note: standard deviation values not reported for the i24 cell data] • The inhibition graphs were presented in the study report, and showed the expected sigmoidal response curves. • The authors conclude that the lower potency observed for the i24 cells compared to the HT29 cells was due to the higher expression levels of IGF1R by the i24 cells. The clinical significance of this finding is unclear.

Report title	**Functional assay to assess inhibition of IGF-1R autophosphorylation**	
Report #s	1027507	
Key findings	• Teprotumumab inhibited IGF1R autophosphorylation induced by IGF-1, with an IC50 = 0.96 ± 0.14 nM	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1027507\1027507.pdf
	Study laboratory	(b) (4)
	Report date	October 4, 2007
Rationale	• Clinical phase 1 trials used the SP2/0 product; to support the change to CHO product for Phase 2, inhibition of autophosphorylation was considered as a comparative functional assay. • Assessment of assay variability determined that "a minimum content of 66% defective antibodies" would be needed to detect a statistically significant change in IGF1R autophosphorylation. • Only data for the SP2/0 product was reported.	
Methods:	• Cell line: 3T3-IGF1R cells (a mouse fibroblast cell line transfected to express human IGF1R. • Cells were incubated a single concentration of IGF-1 (10 nM) and a concentration range of the SP2/0 teprotumumab. • IGF1R phosphorylation was measured using a sandwich ELISA (one antibody against IGF1R, and another antibody specific for phosphorylated IGF1R) o [*Review note*: neither of the anti-IGF1R antibodies used in these experiments were named, and the sources were not reported. These are minor study deficiencies.]	

Report title	**Downregulation of surface IGF-1R by human anti-IGF-1 receptor antibody RO4858696 in H322M tumor cells *in vitro***
Report #s	• Applicant's report #: 1019219 • Laboratory report #: AI4860
Key findings	Authors report for H332M human lung carcinoma cells: • 1 µg/ml resulted in 50% saturation of cell-surface IGF1R • 10 µg/ml resulted in 100% saturation of cell surface IGF1R • Teprotumumab caused internalization of IGF1R from the surface. o At 1 µg/ml, internalization was ~ 40% within 15 minutes, ~ 50% within 1 hour, and ~ 75% by 24 hours.

	o The 0.1 µg/ml concentration was active, but less potent. Internalization was ~ 25% by 1 hour, and ~ 35% by 3 hours.	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019219\1019219.pdf
	Study laboratory	(b) (4)
	Report date	July 7, 2005
Rationale	• The author reports that IGF1R binding to endogenous ligand on the cell surface results in accumulation of the receptor in clathrin-coated pits and subsequent endocytosis ("receptor mediated endocytosis"). The ligand-receptor complex is inactivated by the low pH of the endosomes. The ligand is degraded, and the receptor is recycled back to the plasma membrane. • The purpose of these experiments was to investigate whether teprotumumab also caused receptor internalization.	
Method notes	• Only a sparse description was provided. • Flow cytometry was used to measure the levels of cell-surface IGF1R. • Confocal laser scanning microscopy was used to measure the proportion of IGF1R internalization from the cell surface.	

Report title	**Inhibition of IGF- 1 Mediated Proliferation by Human anti-IGF- 1 - Receptor Antibody RO4858696 in Human Tumor Cell Lines *in vitro***	
Report #s	1019078	
Key findings	• Teprotumumab was screened for inhibition of cell growth with a panel of 21 tumor cell line *in vitro*. o IGF-1 stimulated cell proliferation in 5 cell lines. Teprotumumab inhibited this stimulation, with IC_{50} values ranging from 2.0 to 30 nM o Teprotumumab inhibited proliferation of 3 cell lines in the absence of exogenous IGF (suggesting autocrine production of IGF-1 by these cell types), IC_{50} range 8.0 to 27 nM	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1019078\1019078.pdf

	Study laboratory	(b) (4)
	Report date	November 30, 2003
Methods	• For the cells responsive to IGF-1, the minimum active concentration was 50 ng/ml, and the maximally active concentration was 200 ng/ml. The authors selected 100 ng/ml of IGF-1 as a submaximal concentration, inducing ~ 80% of maximal proliferation for sensitive cells. • Teprotumumab was tested over a range of concentrations to identify IC_{50} values.	
Results		

Affected tumor cell line	Teprotumumab IC_{50} (inhibition of proliferation induced by 100 ng/ml IGF-1), nM	Teprotumumab IC_{50} (inhibition of proliferation in IGF-1 free media), nM
ASPC-1	4.5	n/a
DU-145	29.7	26.8
H322M	2.3	7.9
MCF-7	2.0	n/a
QG56	n/a	15.0
PancTu-1	7.1	n/a

Report title	**Acute effect of treatment with rhu anti-IGF-IR antibody <18> (R04858696-000) on IGF-IR expression of H322M lung tumor xenografts**	
Report #s	101449	
Key findings	In mice bearing H332M (human lung carcinoma cell line) xenografts, a single intraperitoneal dose of 6 mg/kg teprotumumab did not affect tumor growth, but did reduce tumor IGF1R expression	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1014449\1014449.pdf
	Study laboratory	(b) (4)
	Report date	February 25, 2004

Method notes	• Animal model: female B/cABom nude mice • Cell line: H332M human lung carcinoma cells. • Xenograft: $5x10^6$ cells (in Matrigel) per sc injection, into the right flank. • 29 days after xenograft, mice with tumor volumes between 100 and 230 mm^3 were selected for further study. • 15 mice/group mice received a single ip injection of vehicle or 6 mg/kg teprotumumab. 3 mice/group were harvested at 3 days, 1, 2, 3, or 4 weeks post-dose. Blood was collected for TK, and tumors were harvested and flash frozen. • Tumors were lysed (no details reported), and lysate was analyzed by Western blotting (no details regarding the anti-IGF1R antibody used for quantitation).
Results:	• Serum TK for human IgG showed a decrease over time (consistent with ip teprotumumab clearing from circulation) o C_{max} ~ 21 µg/ml o Teprotumumab was still detectable at 4 weeks post-dose. o [no other TK parameters calculated] • Western blot analysis reported a decrease in tumor IGF1R at 72 hours to ~ 20% of control tumor levels. IGF1R remained suppressed at 1 and 2 weeks, and began to recover thereafter. • Authors reported no treatment-related effect on tumor volume or mouse body weight (data not reported)

4.1.3 Mechanism of Action: (b) (4)

- The Applicant submitted revised labeling for section 12.1 Mechanism of Action on November 22, 2019, without comment or annotation.
  - o [Please see section 11.6 of this review regarding P/T review of the original (7/08/2019) proposed mechanism of action language.]

(b) (4)

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(b) (4)

4.2 Secondary Pharmacology

- As labeling indicates, teprotumumab caused hyperglycemia in some patients. From a P/T perspective, the mechanism of action for hyperglycemia is likely cross-reactivity with IR.

(b) (4)

  - However, secondary pharmacology studies did not detect teprotumumab binding to human or mouse IR, or IR downregulation.
  - The Applicant reports that IGF1R and insulin receptor (IR) share 60% amino acid sequence homology overall, and 84% homology in their tyrosine kinase receptor domains.
  - IGF-2 binds to both IGF1R and IR; blockade of IGF1R by teprotumumab may shunt endogenous IGF-2 (released to activate IGF1R) toward IR.
- The previous Sponsor, Roche, conducted several nonclinical oncology proof-of-concept studies (that were submitted to CDER under IND). The Applicant notes that teprotumumab failed to show clinical efficacy for oncology indications. Therefore, the Applicant considered these reports to be secondary pharmacology studies irrelevant to the TED indication, and did not submit these reports to BLA 761143. P/T has no objection to their omission.

Report title	**Cross-reactivity of RO4858696 with human Insulin Receptor**	
Report #s	• Applicant's report #: 1019286 • Study laboratory #: 4860	
Key findings	Dosing of cells transfected to express recombinant human insulin receptor (IR) did not block insulin binding to IR, or cause decreased expression of IR	
Report details	BLA location	BLA module 4.2.1.2 (Nonclinical study reports: pharmacology: secondary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4212-sec-pd\1019286\1019286.pdf
	Study laboratory	(b) (4)
	Report date	July 11, 2005
Competitive assay	Methods	• Cell type: NIH-3T3 (mouse fibroblast) cells were transfected to express human insulin receptor, and grown in high glucose MEM Dulbecco media. • Cells were incubated with 125I-labeled insulin (concentration not reported) + teprotumumab (over a range of concentrations) for 3.5 hours at 4°C. • Cells were pelleted and resuspended to remove the media (but not washed with excess unlabeled insulin). • Radioactivity (as a measure of cell-bound insulin) was measured via gamma counting.
	Results:	No displacement of insulin from IR was detected, up to 1 µM of teprotumumab.
Down-regulation assay	Methods:	• Same cell type (NIH-3T3 cells transfected to express human insulin receptor) • Assay antibodies:

		○ 83-14: commercial murine IgG2 against human IR ○ C-19: commercial rabbit polyclonal antibody against the human IR beta chain • Assay: cells were incubated with either teprotumumab or 83-14 at a single concentration (500 nM) for 24 hours at 37°C. Then, cells were washed, harvested, and lysed. Western blotting (using C-19) was conducted to analyze the cell lysates for IR.
	Results:	• The positive control antibody (83-14) decreased the amount of IR detected by Western blotting by 91%. • Teprotumumab had no effect on IR levels.

Report title	**Lack of Cross reactivity of Human anti-IGF-1-Receptor Antibody RO4858696-000 to Human Insulin Receptor analyzed by Immunocytochemistry and Confocal Laser Scanning Microscopy**	
Report #s	• Applicant's report #: 1019183 • Study laboratory #: AI4860	
Key findings	Temprotumumab binding to human insulin receptor was not detected.	
Report details	BLA location	BLA module 4.2.1.2 (Nonclinical study reports: pharmacology: secondary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4212-sec-pd\1019183\1019183.pdf
	Study laboratory	(b) (4)
	Report date	November 13, 2003
Methods	• Cell type used: ○ i24 cells (mouse 3T3 fibroblasts stably transfected to overexpress recombinant human IGF1R), which produce endogenous mouse IR. ○ Untransfected 3T3 cells (as a negative control). • Assay antibody: SC-710 (a rabbit polyclonal antibody that cross-reacts with the alpha chain of human and mouse insulin receptor) • Assay: "*Double immunofluorescence microscopy in conjunction with confocal laser scanning microscopy (CLSM) was used to investigate the potential cross reactivity of monoclonal human anti-IGF-1R antibody (RO4858696) to human insulin receptor.*"	
Results:	• Authors report being able to visualize teprotumumab binding on the cell surface ("punctuate pattern") and inside the cell (consistent	

	with the biosynthesis of IGF1R protein: “perinuclear region, Golgi and post Golgi compartments”) • IR cell-surface and intracellular distribution (measured with SC-710) was similar, but “there was no significant overlap of the two patterns at a higher level of magnification”

Report title	**RO4858696/F01-01 (huMAb-IGF-1R): Hemolytic Potential and Blood Compatibility Study**	
Report #s	• Applicant #: 1018657 • Study laboratory #: 6131-491	
Key findings	Teprotumumab (6.25 or 12.5 mg/ml) did not cause hemolysis or coagulation of whole human blood or whole cynomolgus monkey blood samples	
Report details	BLA location	4.2.3.7.7 (Nonclinical study reports: toxicology: other toxicity): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\1018657\1018657.pdf
	Study laboratory	(b) (4)
	Report dates	• (b) (4) report date: September 23, 2005 • (b) (4) preface: October 10, 2005
	GLP and QA	Yes, signed
Methods	Test article	Teprotumumab (RO4858696), batch # GGP0438, 25 mg/ml solution, purity 98.1%
	Controls	• Vehicle • Homologous plasma (i.e. human for human, monkey for monkey) was used as a negative control • 1% saponin (0.5% final concentration) was used as a positive control
	Blood sources	Fresh blood samples were collected into heparin tubes from • One healthy volunteer • 3 healthy cynomolgus monkeys (not clear if the blood was combined).
	Assay:	• Test article and controls were mixed at a 1:1 ratio with blood samples. The final concentrations of teprotumumab tested were 6.25 or 12.5 mg/ml. • For evaluation of hemolytic potential: tubes were gently mixed, incubated for 40 minutes at 37^{o}C, then centrifuged. The amount of hemoglobin in the supernatant plasma was analyzed.

		• For evaluation of blood compatibility testing: tubes were gently mixed, incubated for 27 minutes at room temperature, and then examined (grossly and microscopically) for precipitation and coagulation. Evidence of either precipitation or coagulation was considered a positive test result.
Results:	• The positive control, saponin, caused hemolysis (as expected). o [*Review note*: no reporting on whether saponin also caused precipitation or coagulation. This is a minor study limitation.] • No evidence of hemolysis, precipitation, or coagulation was observed for teprotumumab, or the negative control plasma samples.	

Report title	***In Vitro* Evaluation of the Influence of RO4858696 on Human and Cynomolgus Monkey Whole Blood Hemolysis and Plasma Flocculation**	
Report #s	• Applicant # 1026030 • Study laboratory # 600237	
Key findings	Teprotumumab tested at 6.25 and 12.5 mg/ml did not cause hemolysis or flocculation in human whole blood or cynomolgus monkey whole blood	
Report details	BLA location	4.2.3.7.7 (Nonclinical study reports: toxicology: other toxicity): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\1026030\1026030.pdf
	Study laboratory	(b) (4)
	Report date	September 14, 2007
	GLP and QA	Yes, signed
Methods	Test article	Teprotumumab (RO485696), lot # GSO0063, purity 99%
	Controls	• Saline negative control • Saponin (2% final concentration) positive control for hemolysis • Intralipid® positive control for flocculation (a soybean oil emulsion approved by FDA under NDA 17643 and NDA 18449 for parenteral nutrition
	Blood sources:	Collected into Vacutainer® tubes (containing heparin) • 1/sex cynomolgus monkey • 1/sex healthy adult human volunteer

		• *Review note*: blood samples were collected after 8 hours fasting [rationale not stated; presumably to avoid any potential interaction with insulin and/or insulin receptor]

	Assay:	• Teprotumumab was tested at final concentrations of 6.25 or 12.5 mg/ml in blood
		  o 6.25 mg/ml based on 0.5 ml of test article (25 mg/ml) + 1.0 ml of blood
		  o 12.5 mg/ml based on 1 ml of test article + 1.0 ml of blood
		• The negative and positive controls were tested at a 1:1 dilution with blood
		• Samples were gently mixed and incubated for 1 hour at 37°C, then centrifuged.
		• Endpoints: plasma hematocrit (using a standard hemology analyzer), turbidity (by spectrophotometry), visual grading of hemolysis (5 point scale) and flocculation (3 point scale).

Results:	• Teprotumumab did not cause detectable hemolysis or flocculation. • The negative and positive controls gave the expected responses.	

Report title	**Antibody dependent cellular cytotoxicity (ADCC) by RO4858696**	
Report #s	• Applicant #: 1019288 • Study laboratory #: 4860	
Key findings	Teprotumumab did not exhibit detectable ADCC, tested at concentrations up to 10 µg/ml.	
Report details	BLA location	4.2.3.7.7 (Nonclinical study reports: toxicology: other toxicity): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\1019288\1019288.pdf
	Study laboratory	(b) (4)
	Report date	August 19, 2005
Methods	Cell types used:	• Effector cells: peripheral blood mononuclear cells (PBMCs) isolated from whole blood of healthy human donors. • Target cells: DU145 human prostate carcinoma cell line. DU145 cells express IGF1R, and proliferate in response to IGF-1 stimulation.
	Positive control antibodies	• RO4906300-000 (a human IgG1 against keyhole limpet hemocyanin). • 1718100: an IgG against hepatitis B

		• Review note: neither antibody directly target DU145 cells.
	ADCC assay	• Effector (PMBC) cells and target (DU145) cells were added to wells containing vehicle, teprotumumab (over a range of concentrations up to 10 ng/ml), or control antibody, and incubated for 2 hours at 37^{o}C. • A fluorescent assay was used to measure specific lysis of the DU145 cells.
	Dose range justification	• The authors report that 10 µg/ml resulted in saturation of IGF1R binding sites on the cell surface, citing report # 1019287. o However, this is incorrect. Because the molecular weight of teprotumumab is 148 kDa, 10 ng/ml = 6.756 pM [substantially less than the IC_{50} values listed in report # 1019287 for human cancer cell lines. o This review infers that the authors meant to reference report # 1019219 (for H322M cancer cells).
Results:	• Teprotumumab was weakly active for induction of cell lysis at 3.2 and 16 ng/ml, but did not exhibit an dose-response with increasing concentrations. • The control antibodies induced moderate cell lysis ≥ 400 ng/ml • Without a clear positive control, the sensitivity of the assay is unclear.	

4.3 Safety Pharmacology

No stand-alone safety pharmacology studies were submitted to the BLA.

- The 7-week monkey toxicology study (report # 6131-477) included respiratory and cardiovascular safety pharmacology endpoints: no treatment-related effects were apparent.
- The 13-week monkey toxicology study (report # AGD00022) and the 39-week monkey toxicology study (report # AGD00061) included cardiovascular safety pharmacology endpoints; no treatment-related effects were apparent in either study.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 Distribution (tissue cross-reactivity studies)

The Applicant submitted three tissue-cross reactivity studies (two for teprotumumab, one for another anti-IGF1R antibody).

Report title	**Comparison of IGF-1R expression in formalin fixed normal human and normal Cynomolgus monkey tissue (TMAs)**	
Report #s	1033803	
Key findings	• The goal of this study was to investigate the tissue distribution of IGF1R via immunohistochemistry with a different antibody than teprotumumab, to support interpretation of the GLP toxicology studies prior to the (then) planned GLP tissue cross reactivity studies with teprotumumab. • Membrane IGF1R was observed in many tissues; expression in monkeys and humans was similar. • Expression in the eye was evaluated for monkeys but not humans: 1/3 exhibited slight staining in “retinal structures”; no staining was observed in the other two monkey samples tested.	
Report details	BLA location	BLA module 4.2.1.1 (Nonclinical study reports: pharmacology: primary pharmacodynamics): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\1033803\1033803.pdf
	Study laboratory	(b) (4)
	Report date	May 27, 2009
	GLP status	No
Method notes	Diagnostic antibody	G11, a rabbit monoclonal antibody against the beta-chain of human IGF1R
	Tissues screened	• Formaldehyde-fixed normal tissue samples from 2 adult humans (“tissue microarrays” (TMAs) • Formaldehyde-fixed normal tissues from cynomolgus monkeys, 3 donors/tissue (TMAs) • Human-only tissues: placenta, mesothelium • Monkey-only tissues: urinary bladder, eye, larynx, omentum • Both human and monkey: adrenal, ovary, pancreas, pituitary gland, testis, thyroid gland, mammary gland, kidney, prostate, uterus, cervix, lung, heart, esophagus, stomach, colon, small intestine, liver, salivary gland, skeletal muscle,

<table>
<tr><td></td><td></td><td>skin, cerebellum, cerebrum, spleen, tonsil, thymus, peripheral nerve, bone marrow</td></tr>
<tr><td></td><td>Assay</td><td>Immunohistochemistry details not reported</td></tr>
<tr><td>Human tissue results</td><td colspan="2">
<table>
<tr><th>Intensity of membrane binding</th><th>Human tissue responses</th></tr>
<tr><td>Moderate to strong</td><td>• testis
• prostate (glandular epithelium)
• stomach (mucosal epithelium)
• placenta (cytotrophoblast cells)</td></tr>
<tr><td>Slight to moderate</td><td>• ovary (theca cells)
• thyroid gland (epithelium)
• mammary gland (myoepithelial cells)
• kidney (tubular epithelium; mesangium cells)
• uterus (endometrium)
• cervix (basal mucosal cells/ epithelium)
• pancreas (ducts)
• esophagus (basal mucosal cells)
• colon (glandular epithelium)
• small intestine (epithelium in crypts)
• tonsil (epithelial part)
• salivary gland (ducts and glandular epithelium)
• astrocytes (in cerebrum and cerebellum)
• axonal structures (in cerebrum and cerebellum)
• mesothelium (epithelial structure)
• endothelium of blood vessels in different organs</td></tr>
<tr><td>Minimal to slight</td><td>• pancreas (exocrine part)
• pituitary gland
• lung (bronchiolar epithelium)
• liver (bile ducts)
• skin (basal epithelial cells)
• tonsil (epithelial cells, few thymocytes)
• thymus (epithelial cells)</td></tr>
</table>
</td></tr>
<tr><td>Monkey membrane staining results</td><td colspan="2">
<table>
<tr><th>Intensity of membrane binding</th><th>Monkey tissue responses</th></tr>
<tr><td>Moderate to strong</td><td>• pancreas (exocrine cells)
• ovary (follicular cells)
• uterus (endometrium)
• cervix (squamous cells)
• testis (spermatocytes)</td></tr>
</table>
</td></tr>
</table>

		• stomach (mucosal epithelium)
	Variable binding (weak to strong)	• Axonal structures in the cerebrum and cerebellum
	Slight to moderate staining	• adrenal medulla • pituitary gland • thyroid (epithelium) • mammary gland (myoepithelial cells) • tonsil (epithelium) • thymus (epithelium) • esophagus (basal epithelial cells) • small intestine (mucosal epithelium) • colon (mucosal epithelium) • salivary gland (ducts) • kidney (mesangium cells, tubular cells, collecting ducts) • prostate (glandular epithelium) • urinary bladder (transitional epithelium) • larynx (epithelium) • endothelium of blood vessels in different organs
	Minimal to slight staining	• lung (alveolar epithelium) • pancreas (islet cells) • salivary gland (mucus glands) • liver (bile ducts and hepatocytes) • skin (basal epithelial cells and sebaceous glands) • eye (retinal structures) • larynx (basal mucosal cells)

Report title	**RO4858696/F01-01 (huMAb-IGF-1R): Cross-Reactivity Study of RO4858696 with Normal Human Tissues**
Report #s	• Applicant's #: 1019357 • Study laboratory #: IM1163
Key findings	• Teprotumumab specific *membrane* binding was observed for epithelium, endothelium, and monocytes in multiple tissues. • Teprotumumab specific binding (either in the cytoplasm, or unclear whether binding was membrane or cytoplasm) was observed for all tissues. • The authors conclusion is: "RO4858696/F01-01-specific reactivity was present in epithelium, endothelium, smooth muscle, axons (peripheral nerves and nerve roots), ganglion cells (myenteric plexus and ganglion), erythrocytes, mononuclear cells (lymphocytes, monocytes, macrophages (lung alveolar and placental Hofbauer cells), neuropil (including glial cell and neuron cytoplasm),

		retina (inner and outer plexiform layers and granular cell layer), ocular lens fibers, stroma, myocytes (heart and skeletal), colloid, endocrine cells, neurofilaments, reticuloendothelium, interstitial (leydig) cells, spermatogenic cells and spermatids." • This reviewer considers the reported results consistent with what is expected, given known expression of the target (IGF1R). • The results are not useful for identifying or excluding potential off-target binding (because so many tissues showed specific binding)
Literature	The authors (report page 15) cite 28 published papers (1988 to 2005) on IGF1R tissue expression, detected in "*various cell types (epithelium, endothelium, smooth muscle, striated muscle, vascular endothelium) in tissues including adrenal, heart, central and peripheral nervous systems, eye, gastrointestinal tract, male and female genital tracts, kidney, peripheral blood, thyroid, skin, placenta, lung, thymus, mammary gland, pituitary*"	
Report details	BLA location	4.2.3.7.7 (Nonclinical study reports: toxicology: other toxicity studies): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\1019357\1019357.pdf
	Study laboratory	(b) (4)
	Report dates	• (b) (4) preface pages: October 6, 2005 • Study laboratory report: September 20, 2005
	GLP and QA	Yes
Methods	Test article:	Teprotumumab (RO4858696), 25 mg/ml, batch # GGP0438
	Concentration selection	Teprotumumab (without modification for the assay) was tested at 2 and 10 µg/ml
	Tissues	• Normal human tissues from 3 people per tissue were used. • Tissues were obtained via autopsy or surgical biopsy, frozen, and cryosectioned • Tissue list: adrenal, blood cells (granulocytes, lymphocytes, monocytes, platelets), blood vessel endothelium, bone marrow, brain (cerebrum cortex and cerebellum), breast (mammary gland), eye, gastrointestinal tract (colon, esophagus, small intestine, stomach), heart, kidney (glomerulus, tubule), liver, lung, lymph node (location not specified), ovary and oviduct, pancreas, parathyroid, peripheral nerve (location not specified), pituitary, placenta, prostate, salivary gland, skin, spinal cord, spleen, striated skeletal muscle, testis, thymus, thyroid, tonsil, ureter, urinary bladder, and uterus (endometrium, cervix)

	Controls	• Positive tissue control: i24 cells (NIH3T3 cells stably transfected to overexpress human IGF1R) • Negative tissue control: R-fibroblasts derived from IGF1R deficient mice • Negative control antibody: human IgG1 kappa against another target (not specified in the study report) • Immunohistochemistry controls: rabbit antibody against β2 microglobulin
	Immuno-histochemistry method	• Immunoperoxidase staining (using biotinylated secondary antibody) • Intensity of staining was graded on a 5 point scale: "Legend: ± = equivocal, 1+ = weak, 2+ = moderate, 3+ = strong, 4+ = intense" • The authors were able to distinguish membrane-specific and cytoplasm-specific binding only for some tissues.
Human tissue results	Controls	• Control tissues gave the expected responses (i.e. intense staining in i24 cells, no staining in R-fibroblasts)
	Specific membrane-binding	The authors explicitly noted membrane binding for: • Eye endothelium (2-3+) • Endothelium in the heart, kidney (glomerular tubule), liver, esophagus, ovary, parathyroid, placenta, prostate, skin, and cervix • Epithelium in the mammary gland epithelium (duct and acini), small intestine, bile duct, Fallopian tube, prostate, skin (stratified squamous cells, apocrine and sebaceous glands), rete testis, thymus (epithelium in Hassal's corpuscles), tonsil (stratified squamous cells, lymphoepithelium, and stratum basale), ureter, urinary bladder (transitional epithelium) • Mononuclear cells in the GI tract, kidney, lymph node • Placenta Hofbauer cells
	Cytoplasmic binding or binding cellular location unclear	Reported in all tissue samples (1-3 donors)
	Eyes	Because the indication for the BLA is TED, the eye results were examined carefully. Specific staining:

		• Retina: was limited to the cytoplasm of the inner and outer plexiform layers and the granular cell layer (3/3 tissue samples) • Optic nerve: was limited to the axon cytoplasm (1/3 tissue samples) • Lens fibers: limited to cytoplasm (2/3 samples) • Vascular smooth muscle: limited to cytoplasm (2/3 samples) • Endothelium (membrane and cytoplasmic binding, 2/3 samples)

Report title	**RO4858696/F01-01 (huMAb-IGF-1R): Cross-Reactivity Study of RO4858696 with Normal Cynomolgus Monkey Tissues**	
Report #s	• Applicant #: 1019358 • Study laboratory #; IM1202	
Key findings	• Teprotumumab specific *membrane* binding was observed for epithelium and endothelium in specific tissues. • Teprotumumab specific binding (either in the cytoplasm, or unclear whether binding was membrane-bound or cytoplasmic) was observed in most tissues. • The authors conclusion is: "RO4858696/F01-01-specific reactivity was present in epithelium, endothelium, smooth muscle, axons (peripheral nerves and nerve roots), ganglion cells (myenteric plexus and ganglion), erythrocytes, mononuclear cells (lymphocytes, monocytes, macrophages (lung alveolar and placental Hofbauer cells), neuropil (including glial cell and neuron cytoplasm), retina (inner and outer plexiform layers and granular cell layer), ocular lens fibers, stroma, myocytes (heart and skeletal), colloid, endocrine cells, neurofilaments, reticuloendothelium, interstitial (leydig) cells, spermatogenic cells and spermatids." • The authors conclude that these results support considering the cynomolgus monkey a pharmacologically relevant species for teprotumumab, and this reviewer concurs.	
Report details	BLA location	4.2.3.7.7 (Toxicology: other toxicity studies): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42377-other\1019358\1019358.pdf
	Study laboratory	(b) (4)
	Report dates	• (b) (4) preface pages: October 4, 2005 • Study laboratory report: September 20, 2005
	GLP and QA	Yes

Methods	Test article:	Teprotumumab (RO4858696), 25 mg/ml, batch # GGP0438 [same as for the human tissue cross-reactivity study, report # 1019357 reviewed above]
	Concentration selection	Following preliminary optimization experiments, the concentrations selected for the main experiment were 2 and 10 µg/ml teprotumumab (without modification for the assay).
	Tissues	• From 2 healthy monkeys per tissue • Tissues were obtained via autopsy or surgical biopsy, frozen, and cryosectioned • A standard systemic battery of tissues was examined, including the eye (but not the optic nerve)
	Controls	Same assay as for the human tissue cross-reactivity study, report # 1019357 reviewed above)
	Immuno-histochemistry method	Same assay as for the human tissue cross-reactivity study, report # 1019357 reviewed above)
Monkey tissue results	Controls	Control tissues gave the expected responses (i.e. intense staining in i24 cells, no staining in R- fibroblasts)
	Specific membrane-binding	Membrane specific binding was explicitly reported for: • Endothelium: cerebrum, heart, placenta, testes • Epithelium: cornea, esophagus, placenta (cytotrophoblasts and synctiotrophoblasts), prostate, skin (stratified squamous epidermis and adnexa), Thymus (Hassal's corpuscles), thyroid, uterus (squamous epithelium of the cervix)
	Thyroid	Because the indication for the BLA is TED, the thyroid results were examined carefully. Specific staining: • Membrane and cytoplasmic staining of the epithelium • Cytoplasmic binding in: o peripheral nerve axons o endothelium o smooth muscle o myocytes o colloid
	Eyes	Because the indication for the BLA is TED, the eye results were examined carefully. Specific staining: • Cornea membrane and cytoplasmic staining • Retina: cytoplasm only, staining of the inner and outer plexiform layers and granular cell layer • Lens; cytoplasmic staining of fibers only

5.2 Pharmacokinetics (PK) and Toxicokinetics (TK)

In addition to the toxicokinetics (TK) included in the toxicology studies (reviewed below), the Applicant submitted three single-dose pharmacokinetics (PK) studies.

Report title	**RO4858696-000-009 (IGF-1R): A Single Intravenous Dose Pharmacokinetic Study in Male Rats**	
Report #s	1018220	
Key findings	• Teprotumumab is not pharmacologically active in the rat. • Rat PK parameters were calculated for a single IV bolus dose (3, 15, or 50 mg/kg). The mean elimination half-life values ranged from 128 to 172 hours [5.3 to 7.1 days]	
Report details	BLA location	4.2.2.2 (Nonclinical study reports: pharmacokinetics: absorption): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\422-pk\4222-absorp\08864\08864-rat-iv-sd.pdf
	Study laboratory	(b) (4)
	Report date	June 15, 2005
	GLP status	Not GLP
Methods	Test article	Teprotumumab (RO4858696), lot # RO4858696-000-009, produced by Sp20/AG14SF cells.
	Test species	27 males rats were used (9 per dose group) • Age at time of dosing = 8 to 9 weeks, weight range 250 to 300 grams • Review note: the strain of rat is not reported in the study report, or in the Pharmacokinetics Written Summary (BLA module 2.6.4). This is a serious study deficiency.
	Route of administration	Single intravenous (IV) bolus
	Dose groups	Single IV dose of 3, 15, or 50 mg/kg teprotumumab
	Time points	• Blood was collected (3 rats/dose/timepoint) at time: 0, 20 minutes; 2, 6, 12, 48, 72, 96, 120 hours, and then weekly until week 17 (2856 hours) post-dose. o PK analysis was only conducted on samples up to week 8 (56 days). ADA analysis was conducted on all plasma samples. • Serum was immediately collected from the blood, and frozen. Serum samples were analyzed at the

<table>
<tr><td></td><td></td><td>same time for teprotumumab and anti-product antibody (APA, ADA)
Limit of quantitation for teprotumumab in plasma was 30 ng/ml</td></tr>
<tr><td></td><td>Safety endpoints</td><td>The only safety endpoint was clinical signs at each blood collection time point.</td></tr>
<tr><td>Results</td><td colspan="2">Table 12: plasma PK parameters for the rat single dose IV study (report # 1018220)
<table>
<tr><td>PK parameters</td><td>3 mg/kg</td><td>15 mg/kg</td><td>50 mg/kg</td></tr>
<tr><td>C_{max} (µg/ml)</td><td>67.9</td><td>489</td><td>1980</td></tr>
<tr><td>AUC (µg*hr/ml)</td><td>4250</td><td>26,200</td><td>97,800</td></tr>
<tr><td>AUC/dose (µg*hr/ml / mg/kg)</td><td>1420</td><td>1750</td><td>1960</td></tr>
<tr><td>Cl (mg/h/kg)</td><td>0.75</td><td>0.61</td><td>0.56</td></tr>
<tr><td>Vc (ml/kg)</td><td>47.2</td><td>31.0</td><td>48.2</td></tr>
<tr><td>Vss (ml/kg)</td><td>128</td><td>93</td><td>82</td></tr>
<tr><td>$t_{1/2}$ (hr)</td><td>146</td><td>128</td><td>172</td></tr>
</table></td></tr>
<tr><td></td><td>ADA</td><td>• The ADA assay failed when teprotumumab was detectable (LLOQ = 30 ng/ml), reached ≥ 840 hours (≥ week 5).
• ADA detected in:
o 3 mg/kg: 1/9 rats
o 15 mg/kg: 0/9 rats
o 50 mg/kg: 5/9 rats
• The authors considered these ADA results “difficult to explain”. The results may reflect decreased ADA expression in response to decreasing drug product concentrations.</td></tr>
<tr><td></td><td>Safety</td><td>No clinical signs were reported for any animal.</td></tr>
</table>

Report title	**RO4858696 (huMab-IGF-1R): Single Dose Pharmacokinetic Study of RO4858696 Following Intravenous Administration to Monkeys**
Report #s	• Applicant #: 1016690 • Study laboratory #: 6131-471

<table>
<tr><td>Key findings</td><td colspan="2">• Serum PK parameters were calculated for cynomolgus monkeys receiving a single IV infusion. The elimination half-life ($t_{1/2}$) increased with dose, from 3.3 to 10.0 days.
• The purpose of this PK study was to provide data for the design (dose level and frequency) of the planned monkey GLP 7-week study.</td></tr>
<tr><td rowspan="4">Report details</td><td>BLA location</td><td>4.2.2.2 (Nonclinical study reports: pharmacokinetics: absorption): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\422-pk\4222-absorp\6131-471\6131-471-monkey-iv-sd.pdf</td></tr>
<tr><td>Study laboratory</td><td>(b) (4)</td></tr>
<tr><td>Report dates</td><td>• (b) (4) preface: April 21, 2005
• (b) (4) report: March 25, 2005</td></tr>
<tr><td>GLP status</td><td>Not GLP</td></tr>
<tr><td rowspan="7">Methods</td><td>Test article</td><td>Teprotumumab (RO4858696), lot # RO4858696-000-009, cell source Sp20/Ag14SF</td></tr>
<tr><td>Test species</td><td>Cynomolgus monkey</td></tr>
<tr><td>Group size</td><td>3/sex/dose level</td></tr>
<tr><td>Dose levels</td><td>3, 15, 50, or 150 mg/kg</td></tr>
<tr><td>Route of exposure</td><td>IV infusion (via the saphenous vein) given over 10 minutes (dose volume 6 ml/kg) without fasting</td></tr>
<tr><td>Blood collection</td><td>• 16 post-dose time points: 20 minutes, 2, 6, 12, 24, 48, 72, 78, 84, 96, 120, 336 (= D14), then weekly until D49 (1176 hours).
• Blood was processed for serum; serum was stored frozen, and all time points were analyzed together using an ELISA method.
• [Review note: no ADA determination conducted]</td></tr>
<tr><td>Safety endpoints:</td><td>• Daily observations only
• Animals were returned to colony after the study</td></tr>
<tr><td>Results</td><td colspan="2">• In addition to the results collected by (b) (4) sent data for an additional group, dosed with 1 mg/kg (added to the table below).

<table>
<tr><th>PK parameter</th><th>1 mg/kg</th><th>3 mg/kg</th><th>15 mg/kg</th><th>50 mg/kg</th><th>150 mg/kg</th></tr>
<tr><td>C_{max} (µg/ml)</td><td>NR</td><td>68.9</td><td>383</td><td>1310</td><td>4720</td></tr>
<tr><td>AUC (µg*h/ml)</td><td>NR</td><td>4250</td><td>31,900</td><td>117,000</td><td>449.000</td></tr>
<tr><td>Cl (ml/h/kg)</td><td>0.60</td><td>0.71</td><td>0.48</td><td>0.42</td><td>0.34</td></tr>
<tr><td>V_c (ml/kg)</td><td>39.8</td><td>43.7</td><td>42.8</td><td>41.3</td><td>33.7</td></tr>
<tr><td>V_{ss} (ml/kg)</td><td>58.3</td><td>75</td><td>88</td><td>98</td><td>99</td></tr>
<tr><td>$t_{1/2}$ (hr)</td><td>46.1</td><td>81</td><td>143</td><td>200</td><td>242</td></tr>
</table>
NR: not reported</td></tr>
</table>

<table>
<tr><td></td><td colspan="2">

The authors note a dose-response for clearance and the elimination half-life (from 3 to 150 mg/kg).
The authors noted non-linear clearance: “Once the concentration [drops] below a certain level (about 1 µg/ml) there was a steep decline in concentration”. The authors noted that this effect could be down to ADA, receptor down-regulation or receptor internalization.

</td></tr>
<tr><td></td><td>ADA</td><td>The ADA assay failed when teprotumumab was detectable (LLOQ = 30 ng/ml). The authors expect that these results underpredict the true ADA response.
<table>
<tr><td>3 mg/kg</td><td>5/6 positive for ADA
All negative at D14
3 positive by D21
Fourth positive by D28
Fifth positive by D42</td></tr>
<tr><td>15 mg/kg</td><td>1/6 positive for ADA
All negative at D35
1 positive at D42</td></tr>
<tr><td>50 mg/kg</td><td>1/6 positive for ADA
Measuring not begun until D42
1 positive by D42</td></tr>
<tr><td>150 mg/kg</td><td>0/6 positive
Measuring not begun until D42</td></tr>
</table>
</td></tr>
<tr><td></td><td>Safety</td><td>No daily observations were reported for any animals</td></tr>
</table>

<table>
<tr><td>Report title</td><td colspan="2">A Single-Dose Intravenous Comparative Pharmacokinetic and Pharmacodynamic Study of RO4858696 Administered to Male Cynomolgus Monkeys</td></tr>
<tr><td>Report #s</td><td colspan="2">• Applicant’s #: 1026674
• Study laboratory # AGD00037</td></tr>
<tr><td>Key findings</td><td colspan="2">• The purpose of this study was to compare plasma PK results in monkeys for the teprotumumab SP2/0 product versus the CHO product, in support of the planned 13-week monkey toxicology study.
• The results are not concerning. The review division previously considered the results supportive of the switch in drug product source.
• Notably:
o Clearance decreased with increasing dose (attributed to saturation of target-mediated clearance)
o A PD assay (for IGF1R expressed by circulating PBMCs) showed activity lasting 3 weeks after the single IV dose.</td></tr>
<tr><td rowspan="4">Report details</td><td>BLA location</td><td>4.2.2.2 (Nonclinical study reports: pharmacokinetics: absorption): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\422-pk\4222-absorp\agd00037\agd00037-monkey-iv-sd.pdf</td></tr>
<tr><td>Study laboratory</td><td>(b) (4)</td></tr>
<tr><td>Report date</td><td>January 28, 2008</td></tr>
<tr><td>GLP status</td><td>No</td></tr>
<tr><td rowspan="5">Methods</td><td>Test articles</td><td>Teprotumumab (RO4858696)
• SP2/0 material: 10 mg/ml, lot # GSH0067
• CHO material: 25 mg/ml, lot # GSO0061</td></tr>
<tr><td>Vehicle</td><td>0.9% saline for injection</td></tr>
<tr><td>Animal model</td><td>Total of 16 male cynomolgus monkeys</td></tr>
<tr><td>Route of administration</td><td>Single IV fast infusion (over approximately 90 seconds)
• Dose volume 3.33 ml/kg
• Infusion rate 2 ml/minute</td></tr>
<tr><td>Doses and design</td><td>
<table>
<tr><th>Group</th><th>Teprotumumab</th><th>Number of males</th><th>Dose level (mg/kg)</th></tr>
<tr><td>1</td><td>SP2/0</td><td>6</td><td>15</td></tr>
<tr><td>2</td><td>CHO</td><td>6</td><td>15</td></tr>
<tr><td>3</td><td>CHO</td><td>2</td><td>3</td></tr>
<tr><td>4</td><td>CHO</td><td>2</td><td>50</td></tr>
</table>
</td></tr>
</table>

	Safety endpoints	• Post-dose check, twice daily check, daily cage-side observation, weekly veterinary examination daily food consumption, weekly body weight up to 21 days post-dose • Animals were returned to colony after the study
	PK blood collection	• Pre-dose, post-dose at 10, 24, 48, 72, 96, 168 hours, and weekly thereafter
	PD blood collection	• Blood collection pre-dose (D-14, D-7, D-1), and post-dose (D3, 7, 14, 21) for IGF1R

PK results:

Table 13: Plasma PK for the second single-dose monkey IV pharmacokinetic study (report # 1026674)

Parameter	Group 1	Group 2	Group 3	Group 4
Teprotumumab source	SP2/0	CHO	CHO	CHO
Dose (mg/kg)	15	15	3	50
# of monkeys	6	6	2	2
C_{max} (µg/ml)	517 ± 82	589 ± 213	58.2	1520
$AUC_{0\text{-}840\ hr}$ (µg*h/ml)	63,800 ± 13,500	55,500 ± 12,800	7170	304,000
$t_{1/2}$ (h)	204 ± 53	175 ± 36	85	397
Cl (ml/hr/kg)	0.245 ± 0.055	0.284 ±0.073	0.426	0.170
V_{ss} (ml/kg)	58.6 ± 7.60	59.2 ± 11.1	51.6	70.2

- For the CHO product, the authors noted the slower clearance (and resultant longer half-life) with increasing dose (3, 15, 50 mg/kg), and hypothesize the receptor-mediated clearance (i.e. binding to IGF1R, and becoming internalized) as the cause of this effect.

ADA results	• The assay was confounding by the presence of teprotumumab in serum. The 50 mg/kg samples could not be analyzed. • For the 3 mg/kg (CHO) group: all monkeys exhibited ADA • For the 15 mg/kg (SP2/0) group, 2/6 monkeys exhibited ADA • For the 15 mg/kg (CHO) group, 1/6 monkeys exhibited ADA
Safety results	• No clearly treatment-related effects were apparent. • One treated male (#2001, in the 15 mg/kg CHO group) had a swollen left eye prior to dosing. At the 2-hour post-dose check, this monkey exhibited bilateral periorbital swelling and bilateral nasal discharge. Daily checks continued to observe bilateral swollen eyes and reddened area around both eyes through D6. o The authors attributed these effects to a bacterial infection. o However, the clinical TED data raise a question of whether this periorbital swelling might be related to treatment.

<table>
<tr><td rowspan="2">PD assay</td><td>Assay</td><td>

Blood samples were collected pre-dose, and post-dose on D3 (48 hours post-dose), D7, D14 and D21
PBMCs were isolated, then lysed. The lysate was analyzed for IGF1R by ELISA.

Review note: no details on the lysis procedure. This reviewer presumes that the whole cell lysate was measured (i.e. including intracellular IGF1R).
C-20, an antibody directed against the β-chain of IGF1R, was used for the ELISA assay

</td></tr>
<tr><td>Results</td><td>

The authors considered the results “highly variable” from animal to animal.
For the two 15 mg/kg groups (with larger group sizes), a decrease in PMBC IGF1R was apparent over time.
The results for group 3 (3 mg/kg) and 4 (50 mg/kg) were not interpretable.

Table 14: monkey single-dose IV PK study: PD endpoint (IGF1R levels expressed by PBMCs) (report # 1026674)
<table>
<tr><td rowspan="2">Post-dose day</td><td colspan="2">Change from baseline</td></tr>
<tr><td>15 mg/kg (SP2/0)</td><td>15 mg/kg (CHO)</td></tr>
<tr><td>2</td><td>71 ± 20 %</td><td>111 ± 33%</td></tr>
<tr><td>7</td><td>69 ± 28 %</td><td>47 ± 26%</td></tr>
<tr><td>14</td><td>26 ± 17%</td><td>39 ± 19%</td></tr>
<tr><td>21</td><td>18 ± 5%</td><td>27 ± 17%</td></tr>
</table>
</td></tr>
</table>

6 General Toxicology

6.1 Single-Dose Toxicity (no studies conducted)

- No single-dose toxicity studies were performed.

6.2 IV Repeat-Dose General Toxicity

The Applicant submitted one non-GLP 13-day toxicology study, three GLP general toxicology studies, and one GLP juvenile toxicology study.

6.2.1 Study title: RO4858696: 13 - Days Intravenous Pilot Toxicity and Toxicokinetic Study in the Cynomolgus Monkey		
Report #s	• Applicant's #: 1020097 • Study laboratory #: 2136-005	
Key findings	Two cynomolgus monkeys were dosed with 15 mg/kg teprotumumab by bolus IV injection four times (D1, 4, 7, 11), and sacrificed on D13. Thymic involution was noted for the male. In the context of the subsequent studies, this finding is presumed treatment-related. No other remarkable findings were detected. Plasma TK was measured.	
Report details	BLA location	4.2.3.2 (Nonclinical study reports: toxicology: repeat-dose toxicity: nonhuman primate – intravenous – short): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\2136-005\2136-005.pdf
	Study laboratory	(b) (4)
	Report dates	• (b) (4) preface: October 10, 2005 • Study laboratory report: October 10, 2005
	GLP status	No
Methods	Test article	Teprotumumab, batch # RO4858696-000-002
	Vehicle	(b) (4) histidine, (b) (4) sodium chloride, pH (b) (4) (used to dilute the test article
	Test species	1 male and 1 female cynomolgus monkey
	Dose	15 mg/kg bolus IV injection (1 ml/kg)
	Dosing frequency	D1, 4, 7, and 11, with necropsy on D13
	Endpoints	• Twice daily clinical signs and qualitative food consumption check, once daily check for morbidity and mortality, body weight twice weekly • Blood for TK (pre-dose, 5 time points on D1, pre-dose on D4, 6 time points on D11) • Blood for clinical pathology (standard hematology, coagulation, and clinical chemistry endpoints) on D2, 8, and 14 • Overnight urine samples (16 hour) collected without access to water or water: pre-dose and prior to necropsy (standard urinalysis endpoints) • D13 necropsy: o full gross pathology

<table>
<tr><td></td><td></td><td>

limited battery of organ weights (spleen, adrenals, kidneys, liver, ovaries, testes, heart, brain, pituitary)
limited panel for histopathology (brain, heart, skeletal muscle, kidney, liver, spleen, pancreas, colon)

</td></tr>
<tr><td>Safety results</td><td colspan="2">

In life:

The female exhibited low food consumption for 9 of the days between first dose and necropsy.
The authors noted possible clinical chemistry changes:

Trend for decreasing alkaline phosphatase
Slightly increased amylase for the male on D2
Slightly increased blood glucose for the female on D14

Thymus involution was noted for the male (but not the female). No other clearly treatment-related effects were apparent at necropsy.
Notable for the TED indication, gross pathology for eye and thyroid was “not remarkable” for both monkeys.

</td></tr>
<tr><td>PK results</td><td colspan="2">

Plasma teprotumumab was measured using an ELISA assay with a lower limit of quantitation of 0.625 ng/ml

Table 15: Serum PK for the non-GLP 13-day monkey IV toxicology study (report # 1020097)
<table>
<tr><td>15 mg/kg IV</td><td>D1</td><td>D11</td></tr>
<tr><td>C_{max} (µg/ml) [measured at 10 minutes post-injection)</td><td>444</td><td>685</td></tr>
<tr><td>$AUC_{0\text{-}48hr}$ (µg*h/ml)</td><td>12,209</td><td>93,511</td></tr>
</table>
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</table>

6.2.2 Study title: Ro 485-8696/F01-01(huMAb-IGF-1R): A 7-Week Intermittent Intravenous Toxicity, Toxicokinetic, and Immunogenicity Study with Ro 485-8696/F01-01 (huMAb-IGF-1R) in Cynomolgus Monkeys with an 8-Week Recovery Period

Study no.:	• Applicant # 1016123 • Study laboratory # 6131-477
Study report location:	4.2.3.2 (Nonclinical study reports: toxicology: repeat-dose toxicity: nonhuman primate – intravenous – short): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\6131-477\6131-477.pdf
Conducting laboratory and location:	• In-life: (b) (4) (b) (4) • TK and ADA: (b) (4) (b) (4)
Report dates:	• (b) (4) preface dated 10/31/2005 • Study laboratory report dated 10/25/2005
Date of study initiation:	November 3, 2004
GLP compliance:	Yes, signed. The PD assays (flow cytometry and immunophenotyping) were not GLP
QA statement:	Yes, signed
Drug, lot #, and % purity:	Teprotumumab (RO4858696), batch # GGP0438, purity 98.5%

Key Study Findings

- This study did not identify a no observed adverse effect level (NOAEL). The lowest observed adverse effect level (LOAEL) is the low-dose, 7.5 mg/kg/week IV, based on thymus toxicity.
  - The study authors concluded that a no observed adverse effect level (NOAEL) was not identified, because thymic lymphocyte depletion was observed in all teprotumumab dose-groups. This reviewer concurs.
  - Based on the reported age range, the monkeys were adolescents. Most of the males were verified as sexually immature by testes histopathology.
  - Notably, the Applicant does not consider the thymic atrophy adverse (in context with the subsequent nonclinical studies and clinical data), and therefore considers the high-dose to be the study NOAEL.
- All treatment-groups exhibited decreased serum alkaline phosphatase (ALK, ALP), at main-group and recovery-sacrifice.
- All treatment-groups caused reduced thymus weight and thymus lymphocyte depletion.

- Treated recover-group animals exhibited thymus lymphocyte hyperplasia, and a dose-response for partial recovery of thymus lymphocyte depletion.
- Notably, no treatment-related findings were apparent for hematology (i.e. cell counts) or pathology of other lymphoid tissues.
- The study reporting is inadequate regarding ophthalmoscopy. No information regarding the methods or tools was provided. No ophthalmic findings were noted for any animal.
- In support of the clinical indication (TED), it is notable that no treatment-related effects were reported for the eye or thyroid (by gross pathology and histopathology)

Methods

Group	D1 loading dose	Subsequent doses	Dose volume (for the subsequent doses)
Control	0	0	3 ml/kg
Low-dose	15 mg/kg	7.5 mg/kg	0.3 ml/kg
Mid-dose	50 mg/kg	25 mg/kg	1 ml/kg
High-dose	150 mg/kg	75 mg/kg	3 ml/kg

Note: Treated monkeys were dosed with 25 mg/ml teprotumumab (volume adjusted to achieve the desired dose). Monkeys received a loading dose on D1 (twice the subsequent dose and volume).

Frequency of dosing:	Twice weekly (on the 1st and 4th day of each week) for 7 weeks (this reviewer infers that the last dose was on D50, which would be 15 doses total)
Route of administration:	Slow IV bolus injection (9 seconds or less)
Formulation/Vehicle:	(b) (4) L-histidine, (b) (4) sodium chloride, (b) (4) polysorbate 20, pH (b) (4) [this formulation differs from the commercial formulation (b) (4) (b) (4)]
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	Main groups: 3/sex/dose (necropsy on D51) Recovery groups: 2/sex/dose (necropsy on D107, after 8 weeks recovery)
Age at start of dosing:	Approximately 2 to 3 years old
Weight at start of dosing:	Males 2.3 to 3.2 kg; females 1.7 to 2.6 kg

Observations and Results

Mortality

- All monkeys survived to scheduled sacrifice.
- Animals were checked twice daily for morbidity and mortality.

Clinical Signs

- No treatment-related clinical signs were apparent.
- Cage side observations were recorded once daily. Detailed observations and physical examinations were made once weekly and on the day of sacrifice.

Body Weights and Feed Consumption

- Body weight was measured weekly.
- For the high-dose female group, food consumption and body weight gain were slightly reduced compared to controls.

Ophthalmoscopy

- Ophthalmic examinations were performed re-dose and during week 6. The report has no information regarding the methods used, and this is a study limitation.
- No ophthalmoscopy findings were noted for any animal.

Electrocardiography (ECG)

- ECG was performed pre-dose, during week 3 (between 2 and 3 hours after the second weekly dose), and at the end of recovery. The number of leads was not reported; ECG data were provided for heart rate, P-R interval, QRS interval, -T interval, and QTc.
- No treatment-related ECG effects were apparent.

Hematology

- Blood was collected for hematology, coagulation, and clinical chemistry pre-dose and prior to sacrifice.
- No treatment-related hematology effects were apparent.

Clinical Chemistry

- Serum alkaline phosphatase (ALK; ALP) was decreased for all treated dose-group at week 8 (statistically significant with 5/sex/dose). At week 16, the decrease was apparent for high-dose males and all treated female groups (not statistically significant with only 2/sex/dose).
- No other clinical chemistry changes were remarkable.

Table 16: Teprotumumab decreased serum alkaline phosphatase (ALK; ALP) in the GLP 7-week monkey IV toxicology study (report # 1016123)

Week	Males				Females			
ALP (U/L)	0	7.5 mg/kg	25 mg/kg	75 mg/kg	0	7.5 mg/kg	25 mg/kg	75 mg/kg
-1	495 ± 98	581 ± 124	574 ±143	572 ± 87	654 ± 86	523 ± 145	604 ± 77	645 ± 173
8	495 ± 86	286 ± 54*	297 ± 89*	283 ± 57*	565 ± 41	260 ± 274 *	274 ± 37 *	284 ± 56*
16 (recovery)	556 ± 140	514 ± 227	518 ± 222	370 ± 72	670 ± 82	340 ± 130	315 ± 38	299 ± 37

* Statistically significant, P ≤ 0.05 by ANOVA and Dunnett's test

Urinalysis

- Urine samples were collected pre-dose and prior to sacrifice.
- No treatment-related urinalysis effects were apparent.

Gross Pathology

- No remarkable gross pathology findings were reported. Notably, thymus gross pathology was reportedly normal.

Organ Weights

- Thymus weights were decreased for all treated main-group animals. Treated recovery groups showed a dose-response for partial recovery.

Table 17: Teprotumumab decreased thymus weight in the GLP 7-week monkey IV toxicology study (report # 1016123)

	Males				Females			
	0	7.5 mg/kg	25 mg/kg	75 mg/kg	0	7.5 mg/kg	25 mg/kg	75 mg/kg
Main groups								
Body weight (g)	2500	2733	2400	2266	2133	1800	1766	1866
Thymus wt (	5.63	0.99*	1.19*	1.58	4.20	0.85*	0.97*	0.93*
Thymus :body	0.227	0.036* (-84%)	0.050* (-77%)	0.070 (-69%)	0.198	0.047* (-76%)	0.054* (-72%)	0.052* (-73%)
Recovery groups								
Body weight (g)	2600	2350	2350	2500	1950	2100	2000	1700
Thymus wt (	9.52	4.04	2.15	2.60	6.32	3.66	1.89	1.30

Thymus :body	0.335	0.172 (-48%)	0.088 (-73%)	0.103 (-69%)	0.325	0.167 (-48%)	0.099 (-69%)	0.076 (-77%)

* Statistically significant, P ≤ 0.05 by ANOVA and Dunnett's test

Histopathology

Adequate Battery: yes, standard full systemic battery

Peer Review: Yes

- Anatomical pathology was performed by (b) (4) DVM, PhD, Diplomate, ACVP (DACVP).
- Peer-review anatomical pathology was performed by a sponsor representative: Dr. Kathyrn Bowenkamp, DVM, PhD, DACVP, Hoffman-La Roche Inc.

Histological Findings

- Thymus:
  - All teprotumumab-treated monkeys exhibited thymus lymphocyte depletion, described as "decreased overall size of thymus, the cortex being reduced in size more than the medulla. Demarcation between the cortex and medulla remained, and there was no indication of cell death or presence of debris."
  - The treated recovery animals continued to exhibit thymic depletion, but several also had foci of lymphocyte hyperplasia. The authors considered this a compensatory change.
  - *Review note*: the lack of a dose-response indicates receptor saturation at all dose levels by the time of main-group sacrifice.

Table 18: Selected male histopathology for the GLP 7-week monkey IV toxicology study (report # 1016123)

Finding	Severity	Males			
		0	7.5 mg/kg	25 mg/kg	75 mg/kg
Main group					
Thymus: depletion, lymphocyte	All combined	0/3	3/3	3/3	3/3
	Minimal	0	0	1	1
	Slight	0	0	1	0
	Moderate	0	1	1	2
	Moderately severe	0	1	0	0
	Severe	0	1	0	0
Thymus cyst	Present	2/3	2/3	1/3	1/3
Thyroid	Normal	3/3	3/3	3/3	3/3
Eye	Normal	3/3	3/3	3/3	3/3
Testes	Juvenile	3/3	2/3	3/3	3/3

Recovery group					
Thymus: depletion, lymphocyte	All combined	0/2	2/2	2/2	2/2
	Minimal	0	1	1	1
	Slight	0	1	0	1
	Moderate	0	0	0	0
	Moderately severe	0	0	1	0
Thymus focal lymphocyte hyperplasia	Minimal	0/2	1/2	2/2	0/2
Thyroid	Normal	2/2	2/2	2/2	2/2
Eye	Normal	2/2	2/2	2/2	2/2
Testes	Juvenile	2/2	1/2	2/2	1/2

Table 19: Selected female histopathology for the GLP 7-week monkey IV toxicology study (report # 1016123)

Finding	Severity	Females			
		0	7.5 mg/kg	25 mg/kg	75 mg/kg
Main group					
Thymus: depletion, lymphocyte	All combined	0/3	3/3	3/3	3/3
	Minimal	0	0	1	0
	Slight	0	0	2	0
	Moderate	0	3	0	2
	Moderately severe	0	0	0	1
	Severe	0	0	0	0
Thymus cyst	Present	0/3	0/3	2/3	0/3
Thyroid	Normal	3/3	3/3	3/3	3/3
Eye	Normal	3/3	3/3	3/3	3/3
Recovery group					
Thymus: depletion, lymphocyte	All combined	0/2	1/2	1/2	2/2
	Minimal	0	1	1	1
	Slight	0	0	0	0
	Moderate	0	0	0	0
	Moderately severe	0	0	1	1
Thymus focal	Minimal	0/2	2/2	0/2	0/2

lymphocyte hyperplasia	Slight	0/2	0/2	0/2	1/2
Thymus cyst	Present	0/2	0/2	1/2	0/2
Thyroid	Normal	2/2	2/2	2/2	2/2
Eye	Normal	2/2	2/2	2/2	2/2

Special Evaluation: Immunophenotyping

- Blood samples were collected from all recovery animals on D74 and D106. A section of thymus was collected at recovery sacrifice. Samples were analyzed by flow-cytometry, to measure leukocyte sub-populations.
- Results were not interpretable, no treatment-relationship is apparent.

Special Evaluation: IGF1R downregulation

- This was intended as a PD marker to measure IGF1R expression by peripheral blood lymphocytes. However, the authors report (page 6) that "due to errors in sample preparation, the data acquired was not considered interpretable."
- No results were provided in the study report.
- Blood samples were collected on D29, D43, and from recovery animals on D106. Peripheral blood lymphocytes were collected from the blood.

Toxicokinetics

- Blood samples for plasma TK and ADA were collected for: the D1, D22, and D43 doses: pre-dose, 24, 72, 76, 96, and 144 hours post-dose. Additionally, samples were collected from recovery animals (beginning on D57, and then weekly).
- Plasma teprotumumab was measured using a validated ELISA assay with a LLOQ of 25.0 ng/ml.
- The authors note that the D22 data suggest accumulation, compared to D1.
- No ADA results were reported.
    - The ADA assay used an ELISA method with a LLOQ of 30 ng/ml. The assay failed when teprotumumab was present in plasma (i.e. same problem as for the PK monkey studies reviewed above).
    - None of the samples collected had low enough teprotumumab to quantify ADA.
- This TK table was compiled from the Applicant's summary (BLA module 2.6.7 Toxicology Tabulated Summary)

Table 20: Teprotumumab serum TK for the GLP 7-week monkey IV toxicology study (report # 1016123)

TK parameter	Day	7.5 mg/kg		25 mg/kg		75 mg/kg	
		M	F	M	F	M	F
AUC (µg*h/ml)	1	29,300	27,100	116,000	108,000	263,000	276,000
	22	52,700	38,400	284,000	267,000	597,000	579,000

	43	78,000	55,200	356,000	247,000	793,000	613,000
C_{max} (µg/ml)	1	374	306	1160	1440	3320	3460
	22	475	427	2960	2700	7190	6720
	43	808	621	4070	2870	12,700	8670

Dosing Solution Analysis

- No concerns identified
- The placebo and test article were used as shipped (i.e. already reconstituted in water).
- Test articles tested within 1% of nominal by protein content, and within 2% of nominal by size exclusion chromatography.

6.2.3 Study title: RO4858696: A 13-Week Toxicity and Toxicokinetic Study Administered Once Weekly by Intravenous Injection to Cynomolgus Monkeys, with a 12-Week Recovery Period

Study no.:	• Applicant # 1023600 • Study laboratory # AGD00022
Study report location:	4.2.3.2 (Nonclinical study reports: toxicology: repeat-dose toxicity: nonhuman primate – intravenous – medium): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\agd00022\agd00022.pdf
Conducting laboratory and location:	• Main laboratory: (b) (4) (b) (4) • Bone alkaline phosphatase: (b) (4) (b) (4) • ECG evaluation: (b) (4) (b) (4)
Report dates:	March 6, 2008
Date of study initiation:	March 22, 2007
GLP compliance:	Yes, signed ADA analysis was not GLP.
QA statement:	Yes, signed
Drug, lot #, and % purity:	Teprotumumab (RO4858696), lots GSO0063 (purity 99% by SE-HPLC, 87% by potency assay) and GSO0064 (purity 99% by SE-HPLC, 97% by potency assay)

Key Study Findings

- Adult male and female animals were used for groups 1-4 (0, 3, 15, or 75 mg/kg). Juveniles were used for groups 5-6 (0 and 15 mg/kg).
- Teprotumumab decreased weight gain, serum total ALP, serum bone-specific alkaline phosphatase (BAP), thymus gross size and weight. Consistent with the gross pathology and organ weight finding, teprotumumab caused thymus diffuse atrophy.
    - The LOAEL for adults was the lowest dose tested, 3 mg/kg/week, based on thymus diffuse atrophy. No adult NOAEL was identified.
        - The Applicant considered the high-dose, 75 mg/kg, to be the adult NOAEL; this reviewer does not concur.
    - For juveniles, the single test-dose, 15 mg/kg/week, was the lowest observed adverse effect level (LOAEL), based on thymic atrophy (i.e. difference more pronounced between the juvenile control and treated

groups), and decreased spleen weight in treated juvenile females (despite the lack of correlating hematological changes).
    - The Applicant considered the 15 mg/kg/week dose to be a NOAEL for the juvenile group; this reviewer does not concur.
    - The effects in this study are consistent with the stand-alone 13-week juvenile toxicology study (reviewed below).
- The authors considered the decreased in BAP to be treatment-related but not clearly adverse, in the absence of bone histopathology.
- No changes in white blood cell counts or other lymphoid organs was apparent.

Methods

Doses: 0, 3, 15, or 75 mg/kg

Frequency of dosing: Once weekly for 13 weeks

Route of administration: IV bolus injection

Dose volume:
- Control and 75 mg/kg: 3 ml/kg
- 3 mg/kg: 0.12 ml/kg
- 15 mg/kg: 0.6 ml/kg

Formulation/Vehicle: (b) (4) L-histidine/histidine-HCl (pH 5.5), (b) (4) (b) (4) trehalose, and (b) (4) polysorbate 20 [Review note: this is the same as the commercial clinical formulation]

Species/Strain: Cynomolgus monkeys

Number/Sex/Group: Main-groups: 3/sex/dose (necropsy D92)
Recovery-groups: 2/sex/dose (necropsy D176)

Ages:

Group	Dose (mg/kg)	Age range at start of dosing (years)	
		Males	Females
1	0	4.6 to 6.3	4.8 to 5.8
2	3		
3	15		
4	75		
5	0	1.9 to 2	1.9 to 2.3
6	15		

Deviation from study protocol: Documented, unobjectionable

Observations and Results

Mortality

- Checks for morbidity and mortality were performed twice daily.
- One adult male (# 2005) from group 2 (3 mg/kg) was found dead on D109.
    - No clinical signs, morbidity or moribundity was noted prior to the monkey being found dead.
    - Cause of death was attributed to acute gastric dilatation (bloat). The authors report that this is a “common spontaneous condition of captive monkeys”, but did not provide a laboratory historical control incidence. A

review by Pond et al. 1982[28] attributes acute gastric dilation in monkeys to the use of biscuit diet, which were used in this study.

- The authors considered this death unrelated to teprotumumab. Based on the weight of evidence from all of the GLP monkey studies, this reviewer concurs.

Clinical Signs

- No treatment-related observations were apparent.
- Cage side observations were made once daily, in the morning. Post-dose observations were made at 2 hours after each weekly dose.

Body Weights

- Body weight was measured weekly.
- Teprotumumab stopped weight gain, and caused slight weight loss, in treated animals (adults and juveniles); recovery groups showed recovery after cessation of dosing.
  - The authors considered this effect treatment-related, and this reviewer concurs. Based on the magnitude of effect, this reviewer considers the effect on body weight evidence of pharmacological activity, but not adverse.

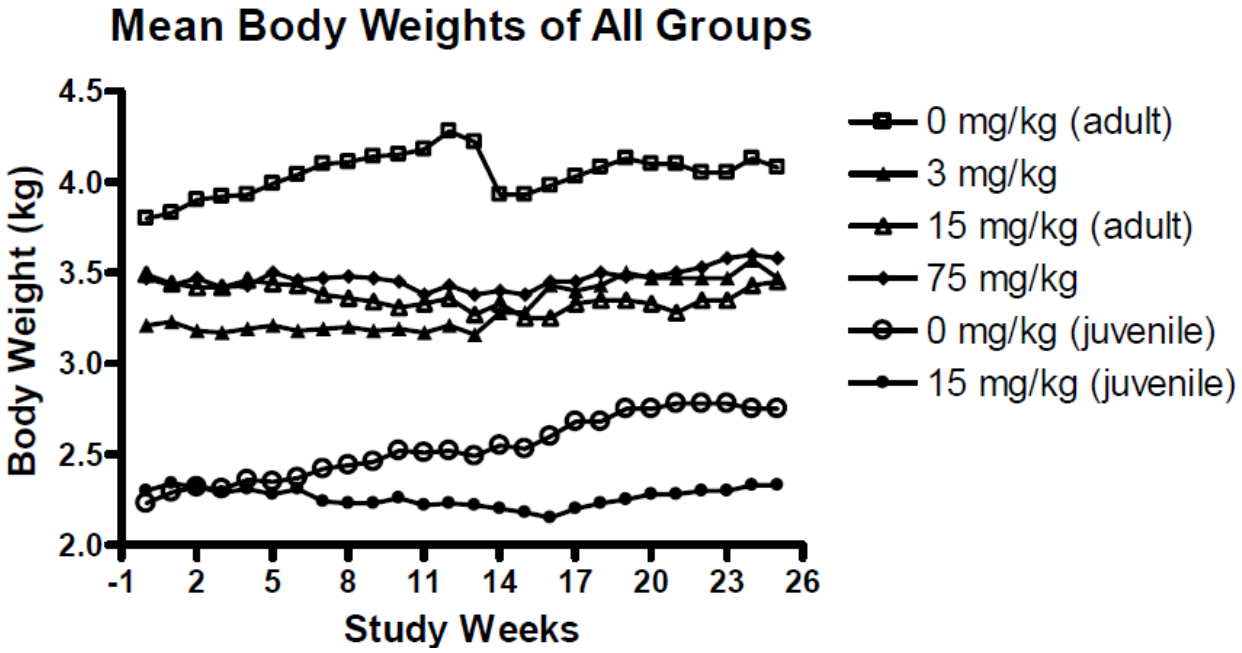
Table 21: Teprotumumab inhibited weight gain in the GLP 13-week monkey IV toxicology study (report # 1023600

Group	Dose (mg/kg/week)	Weight change from week -1 to week 13 (% change from week -1)	Recovery group weight change from week 13 to week 25 (% change from week 13)
1	0	0.4 kg (+10.5%)	-0.1 kg (-2.3%)
2	3	0 kg (0%)	+0.3 kg (+9.3%)
3	15	-0.2 kg (-5.7%)	+0.2 kg (6.0%)
4	75	-0.1 kg (-2.8%)	+0.2 kg (5.8%)
5	0 (juvenile)	+0.3 kg (+13.6%)	+0.3 kg (+12%)
6	15 (juvenile)	-0.1 kg (-4.3%)	+0.1 kg (+4.5%)

[28] Pond CL, Newcomer CE, Anver MR. 1982. Acute gastric dilatation in nonhuman primates: review and case studies. Vet. Pathol. 19(7):126-133. Accessed via: https://journals.sagepub.com/doi/pdf/10.1177/030098588201907s09

- Figure from report page 47:

Figure 1: Teprotumumab inhibited weight gain in the GLP 13-week monkey IV toxicology study (report # 1023600)



Feed Consumption

- No treatment-related effects were apparent for food consumption.
- Food assessment was assessed qualitatively daily, as part of the cage side observation

Ophthalmoscopy

- A veterinarian evaluated the anterior and posterior chambers using a direct ophthalmoscope: pre-dose, during week 13, and during week 25.
- Three new findings were detected at week 13:
  - Group 2 (3 mg/kg): male # 2001: “stellar reflective foci diffuse pattern covering the entire retina on both eyes”
  - Group 3 (15 mg/kg): male # 3104: left eye corneal cloudiness
  - Group 6 (juvenile 15 mg/kg): male # 6102: “mild tortuous retinal vessels in both eyes”
- The relationship of these findings to treatment is unclear.

ECG

- No treatment-related ECG effects were apparent.
- 6-lead ECG was measured pre-dose, and during week 13 (24 to 48 hours after dosing), with restraint but without sedation.

Hematology

- Blood samples were taken for hematology (1 ml) and coagulation (1.8 ml): pre-dose, D28, D91, and from recovery animals on D175. Standard endpoints were measured.
- Slight differences were apparent (discussed in the report by the authors); this reviewer does not consider them remarkable. None are clearly treatment-related.

Clinical Chemistry

- Following overnight fasting, blood samples (2 ml) were taken for clinical chemistry pre-dose, D28, D92, and from recovery animals on D176.
- In addition to the standard clinical chemistry endpoints, bone-specific alkaline phosphatase (BAP) was measured separately using an ELISA kit (results reported in report Appendix 5).
- Teprotumumab decreased serum total ALP for all groups
  - The differences for each treated group were statistically significant compared to controls ($p \leq 0.05$ by ANOVA).
  - [*Review note*: the report tabulated ALP for both sexes combined. The BLA's Toxicology Tabulated Summary[29] provides ALP by dose and sex.]
- Teprotumumab decreased BAP at week 4 (D28) and week 14 (D92); a dose-response is not apparent.
  - Statistical significance from control was not achieved (this may reflect assay variability)
  - Notably, the recovery data (D176) for all groups (including controls) shows a decrease compared to pre-dose. The reason is unclear, and this precludes assessment of BAP recoverability.
  - The study report presented individual animal BAP data, but did not tabulate BAP results [results shown below were copied from the Toxicology Tabulated Summary).

Table 22: Teprotumumab decreased serum ALP and bone-specific alkaline phosphatase in the GLP 13-week monkey IV toxicology study (report # 1023600)

Endpoint	Day	Group and dose)					
		1	2	3	4	5	6
		0	3 mg/kg	15 mg/kg	75 mg/kg	0	15 mg/kg
ALP (U/L) Both sexes combined	-6	269	285	259	265	421	333
	28	270 (+3%)	228 (-20%)	164 (-36%)	171 (-35%)	505 (+19%)	211 (-36%)
	92	263	169	113	117	554	214

[29] BLA module 2.6.7, accessed via: \\cdsesub1\evsprod\bla761143\0001\m2\26-nonclin-sum\267-toxicology-tabulated-summary.pdf

		(-2%)	(-40%)	(-56%)	(-55%)	(+31%)	(-35%)
	176	240 (-10%)	159 (-44%)	217 (-16%)	167 (-36%)	547 (+29%)	349 (-4%)
BAP (U/L)	-6	836	865	783	875	1465	1322
	28	859 (+2%)	694 (-19%)	452 (-42%)	514 (-58%)	1625 (+10%)	922 (-30%)
	92	1094 (+30%)	680 (-21%)	317 (-59%)	380 (-56%)	2237 (+52%)	1057 (-20%)
	176	420 (-28%)	197 (-78%)	333 (-38%)	268 (-75%	811 (-38%)	540 (-49%)

Note: Results presented as group mean, with the percent change from D-6 presented in parentheses

- The authors attributed the treatment-related effect on total ALP to the decrease in BAP, and considered it evidence of primary pharmacological activity on bone.

Urinalysis

- No treatment-related urinalysis effects were apparent.
- Urine samples were collected at sacrifice only (via bladder puncture). Standard urinalysis and urine chemistry parameters were measured.

Gross Pathology

- Standard full gross pathology was performed for all monkeys.
  - Gross findings were not tabulated, and this is a serious reporting deficiency.
- The only notable finding was thymic atrophy, consistent with organ weight and histopathology (not tabulated in this review).

Organ Weights

- A limited battery of organs were weighed at necropsy (adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid with parathyroids).
  - The failure to include uterus and prostate weights is a study limitation.
- Temprotumumab decreased thymus weight for all treated levels.
- Spleen weight was decreased for treated juvenile females (but not males).

Table 23: Thymus weight results for the GLP 13-week monkey IV toxicology study (report # 1023600)

Group:	1	2	3	4	5	6
Dose (mg/kg)	0	3	15	75	0	15
Male main groups (D92)						
Thymus wt (g)	2.174	0.869	0.570	1.078	5.177	0.641
Thymus:body wt	0.392	0.224 (-42%)	0.151 (-61%)	0.303 (-22%)	1.896	0.263 (-86%)
Spleen wt (g)	5.875	3.116	2.749	4.627	3.530	3.141
Spleen:body wt	1.003	0.818 (-18%)	0.722 (-28%)	0.995 (0%)	1.267	1.352 (+6%)
Female main groups (D92)						
Thymus wt (g)	3.146	0.344	0.394	0.382	4.576	0.703
Thymus:body wt	1.088	0.146 (-86%)	0.161 (-85%)	0.155 (-85%)	2.080	0.341 (-83%)
Spleen wt (g)	2.897	1.801	3.514	2.044	5.881	2.696
Spleen:body wt	0.963	0.772 (-19%)	1.382 (+43%)	0.847 (-12%)	2.673	1.306 (-51%)
Male recovery groups (D176)						
Thymus wt (g)	2.145	1.178	0.632	1.328	4.656	3.994
Thymus:body wt	0.406	0.287 (-29%)	0.166 (-59%)	0.231 (-43%)	1.420	1.619 (+14%)
Spleen wt (g)	6.879	6.958	4.782	2.872	4.113	2.750
Spleen:body wt	1.343	1.697 (+26%)	1.272 (-5%)	0.633 (-52%)	1.257	1.104 (-12%)
Female recovery groups (D176)						
Thymus wt (g)	2.412	2.461	0.763	0.685	3.318	1.216
Thymus:body wt	0.854	0.790 (-7%)	0.263 (-69%)	0.288 (-66%)	1.382	0.522 (-62%)
Spleen wt (g)	3.149	2.929	3.036	3.362	3.53	2.306
Spleen:body wt	1.086	0.941 (-13%)	1.050 (-3%)	1.385 (+27%)	1.560	1.005 (-35%)

Note: results presented as means, with percent change from respective control (group 1 for groups 2-4; group 5 for group 6) in parentheses.

Histopathology

Adequate Battery: Yes, a standard battery of systemic tissues and organs was evaluated.

Peer Review: Yes. The study anatomical pathologist was (b) (4) DVM, DACVP, DACLAM. Peer-review anatomical pathology was conducted by a sponsor representative: Michael J. Linn, DVM, DACVP, Hoffman La Roche Inc.

Histological Findings

- Teprotumumab caused an increase in the incidence and severity of thymus diffuse atrophy in the treated adults (groups 2-4); a dose-response was not clear.
- Teprotumumab also caused an increase in the incidence and severity of thymus diffuse atrophy in the treated juveniles (groups 6); the study was not designed to investigate a dose-response relationship.
- The results for monkeys (adults and juveniles) allowed a 12-week post-dose period prior to necropsy show partial, but not complete, recovery of thymus atrophy.

Table 24: Selected adult monkey histopathology for the GLP 13-week monkey IV toxicology study (report # 1023600)

Effect	Severity	Adult males				Adult females			
Group		1	2	3	4	1	2	3	4
Dose (mg/kg)		0	3	15	75	0	3	15	75
Main groups (D92)									
Thymus: diffuse atrophy	Mild	1/3	1/3	0/3	0/3	3/3	0/3	0/3	0/3
	Moderate	2/3	0/3	0/3	1/3	0/3	1/3	0/3	0/3
	Marked	0/3	2/3	3/3	2/3	0/3	2/3	3/3	3/3
Recovery groups (D176)									
Thymus: diffuse atrophy	Minimal	0/2	0/2	0/2	0/2	1/2	0/2	0/2	0/2
	Mild	1/2	0/2	0/2	0/2	1/2	1/2	1/2	2/2
	Moderate	0/2	1/2	0/2	0/2	0/2	1/2	0/2	0/2
	Marked	1/2	0/2	2/2	1/2	0/2	0/2	1/2	0/2

Table 25: Selected juvenile monkey histopathology for the GLP 13-week monkey IV toxicology study (report # 1023600)

Effect	Severity	Juvenile males		Juvenile females	
Group		5	6	5	6
Dose (mg/kg)		0	15	0	15
Main groups (D92)					
Thymus: diffuse atrophy	Mild	0/3	0/3	0/3	1/3
	Moderate	0/3	2/3	0/3	2/3
	Marked	0/3	1/3	0/3	0/3
Recovery groups (D176)					
Thymus: diffuse atrophy	Mild	0/2	0/2	0/2	2/2

- Notably, no treatment-related effects were apparent for the spleen, eye, optic nerve, lymph nodes (iliac, inguinal mandibular, mesenteric, pancreatic, popliteal), or reproductive organs (epididymis, prostate, testes; mammary, ovary, uterus, vagina).
- Bone marrow cytology was evaluated, but no treatment-related effects were apparent.

Special Evaluation – Flow Cytometry

- No clear treatment-related effects apparent.
- Blood samples (1 ml) were collected pre-dose, D28, 91, and 175 (same days as hematology blood collection). Absolute and differential cell counts were taken.
- Flow cytometry (using 7 markers) was used to determine total lymphocytes, B lymphocytes, T lymphocytes, T helper lymphocytes, NK cells, T cytotoxic lymphocytes, and monocytes.

Toxicokinetics

- Blood was collected for the D1 and D85 doses (pre-dose, 10, 24, 48, 72, 96, and 168 hours post-dose) for serum teprotumumab and ADA.
- The authors noted that accumulation was apparent with weekly IV dosing in monkeys, and considered TK parameters generally comparable for the 15 mg/kg adult and juvenile groups.

Table 26: Serum TK for the GLP 13-week monkey IV toxicology study (report # 1023600)

Age	Dose mg/kg/week	Study Day	$AUC_{10\text{-}168h}$ µg•hr/mL		Cmax µg/mL	
			Male	Female	Male	Female
Adult 4.5 – 6 years old	3	1	4010 ± 1960	4180 ± 426	57.1 ± 26.3	55.2 ± 4.27
		85	13000 ± 2320	12500 ± 4670	145 ± 18.4	121 ± 31.9
	15	1	28000 ± 3020	24600 ± 2870	374 ± 53.5	288 ± 26.6
		85	61100 ± 12500	44400 ± 12800	641 ± 77.4	502 ± 84.3
	75	1	151000 ± 15200	146000 ± 17900	2110 ± 159	1710 ± 182
		85	283000 ± 34700	213000 ± 41400	3560 ± 514	2650 ± 558
Juvenile 1.5 – 3 years old	15	1	22100 ± 2040	23000 ± 1330	317 ± 35.4	290 ± 35.4
		85	40900 ± 6660	45700 ± 10600	404 ± 58.1	492 ± 102

- Serum ADA was measured using a validated electrochemiluminescence (ECL) method, was a LLOQ of 16.0 ng/ml. The authors report that the presence of teprotumumab in the serum samples confounded the ADA assay. Therefore, the ADA results may underpredict the true ADA incidence.
- ADA was detected in:
    - During dosing for 3/10 monkeys in group 2 (# 2002, 2004, and 2502) and 1 monkey in group 6 (#6505).
    - During recovery only for both females in group 4 (#4501 and 4502) and both males in group 6 (# 6004 and 6005).

Dosing Solution Analysis

No concerns identified. Test article characterization was performed; samples were within 95% of nominal by protein content and 99% of nominal by size exclusion chromatography. *[Review note: the lack of a potency assay for the dosing solution analysis is a study limitation]*

6.2.4 Study title: A 39-Week Toxicity Study of RO4858696 Administered Once Weekly by Intravenous Injection to Cynomolgus Monkeys, with a 24-Week Recovery Period

Study no.:	• Applicant # 1030337 • Study laboratory # AGD00061
Study report location:	4.2.3.2 (Nonclinical study reports: toxicology: repeat-dose toxicity: nonhuman primate – intravenous – long): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\agd00061\agd00061.pdf
Conducting laboratory and location:	• Main laboratory: (b) (4) (b) (4) • ECG readings by (b) (4) (b) (4) • Bioanalysis of serum for teprotumumab and ADA: (b) (4) (b) (4)
Report date:	April 22, 2010
Date of study initiation:	February 15, 2008
GLP compliance:	Yes, signed
QA statement:	Yes, signed
Drug, lot #, and % purity:	Teprotumumab (RO4858696), CHO derived. 3 lots: • GRD0571 • P 3626 H07a • GRD0582 Supplied as sterile, white lyophilized powder, and reconstituted to (b) (4) with water for injection USP. Purities were ≥ 98% (by SE-HPLC), and 87 to 122% by potency assay.

Key Study Findings

- All dose levels of teprotumumab caused thymus diffuse atrophy (lymphoid depletion; thymic involution). The low-dose of 3 mg/kg/week is the LOAEL; no NOAEL was identified.
  - The authors identified the high dose, 75 mg/kg/week, as the NOAEL; this reviewer does not concur.
- In addition to the thymus atrophy, all dose levels of teprotumumab were pharmacologically active, causing:
  - Cessation of weight gain (during dosing, recovery apparent after cessation of dosing)
  - Decreased ALP (recoverability difficult to assess)

- This study used adolescent animals; most of the males were sexually immature (based on reproductive organ histopathology). Some of the females may have been sexually mature (based on age; not clear from clinical signs or histopathology).

Methods	
Doses:	0, 3, 15, 75 mg/kg
Frequency of dosing:	Once weekly for 39 weeks
Route of administration:	Bolus IV injection
Dose volume:	• control and high-dose: 3 ml/kg • low-dose: 0.12 ml/kg • mid-dose: 0.6 ml/kg
Formulation/Vehicle:	(b) (4) L-histidine/histidine hydrochloride, (b) (4) (b) (4) trehalose, (b) (4) polysorbate 20, pH 5.5 (after reconstitution of the placebo powder or test article power in water) *[Review note: this is the commercial clinical IV formulation]*
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	Main-groups: 4/sex/dose (D275 necropsy) Recovery-groups: 2/sex/dose (D435 necropsy, after 24 weeks of recovery) [One mid-dose animal (# 3501) was included in the female group, but was found to be a male with congenital defect at necropsy]
Age at start of dosing:	Males 2.5 to 3.9 years; females 2.8 to 3.8 years *Review note*: the author describes the groups as "age matched"; individual age information was not identified in the study report
Weight at start of dosing:	Males 2.2 to 3.5 kg; females 2.1 to 2.9 kg
Deviation from study protocol:	This reviewer reviewed the reported study deviations, and considers them acceptable.

Observations and Results

Mortality

- All monkeys survived to scheduled necropsies (D275 for main-group animals; D435 for recovery animals).
- Animals were checked twice daily for morbidity and mortality.

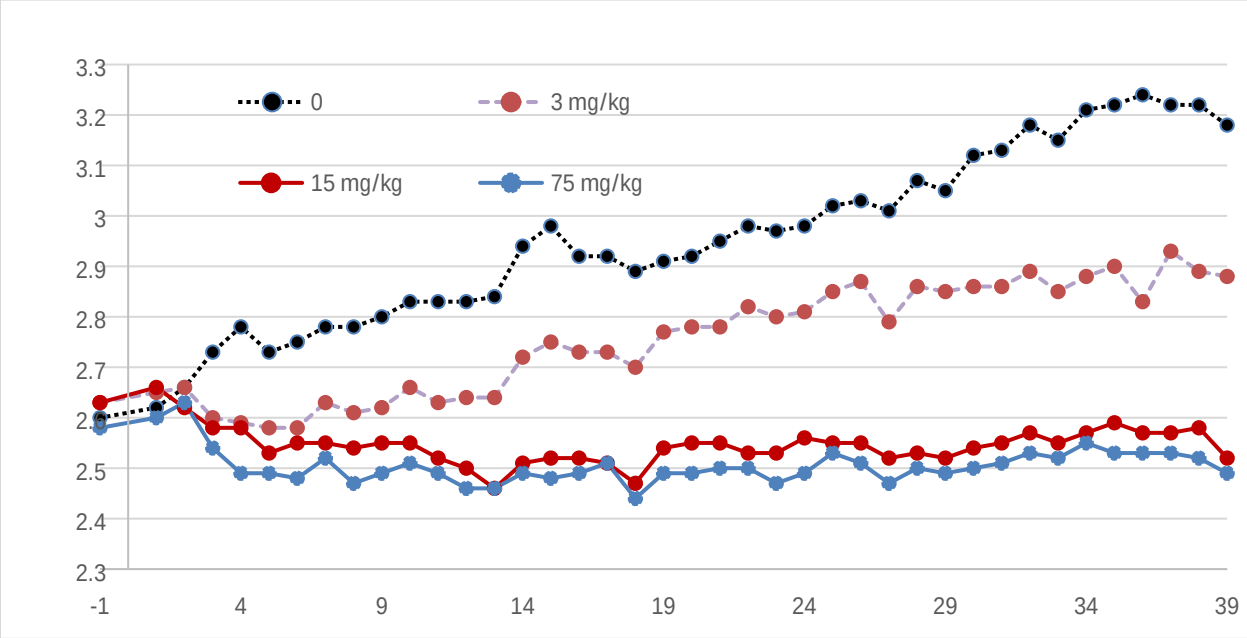
Clinical Signs

- No treatment-related effects were apparent for cage side observations and physical examinations.
- Cage side observations were made once daily, in the morning. Animals were also observed at 2 hours after each dose. Complete physical examinations were conducted pre-dose, week 39 (D267), and during recovery (week 62 at D434).

Body Weights

- Body weight was measured weekly.
- The control and low-dose male groups gained weight over the course of treatment. Teprotumumab prevented weight gain for all treated female groups, and for the male mid- and high-dose groups during treatment.
    - Statistical significance ($p \leq 0.05$ by ANOVA and Dunnett's test) was observed for the mid- and high-dose groups from week 30-39.
- Partial recovery of body weight gain was observed for the treated recovery animals after cessation of dosing.

Figure 2: Weekly body weight 39-week IV monkey toxicology study (report # 1030337)



Note: Y-axis is mean body weight (g) for both sexes pooled. X-axis is weekly body weight (beginning at Week -1)

Table 27: selected weekly body weight 39-week IV monkey toxicology study (report # 1030337)

Week (% change from W-1)	0	3 mg/kg	15 mg/kg	75 mg/kg
-1 (g)	2.60	2.63	2.63	2.58
4	+6%	-1%	-1%	-3%
8	+6%	0%	-3%	-4%
12	+8%	0%	-4%	-4%
16	+12%	+3%	-4%	-3%
20	+12%	+6%	-3%	-3%
24	+14%	+8%	-2%	-3%

28	+18%	+9%	-3%	-3%
32	+22%	+7%	-2% *	-1% *
36	+24%	+9%	-2% *	-1% *
39	+22%	+9%	-4% *	-3% *

Note: this selected results presented in this table are the same data as shown in the figure above. For the mid- and high-dose group, means were statistically different from week 30 to week 39 ($p \leq 0.05$ by ANOVA with Dunnett's test)

Feed Consumption

- No treatment-related effects on food consumption were apparent.
- Food consumption was evaluated qualitatively once daily, as part of the cage side observation.

Ophthalmoscopy

- No treatment-related ophthalmic effects were detected.
- Slit-lamp biomicroscopy and indirect ophthalmoscopy of the fundus and vitreous were conducted by (b) (4) DVM, DACVO: pre-dose, week 39 to 40, and recovery (week 62, at D430-431). Anterior segment findings were scored using a modified Hackett McDonald scale.

ECG

- No treatment-related ECG effects were detected.
- 6-Lead ECG was measured: pre-dose, D1 (after dosing), during week 39 (D268), and during recovery (week 62 at D433). Animals were restrained but not sedated. Standard ECG parameters were reported.

Hematology

- No clearly treatment-related effects were apparent.
    - The authors noted several slight differences between controls and the treated groups (decreased erythrocyte mass, decreased reticulocytes, decreased neutrophil counts), and considered them potentially treatment-related, but not adverse.
    - The relationship to treatment is unclear. Based on the slight magnitudes of the differences, this reviewer does not consider these to be potentially adverse.
    - For context, the clinical trials also observed slight hematology changes, which were considered treatment-related but not clinically meaningful (see section 11 of this review, below).
- With overnight fasting, blood for hematology, coagulation, and clinical chemistry was collected pre-dose, week 13 (D87), week 39 (D269) and during recovery (week 62 at D434). Standard parameters were evaluated.

Clinical Chemistry

- Teprotumumab decreased serum ALP for the mid- and high-dose groups at week 13 and 39 of dosing. Recoverability is difficult to assess, due to the small numbers for the recovery groups (2/sex/dose).
- [*Review note*: BAP was measured in the 13-week study, but not in this 39-week study.]
- The authors provided individual animal ALP data, and provided summary tables for each dose (sexes combined). The Applicant (BLA module 2.6.7 Toxicology Tabulated Summary) provided ALP data by sex and dose for weeks 13, 39, and 62.

Table 28: Serum ALP for the 39-week IV monkey toxicology study (report # 1030337)

	Males				Females			
ALP (U/L)	0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Week 13	547	406	209*	215*	287	258	130*	149*
Week 39	550	375	248*	221*	228	223	110*	121*
Week 62	686	313	659	620	187	226	187	242

* statistically significant, $p \leq 0.05$ by ANOVA and Dunnett's test.

Urinalysis

- No treatment-related urinalysis effects were detected.
- On the same days as blood collection (for hematology and clinical chemistry), cage-pan urine was collected for standard urinalysis and urine chemistry parameters.

Gross Pathology

- Standard full gross necropsy was conducted for all animals.
- The only remarkable gross finding was reduced thymus size for all treated female groups, and for the male mid- and high-dose groups. Recovery was apparent.

Table 29: Thymus gross pathology for the 39-week IV monkey toxicology study (report # 1030337)

	Effect	Males				Females			
		0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main-group (D275)	Thymus size decreased	0/4	0/4	1/4	1/4	0/4	1/4	2/3	2/4

Recovery-group (D435)		0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2

Organ Weights

- A limited panel of organ weights were measured (adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid with parathyroids).
  - The omission of prostate and uterus weights is a study limitation.
- Teprotumumab reduced thymus weight for all treated main-group animals. The effect was not apparent at end-of-recovery.
- *Review note*: the study report provided individual animal data, but did not provide tabulation of thymus weight by dose by sex. This reviewer compiled the following table.

Table 30: Thymus weights for the 39-week IV monkey toxicology study (report # 1030337)

	Males				Females			
	0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main-groups (D275)								
Thymus (g)	1.865	1.389	0.932	0.349	2.531	0.559	0.615	0.482
Thymus:body wt	0.513	0.475 (-7%)	0.361 (-29%)	0.134 (-73%)	0.897	0.235 (-73%)	0.242 (-73%)	0.204 (-77%)
Recovery-groups (D435)								
Thymus (g)	3.702	1.921	4.194	5.954	3.115	2.281	1.844	3.822
Thymus:body wt	0.786	0.577 (-26%)	1.164 (+48%)	1.615 (+2 fold)	1.153	0.702 (-39%)	0.701 (-39%)	1.489 (+29%)

Histopathology

Adequate Battery: Yes; standard battery of systemic tissues and organs were evaluated.

Peer Review: Yes. The study anatomic pathologist was (b) (4), DVM, PhD, DACVP. Anatomic pathology peer-review was performed by a sponsor representative: Michael Linn, DVM, DACVP, Hoffmann-La Roche Inc.

Histological Findings:

- The only notable finding was thymic diffuse atrophy (lymphoid depletion) among treated main-group animals.
  - Described as: "*characterized by a reduction in the number of lymphocytes in the cortex and medulla of the lobes of the thymus and correlated with thymus weight and size decreases*"

- The pathologist considered the effect to be comparable to the normal "thymic involution" observed in sexually maturing monkeys. However, conclusion is not supported by the concurrent control study data.

Table 31: Thymus histopathology for the 39-week IV monkey toxicology study (report # 1030337)

Effect	Severity	Males				Females			
		0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main group animals (D275)									
Thymus: diffuse atrophy	Minimal	0/4	0/4	3/4	1/4	0/4	2/4	1/3	1/4
	Mild	0/4	0/4	1/4	1/4	0/4	0/4	0/3	2/4
	Moderate	0/4	0/4	0/4	0/4	0/4	0/4	1/3	0/4
	Severe	0/4	0/4	0/4	2/4	0/4	1/4	1/3	1/4
Recovery group animals (D435)									
Thymus: diffuse atrophy	Minimal	0/2	1/2	0/2	0/2	0/2	0/2	1/2	0/2
Thymus: cortex involution	Minimal	0/2	1/2	0/2	0/2	0/2	0/2	1/2	0/2

- No treatment-related effects on reproductive tissues was noted. The majority of males were sexually immature (as demonstrated by histopathology).
- Maturity of the females cannot be directly assessed based on reported histopathology (ovary, uterus, vagina).
  - Review note: this reviewer does not consider the clinical signs data (i.e. vaginal discharge observations) clear enough to assess maturity.

Table 32: Selected reproductive tract histopathology shows mixed male maturity for the 39-week IV monkey toxicology study (report # 1030337)

Effect	Effect	Males				Females			
		0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main group animals (D275)									
Epididymis	Immature	3/4	2/4	4/4	2/4	-	-	-	-
Prostate	Immature	2/4	2/4	4/4	2/4	-	-	-	-
Seminal vesicle	Immature	2/4	2/4	4/4	2/4	-	-	-	-
Testis	Immature	3/4	2/4	4/4	2/4	-	-	-	-

Uterus and vagina	Normal	-	-	-	-	4/4	4/4	3/3	4/4
Recovery group animals (D435)									
Epididymis	Immature	0/2	0/2	0/2	1/2	-	-	-	-
Prostate	Immature	0/2	0/2	0/2	1/2	-	-	-	-
Seminal vesicle	Immature	0/2	0/2	0/2	1/2	-	-	-	-
Testis	Immature	0/2	1/2	0/2	1/2	-	-	-	-
Uterus and vagina	Normal	-	-	-	-	2/2	2/2	2/2	2/2

Special Evaluation – first immunohistochemistry experiment

- No results; assay not conducted
- Samples of thymus, spleen, mandibular lymph node, and mesenteric lymph node were collected for all animals (prior to fixation) and were snap frozen.
- Based on the lack of treatment-related changes for PBMC flow cytometry, the sponsor cancelled this evaluation. Samples were discarded (report page 46).

Special Evaluation – second immunohistochemistry experiment

- The results of this assay are not interpretable, due to reporting deficiencies. The assay was not GLP.
- At necropsy, tissue samples were collected from liver, pancreas, lung, mammary gland, kidney, urinary bladder, and prostate. Thymus samples were collected if the whole tissue was not needed for primary histopathology. Tissues were preserved in 10% neutral formalin, and processed into formalin blocks.
- Blocks were shipped to (b) (4); where exploratory immunohistochemistry (not under GLP) was conducted.
- Tissues were stained for IGF-1R, using G11 (a rabbit monoclonal antibody against human IGF1R).
- Results were provided as a separate 23-page report (appendix 9 of the study report).
    - The authors of the IGF1R immunohistochemistry report claimed “minimal to slight down-regulation of” IGF1R in the epithelium tissues. Binding in control tissues was reportedly membrane-bound.
        - Binding remained membrane-bound for: urinary bladder, thymus, mammary
        - Binding reportedly switched from membrane-bound to cytoplasmic for: pancreas, skin, prostate.

Special Evaluation – flow cytometry

- Blood was collected pre-dose, week 4 (D22), week 13 (D87), week 39 (D269), and week 62 (D434). Blood was analyzed for total and differential white blood cell counts.
- PBMCs were prepared, and flow cytometry was performed with 7 markers to measure all lymphocytes, B and T cells, helper T and cytotoxic T cells, NK cells, and monocytes [same design as for the 13-week study].
- The authors concluded that slight reductions in B-cells and T cells at 15 and 75 mg/kg were observed at week 39 and week 62.
- However, this reviewer disagrees – within the observed variability, no treatment-related effect can be discerned.

Toxicokinetics

- Blood was collected (multiple time points) for the D1, D85 and D267 doses
- The authors concluded that slight accumulation was observed with weekly dosing. This reviewer concurs that accumulation is apparent between D1 and D85; however, accumulation is not apparent between D85 and D267.

Table 33: Plasma TK results for the 39-week IV monkey toxicology study (report # 1030337)

dose [mg/kg/week]	day	gender	C_{max} [µg/mL]	$AUC_{(0\text{-}168h)}$
3	1	M	56.9	5440
	1	F	59.8	5900
	85	M	87.2	9790
	85	F	85.7	10600
	267	M	117	14300
	267	F	137	18700
15	1	M	310	31300
	1	F	300	31000
	85	M	698	82800
	85	F	785	101000

	267	M	611	72500
	267	F	647	84500
75	1	M	1990	189000
	1	F	1960	196000
	85	M	3690	449000
	85	F	3490	367000
	267	M	3520	399000
	267	F	2900	314000

- As with the previous study, the ADA assay was confounded by the presence of teprotumumab; ADA could only be assessed for recovery animals. ADA was detected in:
    - all (4/4) low-dose (3 mg/kg) recovery animals
    - 1 (1/4) mid-dose (15 mg/kg) recovery monkey
    - No (0/4) high-dose (75 mg/kg) recovery monkeys
- As with the previous monkey studies, the observed incidence of ADA may have underpredicted the true ADA incidence.

Dosing Solution Analysis

No concerns identified. Dose solution analysis was performed on the initial and end-of-dosing samples. Samples were with 4% of nominal by protein concentration, and within 2% of nominal by size exclusion chromatography.

6.3 IV Repeat-Dose Juvenile Toxicity

6.3.1 Study title: RO4858696: A 13-Week Toxicity Study of RO4858696 Administered by Intravenous Injection to Juvenile Cynomolgus Monkeys, with a 13-Week Recovery Period

Study nos.:	• Applicant #: 1037684 • Laboratory #: AGD00071
Study report location:	BLA module 4.2.3.5.4 (Nonclinical study reports: toxicology: reproductive and developmental toxicity: studies in which the offspring (juvenile animals) are dosed and/or further evaluated): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42354-juv\agd00071\agd00071.pdf
Conducting laboratory and location:	(b) (4)
Report date:	June 10, 2011
Date of study initiation:	June 4, 2009
GLP compliance:	Yes, signed
QA statement:	Yes, signed
Drug, lot #, and % purity:	Teprotumumab, batch RO 485-8696/F05-01, provided as a sterile white lyophilized powder and reconstituted with sterile water for injection. Purity: 99% by SE-HPLC; 117% by potency assay.

Key Study Findings

- The authors concluded that no NOAEL was identified, and considered the lowest dose of 3 mg/kg/week to be the LOAEL based on reduced weight gain, decreased tibia and femur bone mass (without a detectable difference in length) compared to controls.
  - The Applicant and this reviewer concur.
  - This reviewer also considers the thymus effects (decreased size and weight, thymic lymphoid depletion) and spleen effects (decreased weight) to be adverse, based on magnitude of effect.
- In-life radiography (left and right humerus, radius, ulna, femur, tibia, fibular) detected treatment-related decreased growth in all bones for all teprotumumab-treated groups at week 13 (all monkeys) and week 26 (recovery monkeys). Recovery was not apparent.
- Tibia and femur bone densitometry was measured post-mortem.
  - For the femur: bone mineral density (BMD) and bone mineral content (BMC) were reduced main-group animals (males at 3, 15 and 75 mg/kg, females at 15 and 75 mg/kg). Recovery was not apparent.

  - For the tibia, evaluation of trabecular bone of the metaphysis observed reduced MBC and MBD for all treated main-groups. Recovery was apparent.
  - For the tibia, evaluation of cortical bone in the diaphysis observed decreased cortical thickness (and cortical area) for all treated main-groups, and decreased BMC (but not BMD) for treated males, mid- and high-dose males. Partial recovery was apparent (difficult to assess).
- For labeling (section (b) (4)), the Applicant proposed (7/08/2019) to describe the findings as: (b) (4) (b) (4)
  - Review note: assessment of cortical thickness was limited to the left tiba.

Age of animals

- The authors report (page 22) that 9.5 to 9.6 months was the "youngest that could be obtained from a commercial supplier in sufficient number to fulfill the study requirements (i.e., earliest possible time animals could be weaned from the adult females and shipped to the Testing Facility)."
  - From a scientific perspective, this justification is not adequate.
    - Honjo et al. 1984[30] report that cynomolgus monkeys can be weaned as early as 3 months.
    - Other papers report natural weaning at ~ 8 months.
    - Additionally, dosing infants while weaning is feasible, if necessary.
  - For the indication being sought (TED), dosing younger animals is not warranted from a P/T perspective. Therefore, the ages of the animals used in this study are not objectionable.

Methods	
Doses:	0, 3, 15, 75 mg/kg
Frequency of dosing:	Once weekly injection x 13 (last dose on D85)
Route of administration:	IV bolus injection
Dose volume:	• Control and high-dose: 3 ml/kg • Low-dose: 0.12 ml/kg • Mid-dose: 0.6 ml/kg
Formulation/Vehicle:	• The control group received placebo ((b) (4) (b) (4) L-histidine hydrochloride monohydrate, (b) (4) L-histidine, (b) (4) polysorbate 20, (b) (4) trehalose dihydrate)

[30] Honjo S, F. Cho, and K. Terao. 1984. Establishing the cynomolgus monkey as a laboratory animal. Advances in Veterinary Science and Comparative Medicine, Volume 28. Pages 51-80. Accessed via: https://www.sciencedirect.com/science/article/pii/B9780120392285500085/pdf?md5=9a7e0d618874ef33483246bfe8cc3532&pid=1-s2.0-B9780120392285500085-main.pdf&_valck=1

	o [*Review note*: this is very close to the clinical formulation; (b) (4) (b) (4)] • Test article and placebo were diluted with sterile water for injection, USP
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	Main-groups: 3/sex/dose (necropsy on D92, one week after the last dose) Recovery groups: 2/sex/dose (necropsy on D182, after 13 weeks recovery)
Age:	• 20/sex animals were approximately 9.6 to 13.5 months at arrival, and weighed 1.0 to 1.7 kg. • 2/sex alternates were 9.5 to 16.4 months at arrival.
Deviation from study protocol:	This reviewer considers the reported protocol deviations to be acceptable.

Observations and Results

Mortality

- All monkeys survived to scheduled necropsy.
- Animals were checked once daily for morbidity and mortality (as part of the cage side observation)

Clinical Signs

- No treatment-related clinical signs were apparent.
- Cage side checks were done once daily, in the morning.

Body Weights

- Body weight was measured weekly.
- Slight reductions in weight gain were apparent at end of dosing. For D91 compared to controls:
  - 3 mg/kg: 91%
  - 15 mg/kg: 88%
  - 75 mg/kg: 88%
- Body weights recovered by the end of recovery (D175).

Feed Consumption

- No changes to food consumption were apparent.
- Food consumption was measured qualitatively, as part of the daily cage side observations.

Ophthalmoscopy

- No treatment-related ophthalmic effects were apparent.

- Slit lamp biomicroscopy and indirect ophthalmoscopy of the fundus and vitreous were evaluated: pre-dose, week 13, and week 26

ECG

- No ECG-changes were apparent.
- 6-lead ECG was measured predose, week 13, and week 26 with restraint (but not sedation).

Hematology

- Blood samples for hematology, coagulation, and clinical chemistry were collected pre-dose and D85

Clinical Chemistry

- Teprotumumab decreased ALP in all treated groups; only partial recovery was apparent.

Table 34: Serum ALP results for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

ALP (U/L)	Both sexes combined			
	0	3 mg/kg	15 mg/k	75 mg/kg
D85	671.5	374.9* (-44%)	357.0* (-46%)	330.9* (-50%)
D175 (recovery)	603.3	554.5 (-8%)	653.3 (+8%)	463.5 (-23%)

* statistically significant, $p \leq 0.05$ by ANOVA and Dunnett's test

Urinalysis

- Urine samples were collected pre-dose, week 13, and week 26.

Gross Pathology

- Standard full gross pathology was conducted at necropsy.
- The only remarkable finding was decreased thymus size, for 3/18 of the treated main-group monkeys (which correlated with thymus organ weight and thymus histopathology). The effect was not reported for any recovery monkey.
- *Review note*: the study report provided individual animal gross pathology reports, but no tabulation of gross pathology. This is a study limitation. The following table was compiled by this reviewer.

Table 35: Thymus gross pathology results for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

	Effect	Males				Females			
		0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main-group (D92)	Thymus size decreased	0/3	1/3	0/3	1/3	0/3	0/3	0/3	1/3
Recovery-group (D182)		0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2

Organ Weights

- At main-group sacrifice, teprotumumab caused a statistically significant decrease in thymus weight at all dose levels. Teprotumumab also decreased spleen weight at all dose levels (statistical significance not achieved).
- The recovery data for thymus and spleen is difficult to interpret. The data show partial, but not full, recovery.
- *Review note*: the study report provided individual animal data, but did not provide tabulation of organ weight by dose by sex. This reviewer compiled the following table.

Table 36: Selected organ weight data (thymus and spleen) for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

	Males				Females			
	0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main-groups (D92)								
Thymus (g)	3.577	1.878	0.737	0.500	3.162	1.207	1.079	0.709
Thymus:body wt	1.913	1.241 (-35%)	0.520 (-72%)	0.319 (-83%)	2.014	0.765 (-62%)	0.776 (-61%)	0.564 (-71%)
Spleen (g)	5.397	2.175	1.714	2.333	2.652	1.890	2.258	1.734
Spleen:body wt	2.856	1.519 (-46%)	1.223 (-57%)	1.489 (-47%)	1.663	1.216 (-26%)	1.632 (-1%)	1.36 (-18%)
Recovery-groups (D182)								
Thymus (g)	3.378	4.239	3.018	3.609	2.861	4.744	4.548	1.025
Thymus:body wt	1.917	2.315 (-20%)	1.775 (-7%)	2.066 (-7%)	1.575	2.965 (+88%)	2.577 (+63%)	0.675 (-57%)
Spleen (g)	1.926	2.706	1.448	2.055	2.653	2.704	2.366	1.369
Spleen:body wt	1.107	1.458 (+31%)	0.851 (-23%)	1.172 (+5%)	1.437	1.690 (+17%)	1.344 (-6%)	0.921 (-35%)

Histopathology

Adequate Battery: Yes. standard battery of systemic tissues and organs were evaluated.

Peer Review: Yes. The study pathologist was (b) (4) DVM, PhD, DACVP, (b) (4) Peer review was performed by a sponsor representative: Michael Linn, DVM, DACVP, Hoffman La Roche Inc.

Histological Findings

- Teprotumumab caused thymic lymphoid depletion (at all dose-levels) and splenic decreased germinal centers (for 1/3 mid-dose males, and 2/3 high-dose females).
- At recovery, one high-dose female exhibited thymus depletion; no treatment-related spleen effects were apparent.

Table 37: Selected (thymus and spleen) histopathology for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

Effect	Severity	Males				Females			
		0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main group animals (D92)									
Thymus: lymphoid depletion	Minimal	0/3	1/3	0/3	1/3	0/3	1/3	1/3	1/3
	Mild	0/3	0/3	3/3	0/3	0/3	0/3	0/3	0/3
	Moderate	0/3	1/3	0/3	2/3	0/3	1/3	1/3	2/3
Thymus: cyst	Minimal	03/	0/3	1/3	1/3	1/3	1/3	1/3	1/3
Spleen: decreased germinal centers	Minimal	0/3	0/3	0/3	0/3	0/3	0/3	0/3	2/3
	Mild	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3
Recovery group animals (D182)									
Thymus: lymphoid depletion	Mild	0/2	0/2	0/2	0/2	0/2	0/2	0/2	1/2
Thymus: cyst	Minimal	0/2	0/2	0/2	0/2	1/2	0/2	0/2	0/2

Special Evaluation: Bone Densitometry

- Assays were done under GLP and QA:

- At necropsy, whole left tibias and femurs were cleaned of excess tissue without scraping, frozen, and shipped to (b) (4) (b) (4) for analysis.
- Peripheral quantitative computed tomography (pQCT) was used to measure the left tibia. Two scans were taken: one of the proximal metaphysis (growth plate), and another of the diaphysis (shaft). BMD, BMC, and cross-sectional area were measured. Tibia parameters calculated were: periosteal circumference, endosteal circumference, cortical thickness, total and cortical cross-sectional area, total and cortical BMC, total and cortical BMD.
- Dual energy X-ray absorptiometry (DXA) was used to measure left femur bone mineral density (BMD), bone mineral content (BMC) and area. Femur parameters were calculated for the proximal, mid, distal, and whole bone.

- Results were reported in a 95-page bone report (appendix 7 of the study report).

Left tibia data (by pQCT):

- At main-group sacrifice: reduced tibia size (area but not length) and tibia trabecular bone density (at the metaphysis)) for all treated male groups and high-dose females
- The authors reported "*narrower bones with slightly thinner cortices attributed to reduced periosteal expansion with no effect on endosteal circumference relative to controls"* for the main-group (all treated male groups and high-dose females)
  - The author's statement is correct for the tibia diaphysis. Reported diaphysis endpoints were focused on the cortical bone (i.e. compact bone).
  - For the tibia metaphysis, this reviewer disagrees with the author, since cortical thickness was not measured for the tibia metaphysis. The treatment-effect (on area, BMC, and BMD) were slightly more severe for trabecular bone than cortical/subcortical bone.

Table 38: Selected tibia diaphysis density results for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

Effect	Males				Females			
Tibia diaphysis	0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main group animals (D92)								
Diaphysis length (mm)	86	86 (0%)	85 (-1%)	88 (+2%)	85	88 (+3%)	84 (-1%)	84 (-1%)
Cortical area (mm^2)	23.38	17.33 (-25%)	17.66 (-24%)	18.86 (-19%)	21.50	19.79 (-7%)	17.48 (-18%)	16.82 (-21%)
Cortical BMC (g)	23.24	18.35 (-21%)	19.02 (-18%)	19.60 (-15%)	21.7	21.1 (-3%)	18.4 (-15%)	18.0 (-17%)
Cortical BMD (g/mm^2)	993	1061 (+6%)	1077 (+8%)	1038 (+4%)	1010	1066 (+5%)	1051 (+3%)	1071 (+5%)

Cortical thickness (mm)	1.31	1.04 (-20%)	1.10 (-16%)	1.09 (-16%)	1.28	1.17 (-8%)	1.08 (-15%)	1.07 (-16%)
Periosteal circumference (mm)	22.0	19.9 (-9%)	19.6 (-10%)	20.9 (-4%)	20.8	20.6 (-1%)	19.5 (-6%)	18.9 (-9%)
Endosteal circumference (mm)	13.7	13.3 (-2%)	12.7 (-7%)	14.1 (+2%)	12.8	13.2 (+3%)	12.7 (0%)	12.2 (-4%)
Recovery group animals (D182)								
Diaphysis length (mm)	97	102 (+5%)	94 (-3%)	92 (-5%)	99	98 (-1%)	95 (-4%)	98 (-1%)
Cortical area (mm^2)	24.86	27.49 (+10%)	22.68 (-8%)	22.08 (-11%)	22.98	21.97 (-4%)	22.80 (0%)	18.37 (-20%)
Cortical BMC (g)	25.41	28.85 (+13%)	23.88 (-6%)	23.65 (-6%)	23.82	22.59 (-5%)	22.99 (-3%)	19.92 (-16%)
Cortical BMD (g/mm^2)	1022	1050 (+2%)	1053 (+3%)	1071 (+4%)	1037	1023 (-1%)	1010 (-2%)	1084 (+4%)
Cortical thickness (mm)	1.35	1.56 (+15%)	1.42 (+5%)	1.22 (-9%)	1.30	1.40 (+7%)	1.34 (0%)	1.15 (-11%)
Periosteal circumference (mm)	22.5	22.4 (0%)	20.4 (-9%)	21.8 (-3%)	21.6	20.0 (-7%)	21.2 (-1%)	19.6 (-9%)
Endosteal circumference (mm)	14.0	12.6 (-10%)	11.5 (-17%)	14.1 (0%)	13.4	11.1 (-17%)	12.8 (-4%)	12.3 (-8%)

BMD = bone mineral density
BMC = bone mineral content

Table 39: Selected tibia metaphysis results for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

Effect	Males				Females			
Tibia metaphysis	0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main group animals (D92)								
Total area (mm^2)	54.1	44.6 (-17%)	47.3 (-12%)	49.2 (-9%)	48.3	45.6 (-5%)	42.8 (-11%)	44.5 (-7%)
Total BMC (g)	28.7	22.5 * (-21%)	22.1 * (-23%)	24.9 * (-13%)	24.0	25.0 (-4%)	23.6 (-1%)	22.1 (-7%)
Total BMD (g/mm^2)	532	513 (-3%)	481 (-9%)	514 (-3%)	498	549 (+10%)	560 (+12%)	500 (+0.5%)
Cortical/ subcortical BMC (mg/mm)	20.9	17.9 (-14%)	17.7 (-15%)	18.9 (-9%)	17.89	19.71 (+10%)	17.68 (-1%)	17.2 (-3%)
Cortical/ subcortical	775	822 (-6%)	767 (-1%)	781 (0%)	744	867 (+16%)	837 (+12%)	774 (+3%)

BMD (mg/cm^3)								
Trabecular BMC (mg/mm)	7.87	4.67 * (-40%)	4.36 * (-44%)	6.00 (-23%)	6.19	5.35 (-13%)	5.99 (-3%)	4.92 (-20%)
Trabecular BMD (mg/cm^3)	289	206 (-28%)	195 (-32%)	247 * (-14%)	254	231 (-8%)	283 (-11%)	227 (-10%)
Recovery group animals (D182)								
Total area (mm^2)	56.4	54.3 (-3%)	44.9 (-20%)	53.8 (-4%)	51.1	45.0 (-11%)	48.3 (-5%)	44.5 (-12%)
Total BMC (g)	29.1	33.5 (+15%)	26.9 (-7%)	27.8 (-4%)	24.7	25.0 (+1%)	25.8 (+4%)	23.7 (-4%)
Total BMD (g/mm^2)	513	618 (+15%)	600 (+16%)	516 (0%)	485	557 (+14%)	535 (+10%)	532 (+9%)
Cortical/ subcortical BMC (mg/mm)	22.9	25.8 (+12%)	20.9 (-8%)	21.6 (-5%)	21.1	19.7 (-6%)	19.7 (-6%)	19.5 (-7%)
Cortical/ subcortical BMD (mg/cm^3)	809	954 (+17%)	933 (+15%)	801 (0%)	828	869 (+4%)	817 (-1%)	876 (+5%)
Trabecular BMC (mg/mm)	6.21	7.67 (+23%)	5.97 (-3%)	6.27 (0%)	3.63	5.35 (+47%)	6.15 (+69%)	4.20 (+15%)
Trabecular BMD (mg/cm^3)	218	283 (+29%)	268 (+22%)	231 (+5%)	143	245 (+71%)	254 (+77%)	188 (+31%)

Review note: the area units shifted from cm^2 (for femur) to mm^2 (for tibia).
BMD = bone mineral density
BMC = bone mineral content
* = statistically significant ($p \leq 0.05$) by ANOVA and Dunnett's test

Left femurs data

- At main-group sacrifice, femur bone mass (by DXA and BMD) was reduced for all treated male groups (3, 15, 75 mg/kg) and the mid- and high-dose female groups (15 and 75 mg/kg)
- No apparent effect on bone length.
- *Review note*: cortical endpoints were only calculated for the tibia (i.e. not for the femur)
- At recovery-group sacrifice, slightly reduced femur BMC was apparent for males at 15 and 75 mg/kg, and for females at 75 mg/kg
- The table below presents whole femur area, BMC, and BMD data (the values for proximal, mid, and distal area, BMC and BMD were consistent with the whole femur values, and are not captured below).

Table 40: Selected femur bone density results for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

Effect	Males				Females			
Femur	0	3 mg/kg	15 mg/kg	75 mg/kg	0	3 mg/kg	15 mg/kg	75 mg/kg
Main group animals (D92)								
Area (cm^2)	10.36	9.05 (-12%)	9.36 (-9%)	10.05 (-3%)	9.50	10.4 (+9%)	9.30 (-2%)	9.31 (-2%)
BMC (g)	3.35	2.37 * (-29%)	2.51 * (-25%)	2.81 (-16%)	2.87	3.03 (+5%)	2.68 (-6%)	2.48 (-13%)
BMD (g/cm^2)	0.32	0.26 (-19%)	0.27 * (-17%)	0.28 * (-13%)	0.30	0.29 (-3%)	0.29 (-4%)	0.26 (-12%)
Recovery group animals (D182)								
Area (mm^2)	10.80	11.85 (+9%)	9.71 (-10%)	9.74 (-9%)	10.35	9.87 (-4%)	10.04 (-2%)	9.51 (-8%)
BMC (g)	3.61	4.27 (+18%)	3.24 (-10)	3.28 (-9%)	3.35	3.19 (-4%)	3.32 (0%)	2.72 (-18%)
BMD (g/mm^2)	0.33	0.36 (+9%)	0.33 (0%)	0.33 (0%)	0.32	0.32 (0%)	0.32 (0%)	0.28 (-12%)

BMD = bone mineral density
BMC = bone mineral content
Values presented as means, with % difference from control in parentheses
* = statistically significant ($p \leq 0.05$) by ANOVA and Dunnett's test
Review note: the area units shifted from mm^2 (for tibia) to cm^2 (for femur)

Special Evaluation: Radiography

- Skeletal radiographs were taken under sedation: pre-dose, week 13 (for all monkeys), and week 26 (for recovery monkeys). Measurements were: forelimbs (humerus, radius, ulna), hindlimbs (femur, tibia, fibula) from the proximal to the distal diaphysis (inclusive).
    - *Review note*: the exact week pre-dose was not reported (e.g., protocol on report page 516); this is a reporting limitation. Variability in when the pre-dose measurements were recorded would increase the overall variability of the assay.
- The authors concluded that "There were no test article-related changes in forelimb or hindlimb bone lengths as measured prestudy, and during Weeks 13 and 26 of the study". This reviewer disagrees: when the data are tabulated as percent pre-dose, a subtle but clear trend is apparent for reduced growth in all bone measured.
    - The variability in pre-study measurements make assessing changes at week 13 difficult.
    - The authors did not provide tabulation of relative growth, or provide growth figures; this is a minor study limitation.

Table 41: In-life skeletal radiography data for the GLP 13-week IV juvenile monkey toxicology study (report # 1037684)

Bone (both sexes combined)	Week	0	3 mg/kg	15 mg/kg	75 mg/kg
Left humerus (cm)	Pre-dose	7.34	7.56	7.34	7.49
	W13	7.73 (+5%)	7.86 (+3%)	7.73 (+5%)	7.84 (+4%)
	W26	8.50 (+15%)	8.40 (+11%)	8.13 (+10%)	8.20 (+9%)
Right humerus (cm)	Pre-dose	7.26	7.53	7.33	7.43
	W13	7.77 (+7%)	7.79 (+3%)	7.70 (+5%)	7.81 (+5%)
	W26	8.52 (+17%)	8.37 (+11%)	8.04 (+9%)	8.20 (+10%)
Left radius (cm)	Pre-dose	6.96	7.25	6.85	7.16
	W13	7.35 (+5%)	7.44 (+2%)	7.15 (+4%)	7.39 (+3%)
	W26	8.02 (+15%)	7.96 (+9%)	7.47 (+9%)	7.76 (+8%)
Right radius (cm)	Pre-dose	6.90	7.24	6.85	7.12
	W13	7.31 (+5%)	7.42 (+2%)	7.15 (+4%)	7.33 (+2%)
	W26	7.97 (+15%)	7.94 (+9%)	7.50 (+9%)	7.73 (+8%)
Left ulna (cm)	Pre-dose	7.76	8.15	7.77	8.00
	W13	8.34 (+7%)	8.42 (+3%)	8.15 (+4%)	8.34 (+4%)
	W26	8.99 (+15%)	8.97 (+10%)	8.52 (+9%)	8.67 (+8%)
Right ulna (cm)	Pre-dose	7.79	8.16	7.76	8.04
	W13	8.30 (+6%)	8.43 (+3%)	8.10 (+4%)	8.34 (+3%)
	W26	8.99 (+15%)	9.05 (+10%)	8.52 (+9%)	8.66 (+7%)
Left tibia (cm)	Pre-dose	7.73	7.75	7.37	7.76
	W13	7.86 (+1%)	8.06 (+4%)	7.72 (+4%)	7.94 (+2%)
	W26	8.58 (+10%)	8.63 (+11%)	8.10 (+9%)	8.26 (+6%)
Right tibia (cm)	Pre-dose	7.38	7.77	7.33	7.65
	W13	7.86 (+6%)	8.03 (+3%)	7.69 (+4%)	7.92 (+3%)
	W26	8.52 (+15%)	8.66 (+11%)	8.07 (+10%)	8.29 (+8%)
Left femur (cm)	Pre-dose	7.95	8.25	7.87	8.19

	W13	8.43 (+6%)	8.54 (+3%)	8.13 (+3%)	8.40 (+2%)
	W26	9.14 (+14%)	9.11 (+10%)	8.64 (+9%)	8.77 (+7%)
Right femur (cm)	Pre-dose	7.95	8.28	7.89	8.17
	W13	8.39 (+5%)	8.54 (+3%)	8.17 (+3%)	8.37 (+2%)
	W26	9.17 (+15%)	9.11 (+10%)	8.61 (+9%)	8.78 (+7%)
Left fibula (cm)	Pre-dose	6.91	7.28	6.85	7.17
	W13	7.28 (+5%)	7.44 (+2%)	7.05 (+2%)	7.30 (+1%)
	W26	7.87 (+13%)	7.92 (+8%)	7.45 (+8%)	7.54 (+5%)
Right fibula (cm)	Pre-dose	6.91	7.27	6.86	7.13
	W13	7.28 (+5%)	7.44 (+2%)	7.09 (+3%)	7.33 (+2%)
	W26	7.89 (+14%)	7.95 (+9%)	7.41 (+8%)	7.59 (+6%)

Values presented as means for both sexes combined, with % difference pre-dose baseline in parentheses

Special Evaluation: Keyhole limpet hemocyanin (KLH) challenge

- Non-GLP TDAR assay:
  - Monkeys received a subcutaneous injection with 10 mg of KLH (in 1 ml) in the scapula region on D36 and D71 (prior to dosing) and D161 (during recovery).
  - Blood samples were taken over a total of 20 time points (pre-dose, prior to each KLH dose, after each KLH dose at 5, 7, 10, 14, 17, and 21 days).
  - Blood samples were analyzed for IgM and IgG against KLH using an ELISA.
- Results were provided in a 26-page immunology report (Appendix 5).
  - No treatment-related effect was apparent.
  - All monkeys developed antibodies against KLH.

Toxicokinetics

- Blood samples were collected for plasma TK and ADA analysis.

Table 42: Plasma TK for the 13-week IV juvenile monkey study (report # 1037684)

dose [mg/kg]	day	gender	C_{max} [µg/mL]	$AUC_{0\text{-}168h}$
3	1	m	42.0	3530
		f	48.9	3920
	85	m	62.3	6440
		f	68.3	7810
15	1	m	249	23000
		f	244	23000
	85	m	448	64000
		f	446	55600
75	1	m	1500	128000
		f	1620	147000
	85	m	2470	250000
		f	2710	274000

- ADA was detected for:
  - 3 mg/kg: 6/10 monkeys
  - 15 mg/kg: 3/10 monkeys
  - 75 mg/kg: 0/10 monkeys

Dosing Solution Analysis

Dose formulation analysis was reported for the 1st, 6th, and last preparation. All test articles were within 1.3% of nominal.

6.4 Intravitreal (ivt) Repeat-Dose Toxicity

The Applicant submitted one intravitreal toxicity study to the BLA.

<table>
<tr><td>Report title</td><td colspan="2">Ocular Tolerance Study of Teprotumumab Following Intravitreal Administration in Cynomolgus Monkeys</td></tr>
<tr><td>Report #</td><td colspan="2">8250539</td></tr>
<tr><td>Key findings</td><td colspan="2">• This non-GLP ocular tolerability study dosed cynomolgus monkeys with 1.25 or 2.5 mg/eye by intravitreal (ivt).
• The authors considered both dose levels adverse, based on marked ocular inflammation (attributed to ADA response)</td></tr>
<tr><td rowspan="4">Report details</td><td>BLA location</td><td>4.2.3.6 (Nonclinical study reports: toxicology: local tolerance):
\\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4236-loc-tol\8250539\8250539.pdf</td></tr>
<tr><td>Study laboratory</td><td>(b) (4)</td></tr>
<tr><td>Report date</td><td>April 17, 2012</td></tr>
<tr><td>GLP status</td><td>No</td></tr>
<tr><td rowspan="4">Methods</td><td>Test article</td><td>Teprotumumab, batch GD0588. Purity not reported</td></tr>
<tr><td>Vehicle:</td><td>(b) (4) histidine, (b) (4) trehalose, and (b) (4) polysorbate 20 in Sterile Water for Injection, USP; pH (b) (4)
[This is the same as the clinical formulation for IV dosing]</td></tr>
<tr><td>Test species</td><td>6 female cynomolgus monkeys
• 5/6 were non-naïve (previously treated with topical ocular drugs; washout period of 2 months prior to dosing for this experiment)</td></tr>
<tr><td>Route of administration</td><td>Intravitreal (ivt) injection
• Dose volume = 50 µl/eye/dose</td></tr>
<tr><td>Dose groups and timing of doses</td><td>Two groups of 3 female monkeys/group
• Both groups received vehicle in the left eye (OS),
• Both groups received teprotumumab in the right eye (OD), for a total of 3 injections
<table>
<tr><th>Group</th><th>Dosing days</th><th>OD dose of teprotumumab</th></tr>
<tr><td>1</td><td>1
15
43</td><td>1.25 mg/eye/dose
1.25 mg/eye/dose
2.5 mg/eye/dose</td></tr>
<tr><td>2</td><td>15
29
43</td><td>2.5 mg/eye/dose
2.5 mg/eye/dose
2.5 mg/eye/dose</td></tr>
</table></td></tr>
</table>

		• The saline doses and the 1.25 mg/eye dose was given as a single 50 µl injection. • The 2.5 mg/eye doses were given as two injections (50 µl each), spaced 15 minutes apart.
	Endpoints	• Standard in-life endpoints (twice daily checks for morbidity and mortality, once daily cage side check, weekly detailed observations, daily qualitative food assessment, weekly body weight) • Ophthalmoscopy (slit lamp biomicroscopy; fundoscopy using an indirect ophthalmoscope; intraocular pressure using an applanation tonometer): twice weekly until D43, then weekly for 2 weeks (i.e. D49 and D57) • Blood collection for ADA only • Sacrifice on D60 with gross necropsy of the eye
Results: early sacrifice	Two monkeys were sacrificed early • Monkey # I09324 (group 1): sacrificed on D15. o This reviewer did not receive the scheduled doses on D15 (i.e. second OD dose not administered) (clearly stated on report page 125). o OD IOP was normal up to D8, but was dramatically low on D15 (5 mm Hg). o No clinical signs were noted until D15, when the monkey was considered moribund. o On D15, the authors characterized the right eye inflammation as “severe”, based on 4+ anterior chamber cell, fibrin clot in the anterior chamber, extensive white keratic precipitates, 2+ conjunctival hyperemia, and 1+ aqueous flare. o The eye was not infected (based on cytology of vitreous humor samples collected at the D15 sacrifice) • Monkey # I09327 (group 2): sacrificed on D46 o This monkey received the first and second planned doses (on D15 and 29). o OD severe uveitis appeared on D36 (7 days after the second dose), and persisted until sacrifice (11 days later) o Due to OD marked inflammation on D32, the planned OD 3rd dose was not administered. Instead, the 2.5 mg/eye dose was given OS (instead of vehicle) o The rationale for administering teprotumumab OS was to characterize the cause of inflammation (i.e. ADA-mediated toxicity “should produce a rapid-onset uveitis in the left eye”). o Consistent with the authors’ prediction, severe OS intraocular inflammation was observed on D44 and D46	

	(corneal nebula, 4+ anterior chamber cells, 1+ anterior chamber flare, 2+ vitreous cells) o Neither eye was infected (based on cytology of vitreous humor samples collected at sacrifice)
Results: clinical signs and ophthalmo-scopy	• The ivt injection procedure (OS, and the first OD dose) was associated with transient ocular inflammation (1+ conjunctival hyperemia, trace vitreous cell). • The second and third OD doses caused anterior and posterior inflammation, "conjunctival hyperemia, aqueous flare, anterior • chamber cell, fibrin in the anterior chamber, white keratic precipitates, iris swelling, dyscoria, miosis, incomplete pupil dilation following the application of a mydriatic, vitreous cell, degraded views of the fundus, and inflammatory retinal perivascular sheathing." • By D60, all OD eye showed mild to severe ocular inflammation
D60 gross necropsy	For the 4 monkeys sacrificed on D60, no gross observations were reported.
ADA results	5/6 monkeys (including both sacrificed early) exhibited ADA. The authors considered the ADA results "tentative", based on high background.

7 Genetic Toxicology

Consistent with the advice provided in 2012 Guidance for Industry: ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals32, no genotoxicity studies have been conducted with teprotumumab. P/T concurs that no genetic toxicology studies are needed to support the safety of teprotumumab.

8 Carcinogenicity

- No pharmacologically-active rodent model was identified for teprotumumab; therefore, rodent carcinogenicity bioassays are not feasible.
- Consistent with the advice provided in 2012 Guidance for Industry: ICH S6(R1), no rodent carcinogenicity studies have been conducted with teprotumumab.
- The BLA includes a formal request for waiver of carcinogenicity studies for teprotumumab (submitted in BLA module 1.12.5 Request for a Waiver)[31] that discusses the carcinogenic potential of teprotumumab in context with mechanism of action.
    - The Applicant notes the proof-of-concept studies done in preclinical cancer models, and the clinical data from the completed clinical trials in patients with cancer.

[31] BLA location: \\cdsesub1\evsprod\bla761143\0001\m1\us\request-waiver-carcinogenicity.pdf

- P/T concurs that no carcinogenicity studies are needed to support the safety of teprotumumab.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Based on the Applicant's review of the literature, this reviewer concludes that teprotumab's mechanism of action raises concern for toxicity to male and female fertility, but the concern does not rise to the level of labeling. No specific recommendation for labeling is proposed (section 1.3.3 of this review, above).

- No stand-alone studies to assess fertility and early embryonic development (FEED) were conducted with teprotumumab, and P/T concurs that a stand-alone FEED study is not warranted to support the TED indication at the labeled dose level.
- The Applicant submitted a request for waiver of fertility and peri-postnatal studies (to BLA module 1.12.5 Request for a Waiver)[32]. The Applicant notes:
    - Fertility studies are not easily feasible in the monkey, and no feasible animal species to investigate fertility was identified.
    - The general toxicology studies (reviewed above) did not detect treatment-related toxicity for reproductive tissues.
    - Potential off-target toxicity was not apparent.
- P/T sent an Information Request (IR) requesting more information on the available published literature regarding IGF1R deficiency and fertility. The Applicant responded in two parts (8/26/2019, and 9/04/2019[33]), with supporting literature references. Briefly, the Applicant reported:
    - The role of IGF1R signaling for fertility is known to vary by species. For rodents, IGF1R is clearly important and IGF1R inhibition should decrease fertility.
    - For humans, "IGF-signaling could be important", but data are more limited.
- This reviewer notes that the tissue cross-reactivity studies detected specific binding in the testes, ovary, uterus, and placenta.

[32] BLA location: \\cdsesub1\evsprod\bla761143\0001\m1\us\request-waiver-fertility.pdf
[33] \\cdsesub1\evsprod\bla761143\0008\m1\us\response-to-questions-received-on-august-20-2019.pdf

9.2 Embryonic Fetal Development

Study title: Embryo-Fetal Development Study of RO4858696 Administered by Intravenous Injection to Pregnant Cynomolgus Monkeys	
Study no.:	• Applicant #: 1035664 • Study laboratory #: AGD00065
Study report location:	BLA module 4.2.3.5.2 (Nonclinical study reports: toxicology: reproductive and developmental toxicity: embryo-fetal development): \\cdsesub1\evsprod\bla761143\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\agd00065\agd00065.pdf
Conducting laboratory and location:	(b) (4)
Report date:	December 23, 2009
Date of study initiation:	December 15, 2008
GLP compliance:	No (not intended to be GLP)
QA statement:	Yes, signed
Drug, lot #, and % purity:	Teprotumumab (RO4858696), batch H0001, purity 95% (measured by bioassay)

Key Study Findings

- This non-GLP study was intended as a preliminary EFD assay prior to the definitive GLP EFD study. The single teprotumumab dose selected, 75 mg/kg/week, was based on the high-dose for the (then-ongoing) 9-month monkey toxicology study. Based on the results, the Applicant requested that the GLP EFD study be waived, and DTOP concurred for the TED indication.
- The authors (report page 49) concluded that maternal toxicity was not observed; and considered the most important treatment-related fetal toxicities to be small size, multiple external and skeletal abnormalities of the head ("misshapen cranium, micrognathia, and ossification abnormalities).
- The Applicant (BLA module 2.6.6 Toxicology Written Summary) noted that the treatment-relationship of the fetal loss (abortion) could not be discounted, and this reviewer agrees based on the other effects observed at the same dose level.
- For C-section effects, treatment: decreased placenta weight, placenta primary disk size, amniotic fluid volume, and fetal weight.
- For effects on fetus:
  - the decrease in fetal size (55% of control weight) was reflected in in-life ultrasound measurements and body measurements at C-section.
  - Some of the external and skeletal observations may reflect developmental delays rather than malformations (e.g. open fontanelles; lack of ossified carpals and tarsals; reduced number of sternebrae visible on radiograph).

Other abnormalities are clearly malformations (misshapen rounded skull, micrognathia, eye sockets more closely set than normal)

Methods	
Doses:	0 or 75 mg/kg/week of teprotumumab
Frequency of dosing:	• Dosing once on GD20-22 (based on confirmation of pregnancy by ultrasound) • Once on GD 28 • Once weekly thereafter [total of up to 18 doses; last dose administered was on GD140], with C-section scheduled for GD142 ± 1.
Dose volume:	3 ml/kg
Route of administration:	Slow bolus IV injection (saphenous vein preferred, cephalic vein used as an alternate)
Formulation/Vehicle:	The final formulation (for both dose groups) was (b) (4) L-histidine/histidine hydrochloride, (b) (4) (b) (4) trehalose, and (b) (4) polysorbate 20, pH 5.5 [this is the same as the commercial clinical IV formulation] • For the control group, placebo powder was used. • Both the placebo and test article were reconstituted with sterile water injection.
Species/Strain:	Purpose-bred, experimentally naïve adult pregnant female cynomolgus monkeys
Number/Group:	6 controls + 7 treated pregnant monkeys
Deviation from study protocol:	This reviewer concludes that none of the reported deviations would have reduced the adequacy and quality of the study.

Observations and Results

Mortality

- No early mortality of the adult females occurred.

Clinical Signs

- No remarkable clinical signs were reported
- Endpoints:
    - Cage side observations were recorded twice daily, with “particular attention” given to blood or tissue in the cage pan (as evidence of potential abortion or implantation bleeding)

- Additionally, vaginal swabs (as evidence of abortion or implantation bleeding) were taken once daily. The results were recorded but not provided in the study report (page 32). This is a minor study limitation.

Body Weight

- Females were weighed at the breeding facility (at mating, GD10, and GD18) and weekly thereafter (at the test facility)
- The treated group showed slower weight gain than controls, apparent beginning at gestation week 8. The authors attribute the effect to the difference in fetal weight, placental weight, and amniotic fluid (i.e. not attributed to maternal toxicity).

Table 43: Mean body weight (for monkeys still pregnant) for the monkey EFD study (report # 1035664)

Gestation Week	Control body weight mean (kg)	75 mg/kg group body weight mean (kg)	Treated (as % control)
8	4.0	3.6	90
9	4.1	3.7	90
10	4.2	3.7	88
11	4.3	3.7	86
12	4.5	3.8	84
13	4.6	3.8	82
14	4.6	3.9	84
15	4.7	3.9	82
16	4.8	4.0	83
17	4.9	4.0	81
18	5.0	4.0	80
19	5.1	4.1	80
20	5.2	4.2	80

Feed Consumption

- No remarkable differences in food consumption were apparent.
- Food consumption was qualitatively assessed daily.

Ultrasound monitoring

- Endpoints:
  - Ultrasonography for determination of pregnancy was conducted under sedation (method of sedation not reported): once GD18-20, again for confirmation once GD20-GD22, and investigationally for individual females thereafter.
  - Ultrasonography was performed “approximately” every other week for: general condition, heart rate, and developmental landmarks (depending

on the size and position of the fetus) for the "gestational sac (GS) and gestational length (GL).

- Prior to GD50: "*the gestational sac was measured in three dimensions (cephalocaudal, ventrodorsal, and transverse) and a mean value obtained. Greatest length of the embryo/fetus was determined by obtaining a sagittal scan through the midline and obtaining a maximum length from the top of the cranium to the base of the tail (crown/rump length).*"
- Beginning GD50 (when feasible): humerus and femur length, biparietal diameter, occipitofrontal diameter, head circumference, and abdominal circumference.

- Results:
  - the authors concluded that gestational sac dimensions and fetal heart rates were comparable between the two groups, and this reviewer concurs.
  - Fetal size measurements were clearly smaller for the treated group compared to controls, and generally appear proportional.

Table 44: Selected fetal ultrasound measurements for the monkey EFD study (report # 1035664)

Endpoint	GD	Control mean	Treated mean	Difference (% mean)
Gestation sac (mm)	31-33	15.37 ± 4.00	18.18 ± 2.44	+ 18%
	45-47	30.75 ± 5.64	31.81 ± 5.30	+ 3%
Crown-rump length (mm)	31-33	8.13	9.86	+21%
	45-47	25.15	23.24	- 7%
	59-61	50.14	48.20	-3%
	73-75	61.70 (3 measurable, 2 UTD)	63.40 (4 measurable, 1 UTD)	+2%
	85-89	75.20 (2 measurable, 3 UTD)	81.00 (2 measurable, 3 UTD)	+7%
Biparietal Diameter (mm)	45-47	9.42	9.14	- 2%
	59-61	15.98	14.66	-8%
	73-75	22.28	19.64	-11%
	87-89	29.72	25.08	-15%
	101-103	34.06	28.24	-17%
	115-117	37.56	32.78	-12%
	129-131	40.86	35.50	-13%
Occipitofrontal Diameter (mm)	45-47	11.65	11.84	+1%
	59-61	19.18	17.32	-9%

	73-75	26.62	23.04	-13%
	87-89	35.54	29.12	-18%
	101-103	42.86	35.04	-18%
	115-117	48.18	41.54	-13%
	129-131	55.86	45.94	-17%
Head circumference (mm)	45-47	35.34	34.48	-2%
	59-61	57.20	52.08	-8%
	73-75	80.94	70.10	-13%
	87-89	106.80	89.50	-16%
	101-103	125.60	106.30	-15%
	115-117	139.80	120.80	-13%
	129-131	156.00	132.20	-15%
Abdominal Circumference (mm)	45-47	28.70	26.70	-6%
	59-61	47.74	35.42	-25%
	73-75	68.52	48.98	-28%
	87-89	88.44	64.24	-27%
	101-103	101.12	76.10	-24%
	115-117	115.80	87.18	-24%
	129-131	125.60	99.66	-20%
Humerus Length (mm)	45-47	5.59	5.42	-3%
	59-61	13.74	10.73	-21%
	73-75	17.36	14.42	-16%
	87-89	21.84	17.32	-20%
	101-103	25.46	23.08	-9%
	115-117	28.72	25.44	-11%
Femur Length (mm)	59-61	4.55	4.07	-10%
	73-75	12.52	8.99	-28%
	87-89	15.46	12.19	-21%
	101-103	19.88	17.16	-13%
	115-117	26.24	22.38	-14%
	129-131	28.20	26.76	-5%
Heart rate (bpm)	31-33	137	151	+10%
	45-47	178	196	+10%
	59-61	194	193	+7%
	73-75	178	191	+7%
	87-89	193	191	-1%
	101-103	182	191	+4%
	115-117	219	214	-2%
	129-131	180	204	+13%

UTD: unable to determine

Gestation sac size: reported as the mean of the traverse, cephalocaudal, and ventrodorsal measurements.

Blood collection: toxicokinetics, hematology, and clinical chemistry

- Blood was collected after the first dose (GD20-22) for TK, ADA, hematology, and clinical chemistry.
- Blood was collected on GD105 (168 hours after the 13th dose) for TK and ADA
- Blood was collected on GD140 (prior to dosing) for hematology and clinical chemistry
- Blood was collected at C-section for TK

Table 45: Maternal serum TK for the monkey EFD study (report # 1035664)

TK parameter	C_{max} (µg/ml)	$AUC_{0\text{-}168h}$ (µg*h/ml)
GD20	2090	190,000
GD105	3510	385,000

- No ADA was detected after the start of treatment.
- No clearly treatment-related effects apparent for maternal hematology and clinical chemistry.

Dosing Solution Analysis

No concern identified for the dosing solution. Formulation analysis was reported; test article was within 2% of nominal.

Fetal loss (abortion), and pregnant female replacement

- The protocol specified 5 pregnant females/group. For females found to not be pregnant or to have aborted, dosing was stopped and the adult was returned to colony (i.e. without necropsy) and replaced.
- The initial 5/dose group were confirmed pregnant by ultrasound on GD20-22. However, GD 32 ultrasound found that one control female (#1501) and two treated females (#2503 and #2504) were no longer pregnant (report page 52).
    - These animals were replaced (i.e. by control # 1506, and by treated #s 2506 and 2507).
    - The 3 replaced monkeys each received 2 doses.
- The laboratory historical control data (report page 43) was reported as 7.2% abortion incidence (26/360 pregnancies) for GD20-50.
    - The authors note that the incidences for both the control (1/6 = 16.6%) and teprotumumab (2/7 = 28.5%) exceed the historical control rate. However, the small group sizes make attribution difficult.

- Generally, P/T recommends against detailed ultrasound endpoints under sedation, because of the risk of confounding toxicity from the sedation (which increases with duration of sedation).
- Based on the other clearly treatment-related toxicity observed for the 75 mg/kg group, and in the absence of a full GLP EFD study, the observed increase in abortion incidence is considered treatment-related.

Table 46: Abortion incidence for the monkey EFD study (report # 1035664)

Endpoint	Control	75 mg/kg
Abortion incidence	1/6	2/7
Early natural delivery (GF140)	1/5	0/5

Cesarean Section Data

- One control female (#1505) delivered on GD140 (prior to C-section)
- C-section was performed on pregnant females GD142 ± 1.
  - The amniotic fluid and umbilical cord were evaluated grossly (prior to clamping). Umbilical cord blood (and fetal cardiac blood by puncture, if umbilical cord samples were inadequate) were collected for analysis.
  - The placenta was weighed, measured, and grossly examined.
  - [Review note: no evaluation of ovaries]
- Treatment caused decreased placenta weight (and decreased placenta:body weight), decreased placenta primary disk measurement, and decreased amniotic fluid volume. [The secondary disk could not be measured reliably]
  - *Review note*: these results are consistent with the tissue cross-reactivity results, which identified the placenta as a potential target tissue.
- Findings in the placenta and umbilical cord appearance were not clearly treatment-related:
  - One control (female # 1502) had a placenta with “several central infarcts” (up to 3 cm in diameter)
  - One treated female (# 2507) had a twisted umbilical cord.
  - One treated female (# 2501) had “central” cord insertion in placenta (described as “eccentric” for the other monkeys).
  - The authors state that these findings are seen “occasionally” in the historical control database (numerical data not provided).
  - No abnormalities reported for placenta fetal surface, maternal surface, membrane insertion, umbilical cord length, number of vessels in cord, or the amniotic fluid color and clarity was normal for all monkeys.

Table 47: C-section data (placenta, umbilical cord, amniotic fluid) for the EFD monkey study (report # 1035664)

Endpoint	Control	75 mg/kg	Difference
# of females assessed	4	5	[due to 1 natural birth for the control group]
Placenta weight (g)	80.998 ± 5.27	56.330 ± 4.607	-30.4%
Fetal body weight (g)	273.359 ± 63.090	149.417 ± 13.072	-45.3%
Placenta : fetal body weight ratio	0.270 ± 0.016	0.381 ± 0.058	+41%
Placental primary disk length (first direction measured, mm)	108.3 ± 14.5	88.2 ±9.4	-18.5%
Placental primary disk length (shorter direction measured) (mm)	86.4 ± 15.7	72.9 ± 9.3	-15.6%
Amniotic fluid volume (ml)	83 ± 27	33 ± 8	-60.2%
Umbilical cord length (mm)	146 ± 21	143 ± 70	-2.0%
# of vessels in cord	3	3	0

Offspring Data

- Endpoints:
  - Fetal viability and weight were measured.
  - "*The fetuses underwent external (including morphometric measurements), visceral, and detailed ex vivo heart evaluations (evaluation of great vessels and internal structures, including heart valves*)" (report page 38)
  - Skeletal evaluation by radiograph
  - Fetal organ weights: adrenal, brain, kidney, liver, spleen, thymus
  - Systemic tissues were collected and preserved in formalin.
- Growth results:
  - No clear treatment-related effects for fetal hematology and clinical chemistry
  - Fetal body weights were 55% of control weights (as shown above).

- The decrease in body weight is consistent with the ultrasound measurements (above) and the fetal measurements at C-section (below)
- However, organ:body weight rations were not affected (i.e. specific organs were not targeted; data presented in the report but not copied here). Notably thymus:body weight was not different between the two groups (report page 476).

Table 48: Fetal measurements at C-section (GD142 ± 1) (report # 1035664)

Endpoint	Control	75 mg/kg	Difference
# of fetuses assessed	5	5	[i.e. including the control infant born on GD140]
Crown-rump length (mm)	164.4 14.8	141.3 ± 3.6	-12.9%
Crown-hip length (mm)	151.9 ± 12.4	134.0 ± 3.8	-11.7%
Chest circumference (mm)	110 ± 14	92.8 ± 7.5	-15.6%
Femur length (mm)	47.7 ± 4.9	42.1 ± 2.5	-11.7%
Foot length (mm)	57.3 ± 6.2	44.5 ± 1.6	-22.3%
Biparietal distance (mm)	44.7 ± 3.4	40.2 ± 1.1	-10.0%
Occipitofrontal diameter (mm)	57.7 ± 4.3	46.7 ± 1.7	-19.0%
Horizontal head circumference (mm)	155.2 ± 14.9	139.0 ± 7.0	-10.4%
# of males	2	1	NA
Male anogenital distance (mm)	33.5	26.0	-22.3%
# of females	3	4	NA
Female anogenital distance (mm)	14.3 ± 2.1	11.3 ± 1.0	-20.9%

External fetal examination results:

- No external observations were noted for control fetuses (0/5)
- All (5/5) fetuses from the 75 mg/kg group had multiple head external observations
- Two (2/5) from the 75 mg/kg group had external body observations:
  - One (fetus # 2076, from female # 3507) had thoracic scoliosis (“affected region of spine rotated such that left ribs are rotated anteriorly and to the right)
  - One (fetus # 2021 from female # 3502) had undescended testis

Table 49: External fetal anomalies for the 75 mg/kg group (report # 1035664)

External observation	Incidence in the 75 mg/kg group fetuses
Cranium: Rounded “as viewed from the front”	3/5
Cranium: generally rounded	1/5
Eyes “close set” or “narrow set”	3/5
Nose pointed or narrow	2/5
Open fontanelles (brain visible through cranial bones)	4/5
Overbite	2/5
Underbite	1/5
Thoracic scoliosis	1/5
Undescended testis	1/5

Heart evaluation

- No abnormalities of the heart or great arteries was noted for any fetus.

Skeletal evaluation

- Fetal skeletons were evaluated by radiograph.
- No skeletal malformations were noted for the control fetuses.
- Each of the fetuses from the 75 mg/kg group had multiple skeletal malformations. The skull effects, and scoliosis, were consistent with the external observations (noted above).
- For sternebrae:
    - For the control fetuses, the average number was 6.2 (range 5 to 7).
    - For the 75 mg/kg group fetuses, one fetus had 6, two had 4, one had 3, and sternebrae could not be counted in the radiograph for the one fetus with scoliosis.
- For carpals:
    - For the control fetuses, the average number was 4.7 (range 3 to 7)
    - For the 75 mg/kg group fetuses, the average number was 1.1. Three of the fetuses had no carpals detected (one fetus had 2 carpals/arm; the other had 3 left carpals and 4 right carpals).
- Notably, the number of metacarpals (5/forelimb), metatarsals (5/hindlimb), and digits (forelimb and hindlimb) were the same for each fetus.

Table 50: Fetal skeletal anomalies for the 75 mg/kg group (report # 1035664)

External observation	Incidence in the 75 mg/kg group fetuses
Skull rounded (cranial base, cranial vault, midface)	5/5
Skull – lower portion of skull (below eyes) relatively smaller, micrognathia, teeth less developed than	5/5

controls. Overall bone density of skull appears decreased”	
Eyes appear closely set	4/5
Forelimbs: no carpals ossified either side (considered “delayed for gestation age of fetus”)	3/5
Hindlimbs: 2 tarsals ossified each side (considered “delayed for gestation age of fetus”)	3/5
Thoracic vertebrae scoliosis (“thoracic spine curved with convexity to the left). Unable to count sternebrae	1/5
Reduced number of sternebrae	3/4 (plus one unable to evaluate)

Special evaluation: fetal immunohistochemistry

- Based on findings in treated adult monkeys, the protocol included fetal immunohistochemistry for lymph nodes (mesenteric, mandibular, inguinal), spleen, and thymus were stained for B-lymphocytes, T-lymphocytes, and natural killer (NK) cells (using antibodies against CD3, CD4, CD8, CD16, and CD20).
- The stain failed for many slides; the other results appeared highly variable. slides.
- Neither the authors nor this reviewer were able to detect a treatment-effect.

Fetal TK

- For the 75 mg/kg group, adequate umbilical cord blood was collected from three fetuses. For the other two, blood was collected via cardiac puncture. Teprotumumab was detected in the plasma of each pregnant female and each fetus at C-section.
- Results from report page 388:

Table 51: Maternal and fetal teprotumumab plasma concentrations at C-section (report # 1035664)

Maternal mean teprotumumab concentration at C-section	3000 ± 612 µg/ml
Fetal mean teprotumumab concentration at C-section	372 ± 73.3 µg/ml
Fetal-to-maternal ratio	0.124 x

9.3 Prenatal and Postnatal Development

Based on the Applicant's review of the literature, this reviewer concludes that teprotumumab's mechanism of action raises concern for PPND toxicity.

- This is consistent with the Applicant's stated expectation, based on the treatment-related teratogenicity observed in the monkey EFD study, that prenatal and postnatal systemic exposure to teprotumumab would be toxic.
- A recommendation for labeling is proposed (section 1.3.3 of this review, above).

- The Applicant did not submit a prenatal and postnatal development (PPND) study for teprotumumab, and P/T concurs that a PPND study is not warranted to support the TED indication at the labeled dose level.
- The Applicant submitted a request for waiver of fertility and pre-postnatal studies (to BLA module 1.12.5 Request for a Waiver).
- As background information, this reviewer notes:
    - The tissue cross-reactivity studies detected specific binding in the testes, ovary, uterus, and placenta.
    - IGF1R is integrally important for growth and development. Based on mechanism of action, systemic exposure of the developing fetus or newborn to teprotumumab is expected to be toxic.
    - Immunoglobulin transfer across the human placenta increases during the third trimester of pregnancy. Because teprotumumab is a human IgG, maternal dosing is expected to result in fetal exposure (and activity).
- P/T sent an Information Request (IR) requesting more information on the IGF1R knock out mice. The Applicant responded in two parts (8/26/2019, and 9/04/2019[34]), with supporting literature references. Briefly, the Applicant reported:
    - "Igf1r-null mice are nonviable because of respiratory failure immediately after birth due to underdeveloped muscles of the diaphragm. Additional abnormalities include, but are not limited to, decrease in size, hypoplastic muscles, delayed bone development, and thin epidermis"
    - Heterozygous *Igf1r* knockout mice survive and are generally normal.
    - Conditional IGF1R knock out mice had specific disorders (depending on the timing of activation and the tissue targeted).
    - A clinical case study was found (Kawashima et al. 2012) reporting on a family with heterozygous IGF1R mutations, which caused low birth weight and developmental deficits.

9.4 Lactation (no studies conducted)

- P/T did not recommend a milk study to support the BLA, and the Applicant did not submit one.

[34] \\cdsesub1\evsprod\bla761143\0008\m1\us\response-to-questions-received-on-august-20-2019.pdf

- P/T concurs with the Applicant's proposed labeling for section 8.2, "*There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.*"
- Review note:
  - Previous labeling had lactation language such as (b) (4) (b) (4)
  - However, from a scientific perspective, the value of this language for a human IgG such as teprotumumab is unclear.

11 Integrated Summary and Safety Evaluation

- Teprotumumab is an antagonist, binding with high affinity and selectivity to the IGF-1R via the extracellular α-subunit. Teprotumumab inhibits the endogenous ligands, IGF-1 and IGF-2, from binding to IGF-1R.
- IGF1R is known to be expressed on the surface of most cells. The Applicant submitted GLP tissue cross-reactivity studies for human and monkey tissues. In the human, teprotumumab specific membrane binding was detected for:
  - Endothelial cells of multiple organs (eye, heart, kidney, liver, esophagus, ovary, parathyroid, placenta, prostate, skin, cervix), and
  - Epithelial cells of multiple organs (mammary, small intestine, bile duct, Fallopian tube, prostate, skin, testes, thymus, tonsil, ureter, and urinary bladder)
  - Mononuclear cells in multiple tissues

11.1 Nonclinical NOAEL and LOAEL values

Summarizing the reviews above:

Table 52: Toxicology study summary table

Report #	Dosing duration	IV Dose (mg/kg)	Effect	C_{max} (µg/ml)	AUC (µg*h/ml)
1020097 (not GLP)	4 doses over 11 days	15	Study not adequate to identify a NOAEL/LOAEL; Thymic involution detected	685	93,511
1016123 (GLP)	7 weeks	7.5	Low dose LOAEL based on thymic lymphoid depletion	621	55,200

		75	[NOAEL for non-thymus effects]	8670	613,000
1023600 (GLP)	13 weeks	3	Adult low dose LOAEL based on thymic lymphoid depletion	121	12,500
		75	[Adult NOAEL for non-thymus effects]	2650	213,000
		15	Juvenile LOAEL, based on cessation of body weight gain, deceased serum ALP and BAP, thymic effects (decreased size and weight, diffuse atrophy), & decreased spleen weight	404	40,900
1030337 (GLP)	39 weeks	3	Low dose LOAEL based on thymic diffuse atrophy	117	14,300
		75	[NOAEL for non-thymus effects]	2900	314,000
1037684 (GLP)	13 weeks	3	LOAEL, based on reduced weight gain, decreased ALP, thymus effects (decreased size and weight, lymphoid atrophy), decreased spleen weight, decreased long bone growth in-life (humerus, radius, ulna, femur, tibia, fibula), and decreased bone (tibia and femur) density	62.3	6440
1035664 (not GLP)	EFD study (weekly x 18)	75	Maternal NOAEL	3510 (maternal C_{max})	385,000 (maternal AUC)
		75	LOAEL for abortion, decreased fetal growth, and multiple malformations	372 (fetal concentration at C-section)	[not calculated for fetuses]

The lowest mean TK parameters, for the last dose were used for each report.

11.2 Exposure margin calculations

- The Applicant submitted draft labeling in the original (7/08/2019) BLA submission; revised labeling has not yet been submitted. The submitted labeling, in section 12.3 Pharmacokinetics, reports clinical steady-state PK results: (b) (4)

Table 53: Nonclinical exposure margins based on TK

Dose	Description	C_{max}		AUC	
		Monkey result	Exposure margin from the clinical C_{max} = (b) (4)	Monkey result	Exposure margin from the clinical AUC = (b) (4)
75 mg/kg	Adult chronic NOAEL (report # 1030337)	(b) (4)			
3 mg/kg	Juvenile LOAEL (report # 1037684)				
75 mg/kg	Maternal NOAEL (report # 1035664)				
75 mg/kg	Fetal LOAEL (report # 1035664)				

11.3 Considering reversibility of the treatment-related effects in monkeys

As a reference:

13-day study (report # 1020097)	Reversibility not assessed
7-week study (report # 1016123)	0, 7.5, 25, 75 mg/kg/week; included an 8-week recovery group • ALP: the 25 and 75 mg/kg group males recovered; no recovery for the treated females • Thymus weight: partial recovery at 7.5 mg/kg; no recovery at 25 or 75 mg/kg/week • Thymus lymphocyte depletion: partial recovery for all dose groups (no dose response apparent).
13-week study (report # 1023600	0, 3, 15, 75 mg/kg/week; included a 12-week recovery group • Inhibition of weight gain: recovery for all groups • ALP and BAP: recovery not clearly demonstrated (results difficult to interpret) • Thymus weight: partial recovery for the 3 mg/kg group; no recovery at 15 or 75 mg/kg • Juvenile female spleen weight: results suggest partial recovery (results difficult to interpret) • Thymus diffuse atrophy: partial recovery (no dose response)
39-week study (report # 1030337)	0, 3, 15, 75 mg/kg/week; included a 24-week recovery group • Body weight: partial recovery (no dose response) • ALP: recovery apparent for all dose groups • Thymus weight: no recovery apparent • Thymus diffuse atrophy: recovery apparent for all dose groups
Juvenile 13-week study (report #1037684)	0, 3, 15, 75 mg/kg; included a 13-week recovery group • Body weight: recovery for all groups • ALP: recovery for 3 and 15 mg/kg; partial recovery for 75 mg/kg • Thymus weight: recovery for male groups, females at 3 and 15 mg/kg (no recovery for 75 mg/kg females) • Spleen weight: recovery at 3 mg/kg only (not at 15 or 75 mg/kg) • Thymus lymphoid depletion: recovery apparent for all groups • Bone density (tibia and femur): results suggest partial recovery for all groups (results difficult to interpret) • For in-life decreased bone growth: no recovery apparent

11.4 Predictivity of the monkey model for patients with TED

- As noted above (in the Executive Summary of this review), the monkey model predicted the clinical reduced weight gain/weight loss and decreased serum ALP, but not the clinical infusion reactions, exacerbation of inflammatory bowel disease, or hyperglycemia.
- Thymus:
  - The monkeys used for the general toxicology studies were nominally adults. Based on their reported ages and immature testes, P/T considers them adolescents-to-young adults. The control animal results clearly show that their thymuses had not yet undergone natural involution. Therefore, these studies were able to detect teprotumumab targeting of the thymus. It is not clear whether testing in aged monkeys would have been equally sensitive. The omission of exact ages for each monkey in the GLP studies is a reporting limitation.
  - The thymus effects in the juvenile monkeys showed a greater magnitude of effect, consistent with their younger age.
  - From a nonclinical perspective, the monkey thymus data would not be expected to have a clinical correlated in the TED patient population enrolled. However, the results may be relevant to other patient populations.
- The 39-week monkey study (report # 1030337) observed several minimal hematological changes that were of unclear relationship to treatment, and without apparent toxicological relevance. These changes appear to be predictive (although not clinically meaningful).
- This reviewer reaches these conclusions based on the Applicant's reporting in BLA's module 2.7.4 Summary of Clinical Safety[35]

Age range	For the TED trials, the age range was 20 to 79 years (Table 10 on page 35)
ALP	"*For alkaline phosphatase, the observed decreases in the teprotumumab group (range: -11.3 to -24.4 U/L) were larger than the observed decreases in the placebo group (range: -1.8 to -11.8 U/L); however, the magnitude was not considered clinically meaningful*."
Body weight	"*During the Treatment Period, small mean increases in weight were observed in the placebo group at Weeks 12 (0.99 kg) and 24 (1.67 kg), whereas small mean decreases in weight were observed in the teprotumumab group at Weeks 12 (-0.84 kg) and 24 (-1.36 kg; ISS Table 2.5.1)*." "*The majority of the subjects in both treatment groups had a less than 5% change from Baseline in weight at Weeks 12 and 24. However, greater proportions of subjects in the placebo group compared with the teprotumumab group had a CTCAE Grade 1 or 2 increase in weight at*

[35] \\cdsesub1\evsprod\bla761143\0001\m2\27-clin-sum\summary-clin-safety.pdf

	Weeks 12 (16.3% vs. 1.3%, respectively) and 24 (27.8% vs. 11.8%, respectively).”

Table 24: Summary of Weight Gain or Weight Loss by CTCAE Grade During the Treatment Period Visits by Treatment Group (Double-Masked Population)

	Number (%) of Subjects[1]			
	Weight Gain[2]		Weight Loss[3]	
Visit CTCAE Grade	Placebo	Teprotumumab	Placebo	Teprotumumab
Week 12	**(N = 80)**	**(N = 79)**	**(N = 80)**	**(N = 79)**
Grade 0	67 (83.8)	78 (98.7)	75 (93.8)	73 (92.4)
Grade 1	11 (13.8)	1 (1.3)	4 (5.0)	4 (5.1)
Grade 2	2 (2.5)	0	1 (1.3)	2 (2.5)
Grade 3	0	0	0	0
Week 24	**(N = 79)**	**(N = 76)**	**(N = 79)**	**(N = 76)**
Grade 0	57 (72.2)	67 (88.2)	77 (97.5)	62 (81.6)
Grade 1	18 (22.8)	8 (10.5)	1 (1.3)	10 (13.2)
Grade 2	4 (5.1)	1 (1.3)	1 (1.3)	3 (3.9)
Grade 3	0	0	0	1 (1.3)

Source: ISS Table 2.5.2.
CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety.
1. Percentages are based on the number of subjects with non-missing values at the given visit and Baseline in the Double-Masked Population in each treatment group.
2. Weight Gain: Grade 0 = <5% increase from Baseline; Grade 1 = 5% to <10% increase from Baseline; Grade 2 = 10% to <20% increase from Baseline; Grade 3 = ≥20% increase from Baseline.
3. Weight Loss: Grade 0 = <5% decrease from Baseline; Grade 1 = 5% to <10% decrease from Baseline; Grade 2 = 10% to <20% decrease from Baseline; Grade 3 = ≥20% decrease from Baseline.

Thymus	A search of the Summary of Clinical Safety for “thymus” and “thymic” found no results.
Hematology	“*In the teprotumumab group, small mean decreases from Baseline were observed for hemoglobin, erythrocytes, percentage of neutrophils and platelet counts, and small mean increases from Baseline were observed for percentage of lymphocytes. Although different from placebo, the magnitude of the observed differences was not considered clinically meaningful nor associated with clinical events.”*

11.5 Consideration of misuse potential

- The 2017 Clinical Medical Guidance for Industry: Assessment of Abuse Potential of Drugs[36] defines abuse potential in reference to central nervous system (CNS) activity, and references applicable statute and 21 CFR 314.50(d)(5)(vii).
- Separate from CNS abuse potential, P/T identified a theoretical concern for off-label misuse based on mechanism of action. This concern was discussed with the clinical review team (personal communication, McDougal/Chambers, 11/20/2019), and P/T defers to Division management regarding how to address this concern (e.g. adverse event tracking).
    - The IGF1R/IGF-1 pathway is well characterized. Based on mechanism of action, teprotumumab would be expected *a priori* to inhibit normal growth.

[36] Accessed via: https://www.fda.gov/media/116739/download

        - In the juvenile and adult monkeys, teprotumumab caused cessation of weight gain. In the juvenile monkeys, this correlated with decreased bone growth.
        - In patients, a small but detectable decrease in body weight/weight gain was noted (after correcting for intentional weight loss and other factors).
    - Reportedly, hormones and growth factors are used illegally to stunt growth (e.g., delaying puberty for child entertainers, gymnastics and other specific sports, child sex trafficking). The commercial availability of an IGF1R antagonist may put these populations at risk of exposure.
    - Obesity and weight control are major unmet medical needs. Data are lacking regarding the combination of teprotumumab with other tools for weight loss (e.g., caloric restriction, exercise, medicine).

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/s/

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12/06/2019 02:58:09 PM

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